

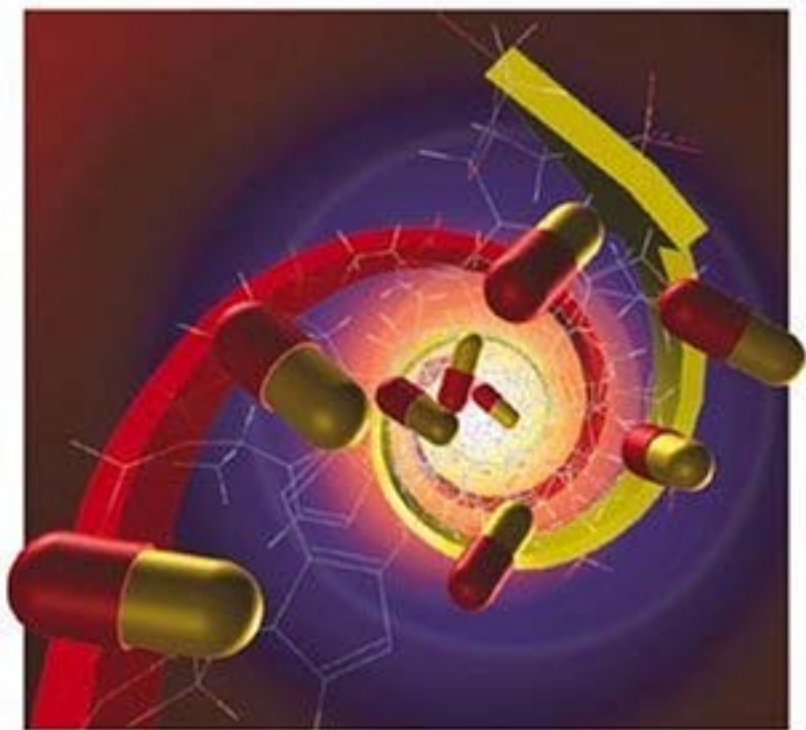
Edited by
Julio Licinio, Ma-Li Wong

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Biology of Depression

From Novel Insights to Therapeutic Strategies

Volume 1



Biology of Depression

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Editors:

Prof. Julio Licinio

University of California, Los Angeles
David Geffen School of Medicine
and Neuropsychiatric Institute
3357A Gonda Research Center
Los Angeles, CA
USA

Prof. Ma-Li Wong

University of California, Los Angeles
David Geffen School of Medicine
and Neuropsychiatric Institute
3357A Gonda Research Center
Los Angeles, CA
USA

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We dedicate this book to Alice and John with much love

Preface

Major depression was meticulously described by Hippocrates nearly 2500 years ago. Melancholia, a subtype of depression, is the only word which was coined by Hippocrates based on his theory of the four humors (melancholia: black bile), and that is still used today to describe a disorder that is part of contemporary official diagnostic systems.

This book covers major depressive disorder, specifically unipolar depression, a condition that we conceptualize as a *common* and *complex* disorder of *gene–environment interactions* for which the specific genetic and environmental substrates are still unknown. These words are simple but are loaded with meaning, as follows.

Common – depression is highly prevalent worldwide. As the disorder is episodic, lifetime rates are higher than point prevalence. Even though figures vary worldwide, depression is indeed very common. It has been estimated that the lifetime prevalence in the United States is 15% and the point prevalence is 3%, being twice as high in women compared to men.

Complex – the fundamental mechanisms underlying depression are complex. It is universally accepted that there is a familial basis for susceptibility to the disorder; however, such a pattern, which does not follow classical Mendelian genetics, is of such complexity that in spite of the sequencing of the human genome and the availability of sophisticated technology, it has not yet been elucidated. Based on currently available evidence it appears to be unquestionable that variations in a single allelic locus will not be sufficient to explain all presentations of the disorder. The prevailing working hypotheses are first that the genetic substrate consists of multiple genes of small effect, and second that the specific combination of genetic variants that are required to reach a depression susceptibility threshold will vary from person to person and from population to population.

Gene–environment interactions – the effects of the still unknown genes are unquestionably interconnected with environmental factors. Some of these factors are evident and include early life stress such as loss of a parent, abuse, or trauma. What makes this field challenging is that while some individuals who are subjected to severe environmental stress, particularly in early life, eventually develop depression, others who are subjected to the same type of stressors develop different psychiatric disorders, while a third group survives unscathed. The relative contribution of genetic and environmental substrates of depression will certainly vary from case to case, and modeling such intricate and variable interactions will become an

area of exciting and necessary future informatics work which will flourish after more specific causative agents have been identified.

How can such complexity be unraveled so that knowledge can be advanced? We felt that a useful contribution would be to bring the most important pieces of this fascinating puzzle together in these two volumes to fulfill the dual purpose of informing the scientific, medical, and academic communities along with the general public of what has been accomplished so far, and also to serve as a foundation on which existing knowledge can be expanded.

Information on depression can be found from a variety of sources that include journal articles, websites, older textbooks, books for the lay public and chapters in various types of textbooks, from general psychiatry to psychopharmacology. This work was specifically designed to be a one-stop shop for a comprehensive and up-to-date reference text on depression. Our goal was to offer in a single source both breadth *and* depth, as we systematically cover the vast field of knowledge related to depression, in this multi-authored two-volume book. We feel privileged to have been able to bring together here eminent researchers and practitioners as well as three patients who shared with us their personal experience. From the outset, our intention was to address the multifaceted biological aspects of unipolar major depression, analyzed and interpreted by a variety of experts in the field, who offer a broad range of perspectives. To carry out our mission, each of these experts presented their contribution which is the distilled product of several decades dedicated to the understanding of different aspects of this disorder. We are also indebted to three generous patients, who have graciously and unselfishly agreed to contribute to this project their personal accounts of their encounters with this disorder.

This book was in preparation long before the current public and regulatory scrutiny of antidepressant usage. The recent interest surrounding the documentation of the increased incidence of suicide in children receiving antidepressant treatment, underscores the fact that this is a critical time in the research and treatment of unipolar major depression. Several controversies have besieged this field, and these included the once heated debate between the schools of biological and psychological psychopathology; these differences are no longer a source of significant discussion. While decades ago orthodox psychologically-based therapists condemned biological treatments as taking away the motivation to seek insight and achieve a psychological cure, today it is accepted that psychological and biological approaches to treatment are not mutually exclusive. Psychoanalytical theories and approaches have waned in the face of new biological insights, which have been fuelled by the development of psychopharmacology. It has been fascinating to keep pace with the transformations on several fronts, including evolution in the areas of public awareness, biological and pharmacological research, regulatory policies and patent laws, and the growth of the drug industry. This is all the more remarkable as we keep in mind that such extraordinary progress and changes in perspectives have occurred in the context of a lack of knowledge regarding the causative mechanisms.

Modern psychopharmacology is now a little over 50 years old. Drugs with antidepressant effects were among the first to be discovered and their ability to

improve mood was found unintentionally by sheer serendipity. Drugs have become the first choice of treatment because other modes of treatment that range from the obsolete to the highly effective (such as cold baths and ECT) are far more cumbersome to implement and are not readily accepted by the public. Psychotherapy is costly and laborious, and its efficacy has been confirmed for specific types of standardized practice such as interpersonal and cognitive therapies; the efficacy of other modalities is much less certain. It is consequently unsurprising that the Holy Grail of antidepressant treatment would be an orally administered drug with a short onset of action, high efficacy, and negligible adverse drug reactions, which is not metabolized by systems that have considerable genetic variability affecting pharmacokinetics. This magic bullet remains elusive. On the contrary, the first antidepressants were not easy drugs to use as they caused many adverse reactions. Some of these drugs could only be taken in conjunction with a strict diet, and could be lethal in cases of intentional or accidental overdose, thus patients receiving these drugs would need to be closely monitored by the treating psychiatrist.

Pharmacological treatment has represented an important advance in the treatment of depression. Suicide, suicide ideation, gestures and plans are among serious manifestations of major depression. An increment in suicide behavior during the first weeks of antidepressant treatment has long been recognized as a feature of the treatment of the disorder since some symptoms, such as psychomotor retardation improve before others, such as suicidality. Close monitoring of depressed patients during this phase of treatment is therefore a key necessity.

A second wave of antidepressant drug development brought to the market the selective monoamine reuptake inhibitors, with milder side-effects and a high therapeutic index without (in the vast majority of cases) lethality in the case of overdose. In a few years, fluoxetine became the new “gold standard” in the treatment of depression. There was a “boom” in the market as the incidence of depression seemed to be on the rise, and the available treatment appeared to be so benign that the terms “cosmetic psychopharmacology” and “lifestyle drugs” were applied to antidepressants. Because such drugs were not perceived to be associated with serious side-effects, the law of supply and demand was approached from two directions: physicians became more liberal in prescribing antidepressants, while simultaneously public demand increased. Psychopharmacology has also brought to the market a new phenomenon of “blockbuster” drugs: one huge financial windfall that generates profit, increases stock prices, pleases investors and shareholders and more than offsets the astronomical costs of pharmaceutical research and development, bringing new medications to the market and paying off the costs associated with unsuccessful compounds. It is logical to conclude that most patients who are treated with newer antidepressants have not been as closely monitored as they should have been and the current focus on the emergence of suicidality will serve as a warning that treating depression requires a combination of close monitoring, expertise, and experience.

In spite of current issues, the absence of knowledge about the causative mechanisms, and lack of curative treatments, enormous progress has been made in our understanding and treatment of depression. It is our hope that these two

volumes will synthesize such progress, serving as a comprehensive source that integrates valuable information from various disciplines, thereby facilitating advances towards the next level of insight and therapeutics.

We would like to thank the staff at Wiley-VCH, particularly Andrea Pillman, for their support of this effort. We are also very grateful to Aimee Midei for her expert assistance during the preparation of this book.

January 2005
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Julio Licinio
Ma-Li Wong

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List of Contributors

Kathy Aitchison
Clinical Neuropharmacology
(PO Box 51)
Institute of Psychiatry
1 Windsor Walk
Denmark Hill
London SE5 8AF
UK

Hagop S. Akiskal
VA Psychiatry Service (116A)
3350 La Jolla Village Drive
San Diego, CA 92161
USA

George Alexopoulos
New York Presbyterian Hospital
21 Bloomingdale Road
White Plains, NY 10605
USA

Michael Bauer
Department of Psychiatry
and Psychotherapy
Charité – University Medicine Berlin
Campus Charité Mitte (CCM)
Berlin,
Germany

Robert D. Beech
Yale University School of Medicine
Department of Psychiatry
Abraham Ribicoff Research Facilities
34 Park St., 3rd Floor
New Haven, CT 06508
USA

Howard G. Birnbaum
Managing Principal Analysis Group,
Inc.
111 Huntington Ave., 10th Floor
Boston, MA 02199
USA

Garth Bissette
Department of Psychiatry
and Human Behavior
University of Mississippi Medical
Center
2500 North State Street
Jackson, MS 39216-4505
USA

Susan Blauner
P.O. Box 1024
Greenfield, MA 01302
USA

Liv Bode
Project Bornavirus Infections
Robert Koch Institute
Nordufer 20
13353 Berlin
Germany

Catherine Bond
Project Return: The Next Step
1138 Wilshire Blvd
Suite 100
Los Angeles, CA 90017
USA

Brigitta Bondy
Psychiatric Clinic
University of Munich
Nußbaumstrasse 7
80336 Munich
Germany

Peter Bongiorno
4 Spring Lane
Great Neck, NY 11024
USA

Blynn G. Bunney
Department of Psychiatry and Human
Behavior
University of California, Irvine
D438 Medical Sciences 1
Irvine, CA 92697-1675
USA

William E. Bunney
Department of Psychiatry and Human
Behavior
University of California, Irvine
D438 Medical Sciences 1
Irvine, CA 92697-1675
USA

Philip J. Burguières
EMC Holdings and Houston Texans
Reliant Stadium
Two Reliant Park
Houston, TX 77054
USA

Lucile Capuron
Department of Psychiatry and
Behavioral Sciences
Emory University School of Medicine
Atlanta, GA
USA

Robert M. Carney
Behavioral Medicine Center
Department of Psychiatry
Washington University School of
Medicine
4625 Lindell Blvd., Suite 420
St. Louis, MO 63108
USA

Elliot J. Coups
Memorial Sloan-Kettering Cancer
Center
Department of Psychiatry and
Behavioral Sciences
330 E. 59th St., 7th floor
New York, NY 10022
USA

Renaud de Beaurepaire
Hôpital Paul Guiraud
54, avenue de la République
94806 Villejuif
France

Maurício Silva de Lima
Gerente Médico-Neurociência
Av. Morumbi, 8264
CEP 04703-002
São Paulo-SP
Brazil

Bernardo Garcia de Oliveira Soares
Departamento de Psiquiatria
Universidade Federal de São Paulo
Brazil

Detlef E. Dietrich
Department of Psychiatry
and Psychotherapy
Medical School of Hanover
Carl-Neubergstr. 1
30625 Hannover
Germany

Wayne C. Drevets
Mood and Anxiety Disorders Program
NIH NIMH/MIB
15K North Dr., MSC 2670
Bethesda, MD 20892-2670
USA

Ronald S. Duman
Yale University School of Medicine
Department of Psychiatry
Abraham Ribicoff Research Facilities
34 Park St., 3rd Floor
New Haven, CT 06508
USA

Adrian J. Dunn
Department of Pharmacology
and Therapeutics
Louisiana State University Health
Sciences Center
P.O. Box 33932
Shreveport, LA 71130-3932
USA

Maurizio Fava
Harvard Medical School
Massachusetts General Hospital
ACC 812, 15 Parkman St.
Boston, MA 02114
USA

Max Fink
P.O. Box 457
St. James
New York 11780-0457
USA

Deborah L. Flores
Univ. of California, Los Angeles
Gonda Ctr. 3357
695 Charles Young Dr. So.
Los Angeles, CA 90095-1761
USA

Kenneth E. Freedland
Behavioral Medicine Center
Department of Psychiatry
Washington University
School of Medicine
4625 Lindell Blvd., Suite 420
St. Louis, MO 63108
USA

Michael Gitlin
David Geffen School of Medicine
Univ. of California, Los Angeles
300 UCLA Medical Plaza, Suite 22000
Los Angeles, CA 90095
USA

Philip W. Gold
NIH, NIMH
Clinical Neuroendocrinology Branch,
Building 10, Rm 2D46
10 Center Dr., MSC 1284
Bethesda, MD 20892-1284
USA

Reed D. Goldstein
Department of Psychiatry
University of Pennsylvania
School of Medicine
210 West Washington Square
Mezzanine
Philadelphia, PA 19106
USA

Paul E. Greenberg
Managing Principal Analysis Group,
Inc.
111 Huntington Ave., 10th Floor
Boston, MA, 02199
USA

Alan M. Gruenberg
Department of Psychiatry
and Human Behavior
Jefferson Medical College
Philadelphia
USA

Christine Heim
Department of Psychiatry
and Behavioral Sciences
Emory University School of Medicine
1639 Pierce Drive
WMRB, Suite 4000
Atlanta, GA 30322
USA

Jimmie C. Holland
Memorial Sloan-Kettering
Cancer Center
Department of Psychiatry
and Behavioral Sciences
330 E. 59th St., 7th floor
New York, NY 10022
USA

Kristopher J. L. Irizarry
Bioinformatics Unit
Center for Pharmacogenomics &
Clinical Pharmacology
Neuropsychiatric Institute
David Geffen School of Medicine
Univ. of California, Los Angeles
3357 UCLA Gonda Center
695 Charles Young Drive, SO.
Los Angeles, CA 90095-1761
USA

Leslie Iversen
The Doctors House
High Street
Little Milton
Oxford OX44 7PU
UK

Lewis L. Judd
Department of Psychiatry
University of California at San Diego
La Jolla (0603), CA
USA

Justine Kent
Department of Psychiatry, Box 28
Morristown Memorial Hospital
100 Madison Ave.
Morristown, NJ 07962-1956
USA

Aleksandra Lalovic
Douglas Hospital Research Centre
6875 LaSalle Blvd.
Verdun, Quebec, H4H 1R3
Canada

Klaus Peter Lesch
Molecular and Clinical Psychobiology
Department of Psychiatry
and Psychotherapy
University of Wuerzburg
Fuechsleinstr. 15
97080 Wuerzburg
Germany

Julio Licinio
Center for Pharmacogenomics and
Clinical Pharmacology
Neuropsychiatric Institute
David Geffen School of Medicine
at UCLA
3557A UCLA Gonda Center
695 Charles Young Drive South
Los Angeles, California 90095-1761
USA

Adrian LLerena
Center for Pharmacogenomics and
Clinical Pharmacology
Neuropsychiatric Institute
David Geffen School of Medicine
at UCLA
Gonda Ctr. 3357
695 Charles Young Dr. So.
Los Angeles, CA 90095-1761
USA

Hanns Ludwig
Institute of Virology
Free University of Berlin
Königin-Luise-Str. 49
14195 Berlin
Germany

Andrew H. Miller
Department of Psychiatry
and Behavioral Sciences
Emory University School of Medicine
Psychiatry and Behavioral Sciences
1639 Pierce Dr., Suite 4000
Atlanta, GA 30307
USA

Francis M. Mondimore
John Hopkins School of Medicine
600 N. Wolfe St
Meyer 3-181
MD 21287-7381
USA

Charles B. Nemeroff
Department of Psychiatry
and Behavioral Sciences
Emory University School of Medicine
1639 Pierce Drive
WMRB, Suite 4000
Atlanta, GA 30322
USA

Edward V. Nunes, Jr.
Department of Psychiatry
Columbia University College
of Physicians and Surgeons
New York State Psychiatric Institute
1051 Riverside Dr., Box 51
New York, NY 10032
USA

George I. Papakostas
Massachusetts General Hospital
Department of Psychiatry
Depression Clinical and Research
Program
15 Parkman Street
WACC 812
Boston, MA 02114
USA

Gordon Parker
School of Psychiatry
University of New South Wales
Mood Disorders Unit
Black Dog Institute
Prince of Wales Hospital
Randwick N.S.W. 2031
Australia

Kay Parker
School of Psychiatry
University of New South Wales
Mood Disorders Unit
Black Dog Institute
Prince of Wales Hospital
Randwick N. S. W. 2031
Australia

Kristin M. Penza
Department of Psychiatry
and Behavioral Sciences
Emory University School of Medicine
1639 Pierce Drive, WMRB, Suite 4000
Atlanta, GA 30322
USA

Cynthia R. Pfeffer
Weill Medical College of Cornell
University
New York Presbyterian Hospital
21 Bloomingdale Road
White Plains, New York 10605
USA

Harold Alan Pincus
RAND
University of Pittsburgh Health
Institute
WPIC, Suite 230
3811 O'Hara Street
Pittsburgh, PA 15213
USA

James B. Potash
John Hopkins School of Medicine
600 N. Wolfe St
Meyer 3-181
MD 21287-7381
USA

Steven G. Potkin
Department of Psychiatry
College of Medicine
University of California Irvine
Med Sci 1, Rm D438
Irvine, California 92617
USA

Joseph L. Price
Mood and Anxiety Disorders Program
NIH NIMH/MIB
15K North Dr., MSC 2670
Bethesda, MD 20892-2670
USA

David C. Purselle
Department of Psychiatry
and Behavioral Sciences
Emory University School of Medicine
1639 Pierce Drive
Suite 40000
Atlanta, GA 30322
USA

Wilfred N. Raby
Department of Psychiatry
Columbia University College
of Physicians and Surgeons
New York State Psychiatric Institute
1051 Riverside Drive, Box 51
New York, NY 10032
USA

Charles L. Raison
Department of Psychiatry
and Behavioral Sciences
Emory University School of Medicine
1639 Pierce Drive
Suite 4000
Atlanta, GA 30322
USA

Alan Schatzberg
Department of Psychiatry
and Behavioral Sciences
Stanford University School
of Medicine
401 Quarry Road, Rm 2138
Stanford, CA 94305-5723
USA

Bindu Shanmugham
New York Presbyterian Hospital
21 Bloomingdale Road
White Plains, NY 10605
USA

Bernardo Soares
Gerente Médico – Neurociência
Av. Morumbi, 8264
CEP 04703-002
São Paulo – SP
Brazil

Pierre Sokoloff
Unité de Neurobiologie et
Pharmacologie Moléculaire
INSERM U 573
2ter rue d'Alésia
75014 Paris
France

H. Brent Solvason
Department of Psychiatry
and Behavioral Sciences
Stanford University School
of Medicine
401 Quarry Road
Rm 2138
Stanford, CA 94305-5723
USA

Artur H. Swiergiel
Department of Pharmacology
and Therapeutics
Louisiana State University Health
Sciences Center
Shreveport, LA 71130-3932
USA

Kopal Tandon
Clinical Neuropharmacology
(PO Box 51)
Institute of Psychiatry
1 Windsor Walk
Denmark Hill
London SE5 8AF
UK

Gustavo Turecki
Douglas Hospital Research Centre
6875 LaSalle Blvd.
Verdun, Quebec, H4H 1R3
Canada

Peter Whybrow
The Neuropsychiatric Institute
and the
Department of Psychiatry
and Biobehavioral Science
David Geffen School of Medicine
Univ. of California, Los Angeles
300 UCLA Medical Plaza, Suite 22000
Los Angeles, CA 90095
USA

Jeremy Winell
Memorial Sloan-Kettering Cancer
Center
Department of Psychiatry
and Behavioral Sciences
330 E. 59th St., 7th floor
New York, NY 10022
USA

Ma-Li Wong
Center for Pharmacogenomics and
Clinical Pharmacology
Neuropsychiatric Institute
David Geffen School of Medicine
University of California, Los Angeles
Gonda Center 3357B
695 Charles Young Dr. So.
Los Angeles
CA 90095-1761
USA

Abbreviations

ACE	angiotensin converting enzyme
ACTH	adrenocorticotrophic hormone
ADRA2A	alpha 2A adrenoceptor/adrenergic receptor gene
AMT	alpha-methyl-para-tyrosine
APA	American Psychiatric Association
BDNF	brain derived neurotrophic factor
B _{max}	maximal binding capacity
CSF	cerebrospinal fluid
CI	confidence interval
CLOCK	circadian locomotor output cycles kaput
COMT	catechol-O-methyl transferase
CREB	cyclic AMP response element protein
D2 receptor	dopamine 2 receptor
D3 receptor	dopamine 3 receptor
D4 receptor	dopamine 4 receptor
DRD4	D4 receptor gene
DβH	dopamine beta hydroxylase
DISC	disrupted in schizophtrenia gene
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	electroconvulsive therapy
HHRR	haplotype-based haplotype relative risk method
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin or 5-hydroxytryptamine
5-HT _{1A}	serotonin 1A receptor
5-HT _{1B}	serotonin 1B receptor
5-HT _{2A}	serotonin 2A receptor
5-HT _{2C}	serotonin 2C receptor
HTR1A	serotonin 1A receptor gene
5-HTTP	5-hydroxytryptophan
5-HTT	serotonin uptake transporter
HVA	homovanillic acid

HPA	hypothalamus-pituitary-adrenal
ICD	International Classification of Diseases and Related Health Problems
LD	linkage disequilibrium
MDD	major depressive disorder
MHPG	3-methoxy-4-hydroxyphenyl glycol
MAO	monoamine oxidase
MAOA	monoamine oxidase type A
MAOB	monoamine oxidase type B
NA	noradrenaline
NAT	noradrenaline transporter
NEO-FFI TM	Neuroticism Extroversion Openness Five Factor Inventory
NEO-PI-R TM	Neuroticism Extroversion Openness personality inventory revised
NPAS	neuronal PAS domain protein 2a
NRI	noradrenaline selective uptake inhibitor
PCPA	para-chlorophenylalanine
PDE	phosphodiesterase
PET	positron emission tomography
QTLs	quantitative trait loci
RDC	Research Diagnostic Criteria
RFPL	restriction fragment length polymorphism
SAD	season affective disorder
SADS-L	schedule for affective disorders and schizophrenia-lifetime version
SCID	structured clinical interview for DSM
SNP	single nucleotide polymorphism
SSRI	serotonin selective reuptake inhibitor
TCA	tricyclic antidepressant
TCI	Cloninger temperament and character inventory, HA1 subdimension: Harm avoidance, worry and pessimism
TD	tryptophan depletion
TDT	transmission disequilibrium test
TPQ	Tridimensional Personality Questionnaire
VNTR	variable number tandem repeat
WHO	World Health Organization
χ^2	chi square

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Classification of Depression: Research and Diagnostic Criteria: DSM-IV and ICD-10

Alan M. Gruenberg, Reed D. Goldstein and Harold Alan Pincus

Abstract

This chapter shall address the classification of depressive disorders and its evolution over the past 50 years. We shall present a brief historical overview of depressive disorders and describe the development of the current nomenclature as incorporated in the *Diagnostic and Statistical Manual of Mental Diseases Fourth edition* (DSM-IV) [1] and the *International Classification of Diseases and Related Health Problems 10th edition* (ICD-10) [2]. We will examine current controversies in the diagnosis of depression, and conclude with comments about the potential impact of new neurobiological and neurogenetic developments on the diagnosis of depression in the future.

1.1

Historical Framework

The history of depressive disorders is described in detail by Jackson [3]. The experience of depression has plagued humans since the earliest documentation of human experience. Ancient Greek descriptions of depression referred to a syndrome of melancholia, which translated from the Greek means black bile. In humoral theory, black bile was considered an etiologic factor in melancholia. This Greek tradition referred to melancholic temperament which is comparable to our understanding of early onset dysthymic conditions or depressive personality. During the late 19th and early 20th centuries, phenomenologists increasingly used the term depression or mental depression to refer to the clinical syndrome of melancholia. Emil Kraepelin [4] distinguished mood which was dejected, gloomy, and hopeless in the depressive phase in manic-depressive insanity from the mood which was withdrawn and irritable in paranoia. In addition, Kraepelin distinguished depression which represented one pole of manic-depressive insanity from melancholia, which involves depression associated with fear, agitation, self-accusation and hypochondriacal symptoms.

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Our current classification systems stem from these important observations. The distinction between manic-depressive (bipolar) conditions and non-bipolar conditions remains a critically important objective. The treatments available for these distinct types of disorders are quite different. We continue to rely on best clinical observation, careful diagnostic interviewing and assessment, family history, and clinical course to make these distinctions.

The evolution of formal classification systems is a 20th century phenomenon. The stated goals of any classification system are to ensure improved communication among clinicians, to enhance understanding of the disorders in question, and to promote more effective treatment. Depression researchers have struggled because of the heterogeneity of the depressive syndrome. Early neurobiological investigation of the biological markers, such as cortisol response or cerebrospinal fluid neurotransmitter metabolites thought to be important in the differentiation of depression, yielded few consistent findings. This likely represented the problem of diagnostic non-specificity in the individuals being investigated. The current classification systems hopefully promote better separation between major depressive disorders and bipolar disorder. More accurate separation between psychotic disorders which are schizoaffective versus major depressive disorders with psychotic features is warranted. In addition, it is increasingly relevant to distinguish comorbidity associated with posttraumatic stress disorder from primary depressive disorders, in which trauma may not be a prominent feature.

More than 50 years ago, the evolution of the US diagnostic approach was first typified by the development of the *Diagnostic and Statistical Manual of Mental Disorders, First Edition* (DSM-I) [5]. DSM-I, published in 1952, was prepared by the Committee on Nomenclature and Statistics of the American Psychiatric Association. This revision of psychiatric nomenclature attempted to provide a contemporary classification system consistent with the concepts of modern psychiatry and neurology of that time. It was limited to the classification of disturbances of mental functioning. The diagnostic classification employed the term “disorder” to designate a group of related psychiatric syndromes. Each group was further divided into more specific psychiatric conditions termed “reactions”. In this system, the mental disorders were divided into two major groups: (1) those in which a disturbance in mental functioning resulted from or was precipitated by a primary impairment of the function of the brain, generally due to diffuse impairment of brain tissue and (2) those which were the result of a more general difficulty in adaptation of the individual and in which any associated brain function disturbance was secondary to the psychiatric disorder.

For example, psychotic disorders were considered “disorders of psychogenic origin or without clearly defined physical cause or structural change in the brain”. Affective reactions such as manic-depressive reactions and psychotic depressive reaction were diagnosed within the psychotic disorders section. Depressive reaction was included within the psychoneurotic disorders in DSM-I.

The *Manual of the International Statistical Classification of Diseases Injuries and Causes of Death* was adopted in 1948 by the World Health Organization [6]. Consistent with the development of DSM-I, international efforts were undertaken

to add an official international classification of mental disorders. In 1948, the World Health Organization (WHO) took responsibility for the sixth revision of the *International List of Causes of Death*, added a mental disorders section, and renamed it the *International Classification of Diseases, Injuries and Causes of Death* (ICD-6) [7]. The section for the classification of mental disorders contained 10 categories of psychosis, nine categories of psychoneurosis, and seven categories of disorders of character, behavior and intelligence.

The mental disorders section of ICD-7 [8] appeared in 1955 and was identical to the section in ICD-6. Because of a lack of international acceptance of DSM-I and ICD-7, the WHO subsequently completed a further evolution of concepts and terms which were included in ICD-8 [9] in 1965. American psychiatrists collaborated in preparation for ICD-8, which was approved by the WHO in 1966 and went into effect in 1968. The effort to revise psychiatric nomenclature and classifications included an effort to upgrade the classification systems in use in the United States which resulted in DSM-II [10].

The nomenclature in DSM-II largely eliminated the concept of reactive conditions, encouraged clinicians to make multiple diagnoses, and incorporated concepts of comorbidity and causation when one disorder was considered to be secondary to another disorder. The DSM-II was published in 1968 and was the result of close collaboration with the international community, such that this system was very similar to the mental disorder section of ICD-8.

Major affective disorders were now considered affective psychoses including involuntional melancholia, and manic depressive illness, depressed type. In addition, depressive neurosis replaced neurotic depressive reaction as a general term for non-bipolar depression.

In the early 1970s, several developments were underway that ultimately significantly impacted future diagnostic schemes. International studies comparing classification practices suggested lack of reliability in earlier diagnostic approaches. The development of explicit diagnostic criteria was led by researchers at Washington University School of Medicine including Eli Robins and Samuel Guze, and they developed the first set of diagnostic criteria for research named the Feighner Criteria [11]. In order to meet the needs of a collaborative project on the psychobiology of depression, Spitzer and colleagues modified the Feighner Criteria and added criteria for several additional disorders, resulting in a classification system called the Research Diagnostic Criteria (RDC) [12]. A structured interview called the Schedule for Affective Disorders and Schizophrenia (SADS) [13] was developed to assist researchers in eliciting symptoms necessary for achieving RDC diagnoses. The major revision in American nomenclature was represented in the adoption of DSM-III [14] in 1980. DSM-III was characterized by a dramatic shift in orientation that was descriptive in nature without regard to etiology, and somewhat influenced by the early 20th century concepts of Emil Kraepelin. In this system, explicit diagnostic criteria were used to improve the reliability of classification, more explicit categories for scientific investigation were established, and there was the development of a multi-axial system of evaluation. At the time of the publication of DSM-III in 1980, the international classification did not include a multi-axial system and

did not use explicit criteria for diagnosis. DSM-III represented a dramatic shift away from the principles and diagnostic approaches used in the ICD-9. ICD-9 [15] maintained the approach for depressive disorders outlined in DSM-II and ICD-8.

The predominant change in terminology for depressive disorders incorporated in DSM-III involved the adoption of a primary distinction between major depressive disorders and bipolar disorders. The specific affective disorders included bipolar disorder and major depression distinguished by presence or absence of an episode of mania. Other specific affective conditions such as dysthymic disorder and cyclothymic disorder were considered conditions within the broad category of mood disorders. DSM-III eliminated the diagnoses of depressive reaction and neurotic depression, which characterized the non-psychotic and non-bipolar conditions within DSM-I and DSM-II. Specific descriptive diagnostic criteria were incorporated into the definition of a major depressive episode. Other conditions which did not precisely meet formal criteria for major depressive disorder, single or recurrent episode, bipolar disorder depressed, or dysthymic disorder were considered residual categories such as bipolar type II and atypical depression. DSM-III retained a concept of adjustment disorder with depressed mood.

Other aspects of the changes in DSM-III incorporated the development of a multi-axial system for evaluation that encouraged clinicians to focus attention during the evaluation process on multiple domains of information. Personality disorders were assigned an independent axis in the diagnostic system, which encouraged clinicians to make a diagnosis of major mood disorder on Axis I as well as a personality disorder diagnosis on Axis II. Relevant general medical conditions, important in the evaluation, were diagnosed on Axis III. Assessment of severity and relevant psychosocial or environmental stressors were diagnosed on Axis IV. Global assessment of functioning was coded on Axis V. This multi-axial system of classification represented a marked differentiation from the system in use in ICD-9.

The atheoretical approach to diagnosing mood disorders as well as other conditions in DSM-III was generally accepted among mental health professionals from various disciplines and backgrounds. Researchers with a biological interest as well as researchers with a cognitive-behavioral interest, for example, might approach the investigation of etiology or treatment of mood disorders from different perspectives, but could reliably agree on the descriptive features of diagnosis within an individual. In this regard, the diagnostic criteria in DSM-III were considered useful for purposes of research.

The process of revising DSM-III was supported by the American Psychiatric Association beginning in 1983 and resulted in the publication of DSM-III-R [16] in 1987. Although the revision was intended originally to provide “fine tuning”, more substantive changes in diagnostic classification were made reflecting new diagnostic evidence. This relatively short period between DSM-III and DSM-III-R ultimately caused some difficulty for researchers as certain criterion sets were changed.

As indicated before, the international community of psychiatrists had expressed dissatisfaction with the classification of mental disorders in ICD-6 and ICD-7, which meant they were little used. The World Health Organization adopted changes to the mental disorders section which were incorporated into ICD-8. Coinciding with

the changes represented in DSM-III, a classification of mental disorders appeared in ICD-9 which incorporated a glossary as an integral part of the mental disorders section. This glossary offered descriptions of abnormal mental experience or behavior that would serve as a common frame of reference for clinicians. This clinical glossary was distinctively different from the organization of DSM-III which incorporated specific operationalized criteria for diagnosis. The World Health Organization subsequently developed the ICD-9-CM [17], the clinical modification, to describe further the clinical picture of the patient such that the coding would become more precise than that needed only for statistical groupings. The ICD-9-CM went into effect in 1979 prior to the publication of DSM-III. It remains a major tool for collection and dissemination of mortality and morbidity data throughout the world. The current coding used for reimbursement includes the ICD-9-CM codes. However, the definitions for disorders used in DSM-III are not comparable to the specific definitions in ICD-9-CM.

1.2

Current Diagnostic Framework

The process of development for DSM-IV published by the APA in 1994, was guided by specific reviews based upon new empirical evidence for diagnosis. In the classification of mood disorders, the major change in DSM-IV from DSM-III and DSM-III-R includes a listing of nine criterion symptoms of which dysphoric mood or depressed mood or loss of interest or pleasure must be present nearly every day most of the day during a 2-week period. Four additional symptoms associated with a primary depressed mood or loss of interest must be met. Previously, in DSM-III, the criteria of depressed mood or loss of interest were listed as criterion A and four of eight additional symptoms were required for the diagnosis of major depressive episode.

More substantial changes were made in the diagnostic criteria for Dysthymic Disorder. In DSM-III, the diagnosis of depressive mood required 2 years duration and three of 13 criteria in the absence of psychotic symptoms or another pre-existing mental disorder. In DSM-IV, depressed mood most of the day for at least 2 years was required in the presence of two of six criterion symptoms. The exclusion criteria again included a chronic psychotic disorder but other common psychiatric disorders did not pose specific exclusion criteria in diagnosis. In DSM-IV, clinically significant distress or impairment in social, occupational or other important areas in functioning was required. In general, DSM-IV permitted more co-occurring diagnoses to be listed on Axis I without specific exclusion factors. An additional difference in DSM-IV represents the diagnosis of secondary mood disorders, characterized as Mood Disorder Due to a General Medical Condition or Substance- Induced Mood Disorder, in which the disturbance in mood is judged to be a direct effect of a general medical condition or due to substance intoxication, withdrawal or other medication use. The clinician then specifically notes the name of the general medical condition on Axis I or the specific substance involved in intoxication or withdrawal.

The *International Classification of Diseases (ICD), Ninth Revision* maintained the concepts of affective psychoses, in which there may be a severe disturbance of mood accompanied by perplexity, delusions or disorder of perception and behavior consistent with the prevailing mood which included manic-depressive psychosis, depressed type as well as psychotic depressive reaction. The ICD-9 maintained the concept of neurotic depression and depressive personality disorder.

The *ICD-10 Classification of Mental and Behavioral Disorders* largely abandoned the traditional division between neurosis and psychosis that was evident in ICD-9. However, the term “neurotic” was retained as representing a group of disorders called “neurotic, stress-related and somatoform disorders”. Instead of maintaining the neurotic–psychotic dichotomy, the disorders are arranged according to major themes or likeness. Classification of affective disorder was particularly influenced with this change such that neurotic depression and endogenous depression are not used, but other types of depression are specified in the affective disorders section such as dysthymia and cyclothymia. In ICD-10, the mood disorders include manic episode, bipolar affective disorder, mild depressive episode, moderate depressive episode, severe depressive episode, recurrent depressive episode, cyclothymia, dysthymia, mixed-affective episode, and recurrent brief depressive disorder.

The description of mood disorder in ICD-10 involves a narrative paragraph with less specific criterion for diagnosis. In addition, severity of the episode represents a distinct syndrome as opposed to a modifier of an episode as is found in DSM-IV.

Table 1.1 outlines differences between the current ICD-10 criteria for depressive disorder and the DSM-IV depressive disorder.

The approach to classification of depressive disorders in DSM-IV and ICD-10 requires a fundamental disturbance in mood, usually depressed mood or loss of interest or pleasure. Neither DSM-IV nor ICD-10 attributes a clear etiology to underlying biochemical processes or considers response to treatment or outcome as factors in the classification of depressive disorder. Definitions of depressive disorder in both ICD-10 and DSM-IV have eight symptoms in common including: depressed mood, loss of interest, decrease in energy or increased fatigue, sleep disturbance, appetite disturbance, recurrent thoughts of death, inability to concentrate or indecisiveness, psychomotor agitation or retardation. The criterion sets differ in that ICD-10 has two additional items: reduced self-esteem or self-confidence and ideas of guilt and unworthiness, whereas DSM-IV combines inappropriate or excessive guilt with feelings of worthlessness (which is qualitatively more severe than loss of self-confidence or self-esteem).

The structure of the diagnostic algorithms also differs between the two systems. ICD-10 groups the items into two sets: one containing three items, depressed mood, loss of interest, and decreased energy; and the other set containing the remaining seven items. The ICD-10 diagnostic thresholds are specified in terms of the number of items required from each of the two sets. DSM-IV instead presents the nine items in one set, but indicates that either depressed mood or loss of interest is required for a diagnosis of Major Depressive Episode.

In ICD-10, separate diagnostic thresholds are established to differentiate between mild, moderate, and severe depressive episodes, depending upon the number of

Table 1.1 Major depressive disorder

	<i>DSM IV</i>	<i>ICD-10 depressive disorder</i>
Clinical significance	Symptoms cause clinically significant stress or impairment in social, occupational or other important areas of functioning.	Some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely in mild depressive episode; considerable difficulty in continuing with social, work or domestic activities in moderate depressive episode; considerable distress or agitation, and unlikely to continue with social, work, or domestic activities, except to a very limited extent in severe depressive episode.
Duration of symptoms	Most of day, nearly every day for at least 2 weeks.	A duration of at least 2 weeks is usually required for diagnosis for depressive episodes of all three grades of severity.
Severity	<p>Five or more of following symptoms; at least one symptom is either depressed mood or loss of interest or pleasure:</p> <ul style="list-style-type: none"> (1) Depressed mood (2) Loss of interest (3) significant weight loss or gain or decrease or increase in appetite (4) Insomnia or hypersomnia (5) Psychomotor agitation or retardation (6) Fatigue or loss of energy (7) Feelings of worthlessness or excessive or inappropriate guilt (8) Diminished ability to think or concentrate, or indecisiveness (9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan 	<p>Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity in typical depressive episodes; other common symptoms are:</p> <ul style="list-style-type: none"> (1) Reduced concentration and attention (2) Reduced self-esteem and self-confidence (3) ideas of guilt and unworthiness (even in mild type of episode) (4) Bleak and pessimistic views of the future (5) Ideas or acts of self-harm or suicide (6) Disturbed sleep (7) Diminished appetite <p>Typical examples of “somatic” symptoms are: loss of interest or pleasure in activities that are normally enjoyable; lack of emotional reactivity to normally pleasurable surroundings and events; waking in the morning 2 h or more before the usual time; depression worse in the morning; objective evidence of definite psychomotor retardation or agitation; marked loss of appetite; weight loss; marked loss of libido.</p> <p>For mild depressive episode, two of most typical symptoms of depression and two of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms.</p> <p>For moderate depressive episode, two of three of most typical symptoms of depression and at least three of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms.</p> <p>For severe depressive episode, all three of the typical symptoms noted for mild and moderate depressive episodes are present and at least four other symptoms of severe intensity are required.</p>

symptoms, type of symptoms, and severity of symptoms present. The ICD-10 specifies grades of severity to cover a broad range of clinical sites. Individuals with mild depressive episodes are noted to present in primary care and general medical settings, whereas psychiatry settings are thought to address depressive episodes defined as moderate or severe. In contrast, DSM-IV provides a single nine-item criteria set that gives priority to depressed mood and loss of interest requiring that one of the two be present. In DSM-IV, severity does not determine a separate diagnostic depressive episode, but is assigned instead after the criteria for a major depressive episode have been met. This specifier in DSM-IV is based on the number of symptoms present and level of functional impairment.

An additional differentiation between ICD-10 criteria and DSM-IV involves the presence or absence of psychotic symptoms. In ICD-10, the criteria must be met for a severe depressive episode (eight out of 10 symptoms including depressed mood, loss of interest and decreased energy). If psychotic features, including non-bizarre delusions and hallucinations or depressive stupor are present, then a diagnosis of severe depressive episode with psychotic symptoms may be assigned. Depressive episodes with psychotic symptoms that are less symptomatically severe cannot be indicated using the “psychotic symptom” specifier. In DSM-IV, it is noted that psychotic symptoms typically occur in the most severe cases. It is not always the case and therefore, the DSM-IV subtype labeled “severe with psychotic features” does not require that the individual have all eight depressive symptoms, only that criteria for Major Depressive episode is met and that delusions or hallucinations of any kind must be present. In ICD-10, a clinical significance criterion is not included, while DSM-IV requires that symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

The ICD-10 criteria do not allow for bereavement to be taken into account in the diagnosis, while DSM-IV excludes a diagnosis of major depression if the symptoms of the depressive episode are better accounted for by bereavement.

These differences suggest that much overlap in diagnosis would be present. However, the definitions would lead to some cases in which the criteria for one definition of a depressive episode would be met in one system, but not the other.

The criteria defining recurrence of depression is significantly different in the two systems. ICD-10 requires that the individual has at least 2 months without any significant mood symptoms, whereas DSM-IV requires an interval of at least two consecutive months in which criteria for a major depressive episode are not met. Therefore, ICD-10 is much more stringent, requiring a full remission between episodes, while DSM-IV would consider an individual to have had separate episodes of depression even if symptoms of depression are reduced from five to four within the 2-month period.

DSM-IV provides multiple options for listing specifiers of the current clinical status, including severity, psychotic, and remission specifiers. DSM-IV also includes descriptive features such as chronic, and other descriptive specifiers such as: with catatonic features, with melancholic features, with atypical features, and with postpartum onset. The DSM-IV also includes longitudinal course specifiers such as:

with seasonal pattern and with rapid cycling. Several of these specifiers are not included in ICD-10.

In summary, the two systems provide for many similarities in defining an episode, but the structure of how the episode is diagnosed is somewhat different. DSM-IV makes much more extensive use of diagnostic specifiers, while ICD-10 conceptualizes major depressive episodes as ranging from mild to severe with different symptom thresholds. DSM-IV provides for more specific inclusion and exclusion criteria, which are not contained in ICD-10.

1.3 Controversies

Both DSM-IV and ICD-10 include “not otherwise specified” (NOS) categories in which atypical conditions are defined as conditions not meeting syndromal criteria for a major depressive episode. Sub-threshold forms of depression are important for classification purposes because they are prevalent, have clinical significance in terms of morbidity and functional impairment, and are associated with increased medical care costs and higher rates of service utilization [18–20].

Kessler et al. [21] concluded that mild cases in the DSM system should be retained because attention to a spectrum of impairment highlights the fact that mental disorders (like physical disorders) vary in severity. It is recommended that cost effective treatments for mild disorders might ultimately prevent progression from a mild to a more severe disorder. In contrast, Narrow et al. [22] have proposed that DSM criteria be limited to decrease the number of persons who would meet current criteria, in order to decrease the overall demand for clinical treatment. This proposal limits exploration of the impact of the wide range of symptomatic presentations within the mood disorder spectrum. Removal of current mild cases would limit genetic exploration and examination of both biological and psychosocial risk factors within depressive disorders [23].

Pincus et al. [24] also reviewed the importance of sub-threshold disorders. In DSM-IV, Minor Depressive Disorder requires at least two, but fewer than five depressive symptoms during the same 2-week period. Recurrent brief depressive disorder requires a depressive episode with symptomatic criteria, but lasting less than 2 weeks and requires that the episodes occur at least once per month for 12 consecutive months. In ICD-10, depressive episodes are defined by a systematic symptom threshold, and mild depressive episode requires the presence of four of 10 symptoms. The ICD-10 definition for recurrent brief depressive disorder requires that the depressive episodes last less than 2 weeks, recur once each month over the past year, and fulfill the symptomatic criteria for mild, moderate, or severe depressive episode. In DSM-IV, proposed research criteria for mixed anxiety–depressive disorder are offered, while no criteria are specified for mixed anxiety–depression in ICD-10. The diagnosis of sub-threshold forms of depression are conceptually important for neurobiologic and molecular genetic investigation. They offer research opportunities to examine hypotheses in which consistent neurobiological findings

or susceptibility genes would be present in both severe and mild forms of the disease. However, many prior investigations have excluded individuals with sub-threshold forms of the condition under investigation.

Both DSM-IV and ICD-10 encourage the specification of additional diagnoses in addition to major depressive disorder. The two exclusion criteria defined by DSM-IV include the direct physiologic effects of a substance or a general medical condition and as mentioned above, bereavement. The ICD-10 criteria requires that clinicians follow the general rule of recording as many diagnoses as necessary to adequately capture the clinical picture. Precedence is assigned to that diagnosis most relevant to the purpose of the consultation, and recognition of the lifetime diagnosis is encouraged. The complexity of comorbidity is reviewed in detail by Pincus, Tew and First [25]. The evolution in the second half of the 20th century of ICD and DSM mandated that an increasing number of separate and co-occurring clinical psychiatric conditions and co-occurring personality disorders be recorded as part of a diagnostic evaluation. The increasing diagnostic comorbidity has not yet been addressed conceptually by neurobiologic researchers or incorporated consistently in ongoing neurogenetic and neurobiologic investigation.

1.4

Future Directions

While there is increasing attention being paid to the specificity of criteria in both DSM-IV and ICD-10, no specific etiologic factors are recognized by either classification system. A research strategy that delineates consistent neurobiologic findings within a syndromic classification would result in less diagnostic heterogeneity as compared to a non-etilogic system of classification. The discipline of psychiatry has failed to identify a single biological marker or gene useful in making a diagnosis of major depression.

Furthermore, no biological marker or genetic finding has yet predicted response to a specific pharmacologic treatment. A future classification system in which etiology and pathophysiology are fundamental in diagnostic decision-making would bring psychiatry closer to other branches of medicine. Most likely, many years will pass before such a pathophysiology is delineated or specific genetic findings replicated such that more homogenous syndromes can be identified. Nevertheless, in our opinion, the current syndromic approach offers researchers a continuing opportunity to improve classification systems through ongoing neurobiologic investigation.

1.5

Conclusions

The classification system used for diagnosis of depression has evolved over the past 50 years. Initially, DSM-I underscored the “reactive” aspects of depression and

other psychiatric disorders. Subsequently, DSM-II emphasized the importance of psychodynamic formulations including the differentiation between depressive neurosis and depressive psychosis. More recent DSM systems have offered a non-etiologic paradigm which emphasized nosologic criteria for diagnosis as typified in DSM-III, DSM-III-R, DSM-IV, and DSM-IV-TR [26]. Upon review of the differences in the diagnosis of depressive disorder in DSM-IV-TR and ICD-10, some individuals may be classified differently based on severity or recurrence.

An etiologic or pathophysiologic approach to classification would emphasize disease-specific or symptom-related genes. In addition, phenotypes could be identified based on consistent neurobiologic markers, such as neuroimaging or cognitive function. These neurobiologic or other markers of specific behavior may challenge the validity of our prevailing classification systems. Inevitably, new genetic information would link susceptibility markers with environmental risk factors to explain phenotypic expression. The question remains of whether gene-finding studies or other molecular genetic studies will define specific pathologic syndromes. Alternatively, genetic studies or advances in molecular genetics will identify alterations in intracellular pathways, cellular organization, or neuroanatomic pathways, which are far removed from our current understanding of major depression. The challenges in the future are to develop a broader explanatory understanding of the syndrome under investigation, ranging from basic cellular processes to brain pathways, and their links with relevant psychological constructs such as self-esteem, resilience to stress or stress vulnerability, and personality, temperament, and character.

As reflected in the following chapters, our discipline should be open to emerging neurobiologic and genetic findings as applied to depression. As that understanding grows, classification systems will be modified to include more specific etiologic, pathophysiologic, or pharmacologic substrates of depression.

References

- 1 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association, 1994.
- 2 WORLD HEALTH ORGANIZATION. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization, 1992.
- 3 JACKSON, S. W., *Melancholia and Depression*. New Haven: Yale University Press, 1986.
- 4 KRAEPELIN, E., *Manic-Depressive Insanity and Paranoia*. Translated by BARCLAY, R. M. Edinburgh, UK: E & S Livingstone, 1921.
- 5 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual: Mental Disorders*. Washington, DC: American Psychiatric Association, 1952.
- 6 WORLD HEALTH ORGANIZATION. *Manual of the International Classification of Diseases, Injuries, and Causes of Death*. Geneva: World Health Organization, 1948.
- 7 WORLD HEALTH ORGANIZATION. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 6th revision*. Geneva: World Health Organization, 1948.
- 8 WORLD HEALTH ORGANIZATION. *International Classification of Diseases: Manual of the International Statistical*

- Classification of Diseases, Injuries and Causes of Death, 7th revision. Geneva: World Health Organization, 1955.
- 9 WORLD HEALTH ORGANIZATION. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 8th revision*. Geneva: World Health Organization, 1965.
 - 10 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders, Second Edition*. Washington, DC: American Psychiatric Association, 1968.
 - 11 FEIGHNER, J. P., ROBINS, S. B., GUZE, R. A., et al., Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiatry* 1972, 26, 57–63.
 - 12 SPITZER R. L., ENDICOTT, J., ROBINS, E., *Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders* (3rd ed.). New York State Psychiatric Institute, 1978.
 - 13 ENDICOTT, J., SPITZER, R. L., A diagnostic interview: The schedule for affective disorders and schizophrenia. *Arch. Gen. Psychiatry* 1978, 35, 773–782.
 - 14 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington, DC: American Psychiatric Association, 1980.
 - 15 WORLD HEALTH ORGANIZATION. *International Classification of Diseases, 9th Revision*. Geneva, World Health Organization, 1975.
 - 16 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association, 1987.
 - 17 WORLD HEALTH ORGANIZATION. *International Classification of Diseases, 9th Revision, Clinical Modification*. Ann Arbor, Michigan: Commission on Professional and Hospital Activities, 1978.
 - 18 HORWARTH, E., JOHNSON, J., KLIERMAN, G. L., et al., Depressive symptoms as relative and attributable risk factors for first-onset major depression. *Arch. Gen. Psychiatry* 1992, 49, 817–823.
 - 19 WELLS, K. B., STEWART, A., HAYS, R. D., et al., The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA* 1989, 262, 914–919.
 - 20 JOHNSON, J., WEISSMAN, M. M., KLIERMAN, G. L., Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA* 1992, 267, 1478–1483.
 - 21 KESSLER, R. C., MERIKANGAS, K. R., BERGLUND, P., et al., Mild disorders should not be eliminated from the DSM-V. *Arch. Gen. Psychiatry* 2003, 60, 1117–1122.
 - 22 NARROW, W. E., RAE, D. S., ROBINS, L. N., et al., Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. *Arch. Gen. Psychiatry* 2002, 59, 115–123.
 - 23 BENJAMIN, J., EBSTEIN, R. P., LESCH, K. P., Genes for personality traits: implications for psychopathology. *Int. J. Neuropsychopharmacol.* 1998, 1, 153–168.
 - 24 PINCUS, H. A., McQUEEN, L. E., ELINSON, L., Subthreshold mental disorders. In PHILLIPS, K. A., FIRST, M. B., PINCUS, H. A. (Eds.), *Advancing DSM: Dilemmas in Psychiatric Diagnosis*. Washington, DC: American Psychiatric Press, Inc. 2003, 129–144.
 - 25 PINCUS, H. A., TEW, J. D., FIRST, M. B., Psychiatric comorbidity: Is more less? *World Psychiatry* 2004, 2 (3), 153–158.
 - 26 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association, 2000.

2

Psychosocial and Environmental Formulations of Depression

Gordon Parker and Kay Parker

Abstract

As “depression” can manifest as a disease, a disorder and a syndrome, the role of psychosocial and environmental factors is likely to vary across such alternate states, but be of greatest relevance to the non-melancholic disorders. Here, a negative environment during early childhood has been found to have a far-reaching impact on psychopathology of the adult, often manifesting in childhood or adolescence. Quality of parenting (or perception of parents) has been found to increase risk of depression, with empirical studies identifying uncaring and over-protective parents as the probable determinant. Other childhood environment factors that can increase vulnerability are the ordinal position of the child in the family and impact of siblings, with positive sibling attachments being associated with lower levels of anxiety and depression. Experience of bullying or sex abuse (particularly parental abuse) are additional risk factors that may be encountered by children being emotionally scarred. Further, psychosocial factors in the individual's life circumstances may be responsible for, or exacerbate existing vulnerability. The impact of social deprivation (perception of available social support in the home or workplace), is mediated by self-mastery. Social class and marital factors have long been obvious causes of vulnerability, but the role of employment and retirement is more complex, being mediated by satisfaction and locus of control.

2.1

Introduction

Biopsychosocial models of “depression” are commonly proposed, essentially arguing for the relevance of psychosocial and environmental factors to all expressions of depression. Conceding a range of etiological factors is appealing while it encourages a pluralistic and multi-faceted approach to management. We, however, argue for a specificity model, which allows that psychosocial and environmental factors may

be all explanatory determinants for some expressions of depression, may contribute to others and may be quite irrelevant to other expressions of depression.

These introductory comments clearly invite some consideration as to how depression is best modeled. There has long been a debate about contrasting unitary and binary views. The unitary view essentially argues that depression is a single condition, varying by severity. The binary view has historically contrasted a more biological type of depression (variably called endogenous or melancholic depression) with a second type (variably called neurotic or reactive depression) and with the latter viewed as more reflecting an interaction between environmental stresses and the individual's personality. We have argued [1], however, as "depression" can variably exist as a disease, a disorder, a syndrome and as a "normal" response, both categorical and dimensional expressions of depression need to be captured in any model.

Premature closure of the unitary versus binary debate in the early 1970s resulted in a strong weighting to a dimensional unitarian view of depression being favored. In 1973, Akiskal and McKiney [2] published an article in *Science* that sought to integrate differing conceptual models of depression, and proposed a "unified hypothesis". This model allowed for a disparate set of etiological factors (biological, psychological, social) having the capacity to act on a biological system in the diencephalon and, via a "single final common pathway", thus lead to depression. This model logically only allows depression (as an end-point state) to vary dimensionally, whether in terms of severity, duration or persistence, and does not allow for separate subtypes. Publication of the influential DSM-III system in 1980 further cemented a dimensional model, in largely distinguishing "major" and "minor" expressions of depression, while the dimensional model was even further cemented by the World Health Organization's current ICD classification distinguishing between "severe", "moderate" and "mild" expressions of depression.

By contrast, our model [1] assumes three principal classes. Firstly, two more categorical conditions (psychotic depression and melancholic depression) with each having specific clinical features. For instance, in melancholic depression there is not only a severe mood disturbance but also psychomotor disturbance (indicated by cognitive processing difficulties as well as motor retardation and/or agitation), with the latter absent in non-melancholic depression. In psychotic depression, psychomotor disturbance is more severe and, in addition, there are psychotic features (e.g. delusions, hallucinations, over-valued ideas of guilt, nihilism and worthlessness). The third class (i.e. non-melancholic depression) is not a pure class, but represents a heterogeneous residue of conditions. Apart from there being a mood disorder component, it lacks specific class-specific features – with the few that have been described (e.g. a reactive mood) being, in fact, the converse of features that are more common in melancholic and psychotic depression.

In the absence of specific or distinctly over-represented features, non-melancholic depression has to be modeled in a different way, and one respecting the heterogeneity of its membership. In essence, we have argued for (1) stress-related and (2) personality-related expressions, although clinical observation suggests that most patients with a non-melancholic disorder present as a consequence of an interaction

between stress and personality style. The “stress” conditions can be usefully divided into acute (or “reactive” or “adjustment” disorders) and more chronic conditions. In the former, the individual has usually become depressed as a consequence of a salient depressogenic stressor impacting on their sense of self-worth or self-esteem. A common scenario would be for an individual to become depressed following a break-up in an intimate relationship, by losing their job or by having their reputation impugned. To the extent that “depression” reflects a drop in the individual’s self-esteem, then wherever the individual invests their self-esteem (i.e. intimate relationship, work) this becomes their vulnerability point in terms of a reactive depressive disorder.

In response to such “object losses”, most individuals in the community will develop some degree of depression but, for the majority, it will be transient as a consequence of spontaneous resolution (associated with coping mechanisms and resilience) and last only minutes to days. In a percentage, the acute reaction may last longer and be impairing, sometimes reflecting the severity of the stressful event, sometimes its salience and, most commonly, the interaction with the individual’s personality style, and thus allow the depression to reach “disorder” status.

We have proposed [3] a “key and lock” model for consideration of some of the non-melancholic disorders, and particularly for “reactive” depressive disorders. The model assumes that individuals develop a specific vulnerability to depression during the developmental years as a consequence of salient stresses (e.g. parental abuse). When exposed to a “mirroring” life-event subsequently, the latter “key” may effectively open the pre-established “lock”. Two examples. A high-achieving medical student became suicidally depressed when a surgeon criticized her, with the latter authority figure activating earlier childhood feelings of worthlessness when her authoritarian father had criticized and ridiculed her. Secondly, a middle-aged woman developed a severe episode of depression when a man accidentally fell on her and caused physical injury. However, the event had a more important psychological impact in that it activated previously unremembered sexual abuse by her father – both by the physical contact and the psychological impact that she was powerless.

The impact of chronic stresses can be modeled somewhat differently. The Seligman [4] model of “learned helplessness” is apposite here. In the early experiment by Seligman, dogs would walk along a race to obtain food when a light went on. Subsequently, they would receive an electric shock if they went to get the food after the light was turned on. As a consequence, they assumed an immobilized position and, even when the shock was removed, would not go along the race to get their food when the light went on. Extrapolated to humans, the model argues that we tend to “give up, become unmotivated and feel depressed” when we feel that nothing we do will have any capacity to influence outcome. A clinical vignette might involve a woman in a dysfunctional marriage, having no money and a number of young children, with such factors preventing her from leaving her bullying husband, and having to deal with and be overwhelmed by a range of major oppressive social factors. Here, depression is often low-grade but persistent and gravid in light of this unrelenting component.

Turning to personality style, we also argue for the salience of a number of personality or temperament dimensions in terms of their capacity to influence the likelihood of developing non-melancholic depression. The commonest construct relates to high trait anxiety and here there can be two common expressions. One is an “anxious worrying” style where, when stressed or depressed, the individual tends to go quiet, keep to his or herself, withdraw and worry excessively about stresses, as they move into a depressed state. The second expression is one of irritability and where, a usually pleasant individual, describes that they are now being crabby and irritable towards people that they normally care for, and feeling somewhat guilty. These styles have a major impact in terms of increasing vulnerability to depression.

A third style is of shyness or behavioral inhibition and this can possibly be distinguished from another style that increases the risk to non-melancholic depression, personal reserve. Another personality style – of “interpersonal sensitivity rejection” – also increases the chance of depression, with the individual being prone to judge themselves negatively in social situations and quickly fall into a depression.

There are two other personality styles commonly associated with non-melancholic depression, although they do not necessarily increase the risk of depression onset or persistence. One personality style has been described as “hostile depression”, and usually involves an individual with a volatile, non-empathic Cluster B personality style, prone to “acting out” behaviors, being volatile and explosive, having a low threshold to stress and frequently developing depressive episodes, but usually of a transient nature. The short duration to their depressive episodes usually reflects the individual not being able to either internalize the depression or to tolerate it, so that they tend to express their frustration and rage on those around them, creating much collateral damage but also exsanguinating their anger and distress. The final personality style of salience involves those who have a distinctly obsessional or perfectionistic personality. As a consequence of this style, they are actually less likely to become depressed (because they expose themselves to fewer life-event stresses) and, if they do get depressed, are more likely to deny it and not want to seek help and, if they do seek help, tend to lack the flexibility that would assist in dealing with the precipitant stresses and bring the episode to an end.

Our articulated model then contrasts sharply with the unitary view of depression, in that it clearly imputes psychosocial stresses having quite differing roles in terms of differing expressions of depression. We view psychotic and melancholic depression as quintessential biological disorders, often genetically determined and with psychosocial stresses not having major etiological salience. This is not to deny that the biological process might be initially activated by a stressful event, but the stressful event is seen as doing little more than activating a biological diathesis. An analogy would be to the individual who has a severe motor vehicle accident and develops thyrotoxicosis or diabetes – here, the stressful event has increased the risk of onset of a disorder but the disorder, once initiated, becomes autonomous. There are some data [5] which have supported such a model for the more biological depressed states, showing that life-event stress appears to be more salient to first and early-onset episodes and less relevant for future episodes. Further, we accept

that many patients with psychotic and melancholic depression do report major life events, often as a consequence of their mood state – but also preceding depression onset. However, we do not necessarily see such stresses as causative. If causal, however, the severity of the stressful event is often disproportionate to the consequential depression. For example, one patient developed psychotic depression following the banging of a house door and another after thinking he had been picked up by a police radar. In both instances, the patients were perfectionistic and catastrophized the stimulus (e.g. “I am being burgled” and “I will be charged and may go to jail”) with severe delusional depressive states rapidly developing, being resistant to medication and with both patients requiring ECT.

Thus, in psychotic and melancholic depression we view psychosocial stressful events as either epiphenomena or, if linked, acting merely as activators or releasers of a cascading set of biological consequences and with the severity of depression then commonly seeming disproportionate to the stressor. Conversely, we see psychosocial life-event stresses as highly salient and largely explanatory in considering the etiology and onset of the non-melancholic disorders.

In the preceding sections, we have attempted to give some understanding as to how psychosocial stresses may variably initiate an episode of depression. We now review research studies considering how distal and proximal psychosocial environmental factors may increase the chance of depression. A predictable and immediate problem in reviewing the literature is that most studies fail to concede a subtyping model of depression. By homogenizing various expressions of depression and then examining the relevance of differing environmental risk factors, results risk being quite distorted. For instance, any study of depressed patients with a non-melancholic disorder might identify a social environmental factor as highly salient. An equivalent study undertaken in a group of individuals with a melancholic disorder might give a quite differing result. Thus, the literature is constrained by the very definition and modeling of depression. We now review representative literature.

2.2 Parenting

Consistently, quality of parenting (or perception of parents) during early childhood has been held to be a probable determinant of vulnerability to later psychopathology and to non-melancholic depression. Conclusions drawn by Bowlby [6] in his theory of “attachment” have led to further studies examining the relevance of parental loss and anomalous parenting. However, a review of studies on “loss” of parents did not find support for death or separation *per se* to be responsible for adult depression, with the consensus being that the relevant risk factor was the quality of parenting available to the child before and/or after the loss [7].

One empirical approach to measuring the impact of anomalous parenting in early childhood has been defining central parental attitudes and behaviors – and which have consistently identified two constructs, “care” (a dimension ranging from caring to indifference) and “overprotection” or “control” (a dimension ranging

from being over-protective and encouraging dependency to encouraging development of independence). A self-report questionnaire of perceived parenting (the Parental Bonding Instrument or PBI) [8], enables four parenting styles to be generated from the “care” and “control” dimensions: “optimal parenting” (high care, low control), “affectionate constraint” (high care, high control), “affectionless control” (low care, high control), and “neglectful parenting” (low care, low control). Studies using the PBI have generally found support for low “care” and high “control” to be reported by depressed patients.

Further support for the relevance of dysfunctional parenting to depression has been provided in studies that indicate specificity, with non-melancholic depressives being more likely than both matched controls and melancholic depressives to report parents as having been uncaring and over-protective [9]. This study also sought to examine whether there were additive effects of both parents rather than just considering them separately (i.e. a greater risk if both parents have an anomalous style). The highest risk was associated with the following combinations: maternal plus paternal “neglectful parenting” (odds ratio or OR = 26.6); paternal “neglectful parenting” plus maternal “affectionless control” (OR = 22.6); and paternal “affectionless control” plus any maternal quadrant other than “optimal parenting” (ORs of 6.1 to 15.4).

While parenting style examines a vulnerability that disposes to de-compensation by lowering the threshold to a wide range of triggering factors, another theoretical approach is that the vulnerability may be more selective to triggers that have specific salience. An empirical examination of a “lock and key” hypothesis (postulating that early adverse experiences establish locks that are activated by keys mirroring the earlier adverse experience to induce depression) has been conducted to test the theory [3]. Qualitative analyses identified 13 categories of “locks” and 17 “keys”. Quantitative analyses identified significant associations between these “locks” and “keys” (e.g. “over-controlled” (lock) with “over-controlled” (key) $r = 0.42$; “not emotionally supported” (lock) with “lack of support in times of distress” (key) $r = 0.43$; “emotional/verbal abuse” (lock) with “emotional/verbal abuse” (key) $r = 0.40$; “leaving child alone” (lock) with “abandoned” (key) $r = 0.48$; “leaving child alone” (lock) with “deserted” (key) $r = 0.36$; “criticism” (lock) with “criticism” (key) $r = 0.34$; “leaving child alone” (lock) with “rejected” (key) $r = 0.37$; “criticism” (lock) with “emotionally/verbally abused” (key) $r = 0.43$).

2.3 Ordinal Position

Results of studies examining the effect of birth order on mental health are confusing and contradictory, suggesting that the relationship is more complex with other mediating factors making a contribution. Adler [10] has postulated that the second-born child is in a superior position to the first-born – who never recovers from the trauma of being dethroned. Various studies would appear to support this view. For example, adolescents who were only children being found to be the most mal-

adjusted on the Bell Adjustment Inventory and fourth- and fifth-born the best adjusted [11]. However, other studies have not been able to find any differences between birth order and anxiety, immaturity or psychosis [12], while, in a representative study, no relationship was found between birth order and depression among college students [13].

Among other studies which do not support Adler's notion, first-born children have been found to score significantly lower on depression than second-, third-fourth-born and youngest children [14]. As a group, the first-born tended to be healthier, less depressed and score higher on self-esteem. Reconciling these results with Adler, these findings may be attributed to a strong positive influence of the exclusive and generous attention the first-born received before the birth of a sibling that more than compensated for the pain of dethronement [14]. In addition, while not saying anything directly about mental health, there is a general consensus that higher birth rank favors higher attainment and higher occupational status [15], with first-borns being more achieving and conscientious and later-borns more rebellious, liberal and agreeable [16]. More maladaptive perfectionists have been found among middle-birth order and non-perfectionists to be more likely among the youngest child [17].

Other factors need to be taken into account when interpreting results of studies on mental health, such as whether the sample is a clinical or healthy sample, and other family variables. For example, a study comparing siblings of well or chronically ill children found that, while all siblings of ill adolescents were at risk for depression, among well siblings, only the older sister was most vulnerable [18]. However, this was a minority sample with members living with one biological parent, so there would be a high probability that the older sister would carry the responsibility of being a surrogate mother to her siblings while her own needs were neglected, so for the older sister of well siblings there may have been a feeling of burden, deprivation and resentment.

2.4

Impact of Siblings

While the quality of attachment to parents has been acknowledged as influential in risk of later depression, the extension of attachment to siblings has also been found to have an impact on mental well-being, with depressed children tending to have less warm relationships with both mother and siblings [19]. Numerous studies have confirmed that closeness with siblings is inversely related to depression [20] and perception of a positive sibling relationship (high support/low negativity) is associated with low levels of anxiety and depression [21]. Adolescent studies have demonstrated that perception of positive sibling relationship provides a buffer effect for later adolescent development problems, with higher self-esteem, more friendships, less loneliness and depression [22]. This effect has been found to be bi-directional, with the higher self-esteem resulting in more positive sibling relationship. Conversely, childhood conflict, aggression and violence among siblings have

been found associated with depression [23], with implications for the benefits of family therapy that also involves siblings of depressed adolescents [24].

An important area of research has revealed that well siblings of children with chronic illness are at increased risk of depression, as they are often overlooked [18]. Well siblings may experience adjustment difficulties (depression, anxiety, guilt, social isolation) due to separation from an attachment figure as the mother is busy caring for a chronically sick child, coping with household disruption, less attentive, and worrying about the sick sibling [25, 26]. Siblings of previously hospitalized adolescents have reported more psychological distress, poorer social relationships, a more negative view of the hospitalized sibling and also appear to identify less with them [27].

The contribution of sibling relationships to adjustment early in life continues into old age, with those who interact more frequently with siblings having a greater sense of well-being and maintaining a greater sense of control in their life [28]. Preserving bonds becomes more important as they grow older, with siblings becoming closer as they age and attempting to mend rivalries and estrangements [28]. Having the availability of a sister was related to greater life satisfaction, whereas disruption of the attachment bond to sisters through conflict/indifference increased the risk of depression [29]. However, brothers had no relevance to well-being, probably because traditionally women are seen as the caregivers so there is the expectation that a sister will continue to fill that role [30]. This influence of tradition has been further highlighted by China's one-child policy, where children with siblings now report higher levels of fear, anxiety and depression [31] and there is increased anxiety, aggression and depression in students with siblings, competing for higher education and reduced benefits from society [32].

2.5 Bullying

Bullying by peers at school is regarded as being not just a distressing experience, but also having a detrimental impact on mental well-being, although some results are contradictory. A meta-analysis of cross-sectional studies examining relationships between bullying and psychosocial maladjustment of victims found a stronger association with depression than with anxiety, loneliness and general self-esteem [33]. In a prospective study, support has been found for a history of victimization being a strong predictor of onset of symptoms of anxiety or depression (more clearly for girls) [34], but the hypothesis that poor emotional health in some way invites victimization [35] was not supported.

Studies on both bullying and victimization variably describe bullies as aggressive and dominant [36], and using "externalizing" (characterized by dysregulated behaviors such as substance abuse and behavioral problems) or other aggressive behaviors to mask anxiety and insecurity. Victims, on the other hand, are characterized mainly by being introverted, passive and submissive, with low self-esteem, are sensitive and tend to blame themselves for difficulties [37, 38], "internalize"

emotional difficulties (characterized by disordered mood) and perhaps signal in some way that they will not retaliate if attacked [36].

Of particular interest was a study [39] in which not only bullies and victims were examined, but also bully–victims (involved in roles of both bully and victim) who have been suggested to differ from both bullies and victims in their personality and family relationships. They were more likely than victims or bullies to perceive their parents as lacking warmth and effecting inconsistent discipline practices (i.e. both overprotection and neglect), while bullies come from a home where parents were hostile and directive, lacked warmth, and provided inadequate monitoring and inconsistent discipline. For victims, however, there is a tendency for parental over-involvement [40]. Bully–victims tended to be more ambivalent about themselves, have lower levels of social acceptance and score higher on Eysenck’s neuroticism and psychoticism, tended to be more like bullies than victims [38] and differed particularly from victims in being provocative and starting fights [40].

The traditional dichotomy of child and adolescent mental disorders to internalizing and externalizing disorders is challenged, since depression, anxiety, psychosomatic symptoms and eating disorders have been found to be equally common among bullies and victims, and most common among bully–victims [39]. However, that study did identify a difference between bullies and victims, with the former more likely to engage in alcohol and drug abuse and also to be more likely to have multiple mental health problems, which supports the view that bullies may also exhibit internalizing disorders associated with insecurity. Bully–victims would appear to be the group at particular vulnerability for both internalizing and externalizing disorders, co-occurring disorders, and more contradictory and disturbed personalities, suggesting a need for further study to understand the risks for mental disorders and interventions to assist in training adolescents in more constructive interpersonal peer interactions.

2.6

Sexual Abuse

Studies on clinical samples have indicated associations between psychological and emotional problems in adulthood and a history of childhood sexual abuse (CSA) [41]. While a history of CSA may be reported among depressed patients, there is usually also an association with a dysfunctional childhood environment such as maternal indifference or parental conflict, so it has remained unclear whether CSA is an independent risk factor for depression. A study of depressed women seeking to clarify this point found that it was unlikely that depression was a direct consequence of CSA, although CSA was associated with a greater chance of early-onset depression, deliberate self-harm (DSH), borderline personality and suicide attempts [42]. The study also confirmed that, for depressed women with a history of CSA, there was a greater incidence of detrimental parental environment such as parental neglect or having an alcoholic father, compared with depressed women lacking a history of CSA. Support was found for earlier findings that children raised

in such an environment are vulnerable to sexual abuse by perpetrators outside the family, with sex offenders actually targeting children in families with problems [43].

In a second study [44] involving a different sample of depressed women, path analysis identified child physical abuse (CPA) by parents to be a key factor in vulnerability to CSA, with parental conflict and domestic violence being associated with both CPA and CSA. Emotional abuse and neglect, although found to not be directly predictive of CSA, were indirectly associated via a link with CPA. This study also confirmed higher rates of DSH among women with a history of CSA, and when abused women who self-harmed were compared with those who did not self-harm, results supported earlier findings that those who had reported more physical abuse from parents and more parental conflict, became depressed at a younger age, and were more likely to abuse drugs and alcohol [45]. Examining the question of re-victimization as adults confirmed no direct links with CSA, but appears to be largely dependent on the additional experience of CPA [46]. Other factors that may increase the likelihood of depression for victims of CSA may be the age of the child, severity of the abuse, connection to the perpetrator (i.e. trust violation), and family reaction to disclosure that may result in lack of validation and self-blame for the abuse [47].

2.7

Social Deprivation

There is a consensus that availability of social support has a main effect on improved mental health, while deprivation in social support increases the risk of depression. A buffering hypothesis argues that the benefit of social support is only apparent when the individual is exposed to stressful life-events [48], although support for this model has been inconsistent due to methodological approaches. A modified model, a stress-resource matching model, suggests that buffering occurs only when there is a match between needs elicited by the stressful event and functions of support (e.g. emotional, appraisal, instrumental, informational) perceived to be available [49, 50]. For example, instrumental support from co-workers relieves high levels of stress in the workplace, and emotionally supportive communications from family are beneficial to a woman with multiple demands of family and work roles [51].

The mediating mechanism of effect of emotional support on well-being has been demonstrated to be via self-mastery. Various studies have found that enhancement of sense of control or self-efficacy in specific domains may contribute to the overall sense of well-being [52]. Domain-specific self-efficacy is most likely to occur when support is provided by an individual who is most able to appreciate the recipient capabilities and performance in that domain (i.e. a role partner) [53], hence support in the workplace from a supervisor is of greater benefit than that from fellow workers [54]. A study [55] of women engaged in juggling demands of four roles (i.e. wife, mother, employee and caring for an aged parent) provided evidence that com-

plemented previous studies. Emotional support from husband, children, or work supervisor led to self-mastery and improved well-being, but while support from parents led to self-mastery, there was no positive effect on well-being, probably due to the stress of caring for an elderly parent outweighing the benefits of their support.

Other variables that influence the stress–resource match are the differences between expected and actual support, perceived and actual support, and also personality. For example, women who thought they had good social support, but, when needing to access that support in a crisis, found it to be less than adequate, were at particular risk of depression [56]. An explanation has been offered that depression effects perception of social support, rather than support exerting an effect on depression (i.e. it is the depression that diminishes their ability to perceive support as satisfactory). Perhaps in a similar vein, individuals who perceived their support to be low were actually benefiting from the unacknowledged “invisible” support they received.

Individuals with a ruminative personality style have been found to experience more prolonged depressive and anxiety reactions to trauma, access social support more and benefit more from that support than non-ruminators, but their perception was that they were receiving less support, primarily because they continued to make demands on their social support beyond the socially-accepted time limit rather than “getting over it” and “moving on” [57].

On the other hand, individuals with a strong internal locus of control may resent unwanted instrumental support, feeling constrained and overprotected, resulting in increased depression symptomatology [58], although people with an external locus of control may benefit from high levels of functional support. Underestimating the patient’s ability [59] by providing too much functional support can erode self-confidence and sense of competence [60], foster dependency, reinforce inactivity, and also undermine motivation to engage in self-care behaviors that promote health [61, 62]. However, women with a strong internal locus of control who are in need of care do not appear to resent functional support from a spouse, presumably because of the interdependent nature of the marital relationship, whereas they may feel hostile and their independence threatened by the same type of support from non-marital caregivers such as their adult children [63].

Associated with aging is a greater need for support, and to compensate for loss of sense of control, the elderly tend to downgrade the importance of domains such as physical health and personal independence [64]. The key conclusion from the research is of the importance of matching the type and level of support to the recipient’s needs if support is to enhance mental well-being, without taking away the sense of personal control.

2.8 Social Class

It is generally accepted that low socioeconomic status is associated with high psychiatric morbidity across a range of age groups (i.e. adults, adolescents, and the

elderly) with socioeconomic impact on adult depression being predictable even in childhood.

A longitudinal study from birth confirmed that participants with parents of low socioeconomic status experienced a two-fold increase in adult depression, independent of their own socioeconomic status [65], and a study assessing joint effects of socioeconomic status and birth risks found that low socioeconomic status mitigated effects of birth problems on adult depression [66]. Adolescent studies have found parental socioeconomic status to be associated with adolescent depression, which in turn is predictive of adult depression. A study confirming an association between socioeconomic status and depression identified low parental income as being associated with suicidality, postulating that lower household income may acutely affect adolescent mood, social integration and self-esteem, while chronic measures of socioeconomic status such as parental education may cause affective changes but not increase suicide risk [67].

A meta-analysis of 60 longitudinal studies of community samples concluded that low socioeconomic status was associated with higher odds of being depressed ($OR = 1.81$) and higher odds of persistent depression ($OR = 2.06$) [68]. Poverty and unemployment have been found to be associated with maintenance but not onset of depression, and financial strain at baseline was independently associated with both onset and maintenance [69], while low socioeconomic status provided an increased risk of depression for older individuals [70].

For the same level of depression severity, those in lower socioeconomic groups faced more disabilities [71] and a poorer prognosis [69], with these differences being seen to be due to poorer coping styles, ongoing life-events, stress exposure and weaker social support, suggesting support for the argument that the social system tends to confer social and psychological resources on some of its members while exposing these same members to fewer potentially harmful experiences [72].

Stress and strain theories of the association between socioeconomic status and depression argue that risk is mediated via personal resources such as coping style, self-esteem, mastery and locus of control, with those of high socioeconomic status being better endowed with these resources, on the one hand, or mediated by external community factors. An attributional model posits the mediating variable to be fatalism, whereby low socioeconomic status, either in childhood or adult life, will socialize individuals to be more fatalistic in their causal perceptions (i.e. to emphasize environmental rather than personal causation of behavior) and that fatalism will increase vulnerability to depression because it undermines persistence and effort in coping situations [73]. The converse of fatalism is instrumentalism (i.e. belief in internal causes) which is not always adaptive, since there may be events truly outside the control of the individual. However, a major problem with always making external attributions is that the individual is unlikely to ever make an effort. Hence, there would be an adaptive benefit in encouraging flexibility of making attributions.

2.9

Employment

While job satisfaction can enhance mental well-being, the workplace can also be a source of stress and depression, particularly where there is high demand and little control or other dissatisfactions with a job. However, the consequences of unemployment probably have far greater negative impact on mental health because of the economic hardship to the unemployed and their families, with depression due to long-term unemployment hindering job seeking and re-employment prospects, exacerbated by loss of confidence and perceived loss of skills. Depression due to economic strain can be alleviated by generous unemployment benefits, but the downside is that this also serves to discourage job seeking, leading to “self-selected” long-term employment [74].

Sources of stress in unemployment are mainly seen as psychological (i.e. coping style and control beliefs). Degree of distress after involuntary unemployment can be determined by attribution about the job loss, with those who have an internal locus of control being less vulnerable to depression [75], and also more likely to successfully engage in active job seeking [76]. However, long-term unemployment has been found to decrease internal locus of control [77]. Re-employment projects have found the negative effect of unemployment can be reversed restoring previous levels of mental health. Interventions aimed at fostering a sense of mastery in re-employment programs have resulted in decreased depression and increased motivation for job seeking with benefits maintained when followed up 2 years later [78].

While an active or solution-focused coping style is generally viewed as being better for mental-health outcomes, social factors in the real world can also come into play so that when the situation is controllable, action solutions are best, but when the situation is truly uncontrollable, then emotion-focused coping may be better for mental health [79]. In a study of involuntary unemployment, when General Motors plants closed down, what was found to be more relevant than coping style *per se* was whether the unemployed received what they wanted (i.e. found a job if they want one, did not look for a job if they did not want one, or lost a job they did not like) [79] which does in a way support the hypothesis of the importance of a sense of mastery to mental health.

2.10

Marital Factors

While in general, less depression is reported by married individuals, those in a poor marriage with deficient intimacy are at increased risk [80], with marital dissatisfaction pre-dating depression (and therefore possibly causal) [81] and endorsement of marital dissatisfaction as being a causal factor in depression [82]. Global measures of intimacy or social support have been problematic, but the Intimate Bond Measure (IBM), a measure consisting of “care” and “control” scales

which captures care expressed emotionally and physically, has been shown to assess “perceived” as well as “actual” levels of care [83].

Marital dissatisfaction is not only a risk factor for depression, but has also been found to be a predictor of poor participation in and expectation of therapy [82], poor outcome [84], relapse after hospitalization [85], and increased severity at follow-up, regardless of type of treatment [86]. There appears to be a specificity of significance of deficient intimate care to non-melancholic depressives who are more likely than melancholic depressives to report depression due to partnership-related events. This vulnerability is hypothesized to have its antecedents in childhood from deficient parental care [87] or childhood abuse or neglect [88].

However, in the other direction, having a depressed spouse can also contribute to marital dissatisfaction, separation and divorce [89], while both depression and marital satisfaction have been hypothesized to be determined by quality of interpersonal interactions [90]. In acknowledging the close association between marital satisfaction and depression, a promising solution for treating depressed individuals in unhappy marital situations is conjoint marital therapy, either as a primary or maintenance treatment, and a review of several such studies have revealed this approach to be effective [91].

2.11

Retirement

Inconsistent results on the effect of retirement variably conclude that retirement is beneficial to mental health, detrimental or has no effect at all. Inconsistencies can be due to longitudinal studies and comparisons between cohorts in cross-sectional studies being confounded by effects of aging, or measures used for assessing depression symptomatology. For example, there is a tendency for less reporting of dysphoric mood and greater experience of somatization among older people, so focusing on dysphoria alone would conclude that there is less depression, while inclusion of somatic symptoms would indicate higher levels [92].

Support has been found for theories based on the significance of the job as an indicator of adjustment in retirement. If individuals positively identify with their work, they may be vulnerable to feelings of role loss, whereas retirement from a stressful job may bring relief and enhanced mental well-being. However, what does consistently emerge is the importance of a sense of personal control (e.g. whether continuing to work or retiring is a personal choice) [93]. Consensus about factors relevant to retirement adjustment are economic resources (reduced income), personal resources (pre-retirement psychological well-being, health, active coping, locus of control) and social-related resources [94]. Studies comparing retired, still working and people in transition to retirement [95], and a cross-sequential format [96] conducted over 8 years comparing six age-cohorts (age range from 54 to 77 years), supported the view that transition into retirement improves morale, but after a few years in retirement, depression increases.

Couples retiring at different times brings in an added dimension, with retired men whose wives are still working being likely to be the least depressed while working men whose wives have retired are likely to be the most depressed [95]. Among couples, gender differences reveal that finance issues in retirement are more important to men than to women, while the quality of the marital relationship is more important to women than to men.

With aging, depression may be associated with life events such as serious illness, widowhood, going into nursing home, death/illness of close friend, loss of meaning in life derived from personal goals and actions, loss of active resources (health, residual life time, money, cognitive functioning, social support) [97]. Age-related depression may be mediated by reduced openness, concreteness, controllability of future time perspectives, associated feelings of obsolescence [96] and expectation of death [98]. However, goal adjustment, positive reappraisal and transcendental meaning resources can offset loss of action resources [99]. Although a trend has been found for increased depression over the age of 75 years, the change found across the six cohorts over 8 years was only a small effect, which was regarded by the authors as indicating the large potential of reserve capacity and resilience in older people to accommodate age-related losses [96].

2.12

Conclusions

We initially suggested that psychosocial and environmental factors may have quite differing relevance to differing expressions of depression. Regrettably, as most of the published literature “homogenizes” depression, it remains unestablished whether social factors have specific relevance only to certain expressions of depression. We argue the need for such specificity effects to be conceded in research, to avoid the current risk of having literature reviews and conclusions based on generalizations.

References

- 1 PARKER, G., Classifying depression: should paradigms lost be regained? *Am. J. Psychiatry* **2000**, *157*, 1195–1203.
- 2 AKISKAL, H. S., MCKINNEY, W. T. JR., Depressive disorders: toward a unified hypothesis. *Science*. **1973**, *182*, 20–29.
- 3 PARKER, G., GLADSTONE, G., ROUSSOS, J., WILHELM, K., MITCHELL, P., HADZI-PAVLOVIC, D., AUSTIN, M.-P., HICKIE, I., Qualitative and quantitative analyses of a “lock and key” hypothesis of depression. *Psychol. Med.* **1998**, *28*, 1263–1273.
- 4 SELIGMAN, M. E., Learned helplessness as a model of depression. Comment and integration. *J. Abnorm. Psychol.* **1978**, *87*, 165–179.
- 5 BROWN, G. W., HARRIS, T. O., HEPWORTHY, C., Life events and endogenous depression: a puzzle re-examined. *Arch. Gen. Psychiatry* **1994**, *51*, 525–534.
- 6 BOWLBY, J., The making and breaking of affectional bonds. *Br. J. Psychiatry* **1977**, *130*, 201–210.

- 7 PARKER, G., Early environment. In *Handbook of Affective Disorders*, PAYKEL, EUGENE S. (Ed.). Churchill Livingstone, London, 1992.
- 8 PARKER, G., TUPLING, H., BROWN, L. B., A parental bonding instrument. *Br. J. Med. Psychol.* 1979, 52, 1–10.
- 9 PARKER, G., HADZI-PAVLOVIC, D., Parental representations of melancholic and non-melancholic depressives: examining for specificity to depressive type and for evidence of additive effects. *Psychol. Med.* 1992, 22, 657–665.
- 10 ANSBACHER, M., L., ANSBACHER, R., *The Individual Psychology of Alfred Adler*. Basic Books, New York, 1956.
- 11 DOSS, S., A study of maladjustment in relation to birth order. *J. Psychol. Res.* 1980, 24, 156–159.
- 12 TOULIATOS, J., LIDHOLM, B. W., Birth order, family size and children's mental health. *Psychol. Reports* 1980, 463, 1097–1098.
- 13 LESTER, D., CAFFERY, D., Birth order, depression and suicide. *Psychol. Reports* 1989, 64, 18.
- 14 GATES, L., LINEBERGER, M. R., CROCKETT, J., HUBBARD, J., Birth order and its relationship to depression, anxiety, and self-concept test scores in children. *J. Gen. Psychol.* 1988, 149, 29–34.
- 15 HERRERA, N. C., ZAJONC, R. B., WIECZORKOWSKA, G., CICHOMSKI, B., Beliefs about birth rank and their reflection in reality. *J. Pers. Soc. Psychol.* 2003, 85, 142–150.
- 16 PAULHUS, D. L., TRAPNELL, P. D., CHEN, D., Birth order effects on personality and achievement within families. *Psychol. Science* 1999, 10, 482–488.
- 17 ASHBY, J. S., LOCICERO, K. A., KENNY, M. C., The relationship between multidimensional perfectionism to psychological birth order. *J. Ind. Psychol.* 2003, 59, 42–51.
- 18 FROHLONGER, M. J., Psychological adjustment of siblings of chronically ill adolescents. *Dis. Abs. Int. Sect. B: Sc. Eng.* 1996, 57 (3-B), 2174.
- 19 WEAVER-GRAHAM, W., Dyadic relationships within the families of prepubertal depressed children, children at high risk for depression and normal children. *Dis. Abs. Int. Sect. B: Sc. Eng.* 1999, 60 (2-B), 0860.
- 20 PALSZNY, M., SELZER, M. L., VINOKUR, A., LEWANDOWSKI, L., Twin relationships and depression. *Am. J. Psychiatry* 1977, 134, 988–990.
- 21 MASSEY, C. J., Parent and sibling relationship influences on late adolescent social anxiety and other adjustment outcomes. *Dis. Abs. Int. Sect. B. Sc. Eng.* 2001, 62 (2-B), 1116.
- 22 YEH, H.-C., The influences of sibling relationships in adolescence. *Dis. Abs. Int. Sect. B: Sc. Eng.* 2001, 62 (2-A), 794.
- 23 SCHREPFERMAN, L. M., The validity of retrospective reports of childhood experiences: factors affecting accuracy of the recall of sibling relationships. *Dis. Abs. Int. Sect. B. Sc. Eng.* 2002, 62 (9-B), 4236.
- 24 DAVIS, C. W., Adolescent depression and the effect of sibling relationships. *Dis. Abs. Int. Sect. B: Sc. Eng.* 2000, 61 (2-B), 1076.
- 25 MURRAY, J. S., Attachment theory and adjustment difficulties in siblings of children with cancer. *Issues Ment. Health Nurs.* 2000, 21, 149–169.
- 26 SHARPE, D., ROSSITER, L., Siblings of children with a chronic illness: a meta-analysis. *J. Ped. Psychol.* 2002, 27, 699–710.
- 27 DEAL, S. N., MACLEAN, W. E. JR., Disrupted lives: siblings of disturbed adolescents. *Am. J. Orthopsych.* 1995, 65, 274–281.
- 28 CICERELLI, V. G., Relationships of family background variables to locus of control in the elderly. *J. Gerontol.* 1980, 35, 108–114.
- 29 CICERELLI, V. G., Feelings of attachment to siblings and well-being in later life. *Psychol. Aging* 1989, 4, 211–216.
- 30 MCGHEE, J. L., The effects of siblings on the life satisfaction of the rural elderly. *J. Mar. Fam.* 1985, 47, 85–91.
- 31 YANG, B., OLLENDICK, T. H., DONG, Q., XIA, Y., Only children and children with siblings in the People's Republic of China: levels of fear, anxiety and depression. *Child Dev.* 1995, 66, 1301–1311.
- 32 WANG, W., DU, W., LIU, P., LIU, J., WANG, Y., Five-factor personality measures in Chinese university students: effects of one-child policy? *Psychiatry Res.* 2002, 109, 37–44.

- 33 HAWKER, D. S. J., BOULTON, M. J., Twenty years' research on peer victimisation and psychosocial maladjustment: a meta-analytic review of cross-sectional studies. *J. Child Psychol. Psychiatry* **2000**, *41*, 441–455.
- 34 BOND, L., CARLIN, J. B., THOMAS, L., RUBIN, K., PATTON, G., Does bullying cause emotional problems? A prospective study of young teenagers. *Br. Med. J.* **2001**, *323*, 480–484.
- 35 HODGES, E. V. E., PERRY, D. G., Personal and interpersonal antecedents and consequences of victimisation by peers. *J. Pers. Soc. Psychol.* **1999**, *76*, 677–685.
- 36 OLWEUS, D., Annotation: Bullying at school: Basic facts and effects of a school based intervention program. *J. Child Psychol. Psychiatry Allied Discipl.* **1994**, *35*, 1171–1190.
- 37 BOULTON, M. J., SMITH, P. K., Bully/victim problems among middle school children. *Br. J. Dev. Psychol.* **12**, *315*, 315–329.
- 38 MYNARD, H., JOSEPH, S., Bully/victim problems and their association with Eysenck's personality dimensions in 8- to 13-year-olds. *Br. J. Educ. Psychol.* **1997**, *95*, 1255–1263.
- 39 KALTIALA-HEINO, R., RIMPELA, M., RANTANEN, P., RIMPELA, A., Bullying at school – an indicator of adolescents at risk for mental disorders. *J. Adol.* **2000**, *23*, 661–674.
- 40 BOWERS, M. J., SMITH, P. K., BINNEY, V., Coercion and power in families of children involved in bully/victim problems at school. *J. Fam. Ther.* **1992**, *62*, 73–87.
- 41 MULLEN, P. E., MARTIN, J. L., ANDERSON, J. C., ROMANS, S. E., HERBISON, G. P., Childhood sexual abuse and mental health in adult life. *Br. J. Psychiatry* **1993**, *163*, 721–732.
- 42 GLADSTONE, G., PARKER, G., WILHELM, K., MITCHELL, P., AUSTIN, M.-P., Characteristics of depressed patients who report childhood sexual abuse. *Am. J. Psychiatry* **1999**, *156*, 431–437.
- 43 ELLIOT, M., BROWNE, K., KILCOYNE, J., Child sexual abuse prevention: what offenders tell us. *Child Abuse Negl.* **1995**, *19*, 579–594.
- 44 GLADSTONE, G. L., PARKER, G., MITCHELL, P., MALHI, G., WILHELM, K., AUSTIN, M.-P., Implications of childhood trauma and its implications for depressed women: an analysis of pathways from childhood sexual abuse to deliberate self-harm and re-victimization. *Am. J. Psychiatry* **2004**, *161*, 1417–1425.
- 45 ROMANS, S. E., MARTIN, J. L., ANDERSON, J. C., HERBISON, G. P., MULLEN, P. E., Sexual abuse in childhood and deliberate self-harm. *Am. J. Psychiatry* **1995**, *152*, 1336–1342.
- 46 WIND, T. W., SILVERN, L., Parenting and family stress as mediators of long-term effects of child abuse. *Child Abuse Negl.* **1994**, *18*, 439–453.
- 47 LANGE, A., DE BEURS, E., DOLAN, C., LACHNIT, T., SJOELLEMA, S., HANEWALD, G., Long-term effects of childhood sexual abuse: Objective and subjective characteristics of the abuse and psychopathology in later life. *J. Nerv. Ment. Dis.* **1999**, *187*, 159–158.
- 48 MCNEIL, K., NEWMAN, I., KELLY, F. J., *Testing Research Hypotheses with the General Linear Model*. Southern Illinois University Press, Carbondale, **1996**.
- 49 COHEN, S., Stress, social support and disorder. In *The Meaning and Measurement of Social Support*, VEIEL, O. F., BAUMANN, U. (Eds.), Hemisphere Publishing Corporation, New York, **1992**.
- 50 PENNINX, B. W. J. H., VAN TILBURG, T., BOEKE, A. J. P., DEEG, D. J. H., KRIEGSMAN, D. M. W., VAN EIJK, J. T. M., Effects of social support and personal coping resources on depressive symptoms: different for various chronic diseases? *Health Psychol.* **1998**, *17*, 551–558.
- 51 GREENGLASS, E. R., Social support and coping of employed women. In *Women, Work and Coping: A Multidimensional Approach to Workplace Stress*, LONG, B. C., KAHN, S. E. (Eds.). McGill-Queen's University Press, Montreal, Canada, **1993**.
- 52 KRAUSE, N., BORAWSKI-CLARK, E., Clarifying the functions of social support in later life. *Res. Aging* **1994**, *16*, 251–279.
- 53 BANDURA, A., Self-efficacy: toward a unified theory of behavioral change. *Psychol. Rev.* **1997**, *84*, 191–215.
- 54 TERRY, D. J., NIELSEN, M., PERCHARD, L., Effects of work stress on psychological well-being and job satisfaction: the stress-

- buffering role of social support. *Aust. J. Psychol.* **1993**, 45, 168–175.
- 55 MARTIRE, L. M., STEPHENS, M. A. P., TOWNSEND, A. L., Emotional support and well-being of midlife women: role-specific mastery as a mediational mechanism. *Psychol. Aging* **1998**, 13, 396–404.
 - 56 BROWN, G. W., ANDREWS, B., HARRIS, T., ADLER, Z., BRIDGE, L., Social support, self-esteem and depression. *Psychol. Med.* **1986**, 16, 813–831.
 - 57 NOLEN-HOEKSEMA, S., DAVIS, C. G., “Thanks for sharing that”: ruminators and their social support networks. *J. Pers. Soc. Psychol.* **1999**, 77, 801–414.
 - 58 NEWSOM, J. T., SCHULZ, R., Caregiving from the recipient’s perspective: negative reactions to being helped. *Health Psychol.* **1998**, 17, 172–181.
 - 59 CLARK, S. L., STEPHENS, M. A. P., Stroke patients’ well-being as a function of caregiving spouse’ helpful and unhelpful actions. *Pers. Relat.* **1996**, 3, 171–184.
 - 60 SEEMAN, T. E., BRUCE, M. L., McAVAY, G. J., Social network characteristics and onset of ADL disability: MacArthur studies of successful aging. *J. Gerontol: Soc. Sc.* **1996**, 51, S191–S200.
 - 61 COYNE, J. C., SMITH, D. A., Couples coping with myocardial infarction: a contextual perspective on wives’ distress. *J. Pers. Soc. Psychol.* **1991**, 61, 404–412.
 - 62 ROMANO, J. M., TURNER, J. A., FRIEDMAN, L. S., BULCROFT, R. A., JENSEN, M. P., HOPS, H., WRIGHT, S. F., Sequential analysis of chronic pain behaviors and spouse responses. *J. Consult. Clin. Psychol.* **1992**, 60, 777–782.
 - 63 MARTIRE, L. M., STEPHENS, M. A. P., DRULEY, J. A., WOJNO, W. C., Negative reactions to received spousal care: predictors and consequences of miscarried support. *Health Psychol.* **2002**, 21, 167–176.
 - 64 BRANDSTADTER, J., ROTHERMUND, K., Self-percepts of control of in middle and later adulthood: buffering losses by rescaling goals. *Psychol. Aging* **1994**, 9, 265–273.
 - 65 GILMAN, S. E., KAWACHI, I., FITZMAURICE, G. M., BUKA, S. L., Socioeconomic status in childhood and the lifetime risk of major depression. *Int. J. Epidemiol.* **2002**, 3, 359–367.
 - 66 FAN, A. P., EATON, W. W., Longitudinal study assessing the joint effects of socioeconomic status and birth risks on adult emotional and nervous conditions. *Br. J. Psychiatry* **2001**, 178, 78–83.
 - 67 GOODMAN, E., The role of socioeconomic status gradients in explaining differences in US adolescents’ health. *Am. J. Pub. Health* **1999**, 89, 1522–1528.
 - 68 LORANT, V., DELIEGE, D., EATON, W., ROBERT, A., PHILIPPOT, P., ANSSEAU, M., Socioeconomic inequalities in depression: a meta-analysis. *Am. J. Epidemiol.* **2003**, 157, 98–112.
 - 69 WEICH, S., LEWIS, G., Poverty, unemployment, and common mental disorders: a population based cohort study. *Br. Med. J.* **1998**, 317, 115–119.
 - 70 RIOS, D. A., ABDULAH, D. R., WEI, J. Y., HAUSDORFF, J. M., Disparate effects of socioeconomic status on physical function and emotional well-being in older adults. *Aging-Clin. Exp. Res.* **2001**, 13, 30–37.
 - 71 BEBBINGTON, P., BRUGHA, T., MELTZER, H., FARRELL, M., CERESA, C., JENKINS, R., LEWIS, G., Psychiatric disorder and dysfunction in the UK National Survey of Psychiatric Morbidity. *Soc. Psychiatr. Epidemiol.* **2000**, 35, 191–197.
 - 72 TURNER, R. J., LLOYD, D. A., The stress process and the social distribution of depression. *J. Health Soc. Behav.* **1999**, 40, 374–404.
 - 73 WHEATON, B., The sociogenesis of psychological disorder: an attributional theory. *J. Health Soc. Behav.* **1980**, 21, 100–124.
 - 74 STRANDH, M., State intervention and mental well-being among unemployed. *J. Soc. Policy.* **2001**, 30, 57–80.
 - 75 FEATHER, N. T., DAVENPORT, P. R., Unemployment and depressive affect: a motivational and attributional analysis. *J. Pers. Soc. Psychol.* **1981**, 41, 422–436.
 - 76 HOLMES, B. H., WERBEL, J. D., Finding work following job loss: the role of coping resources. *J. Employ. Couns.* **1992**, 29, 22–29.
 - 77 FRESE, M., MOHR, G., Prolonged unemployment and depression in older workers: a longitudinal study of intervening variables. *Soc. Sc. Med.* **1987**, 25, 173–178.

- 78 VINOKUR, A. D., SCHUL, Y., VUORI, J., PRICE, R. H., Two years after job loss: long-term impact of the JOBS Program on Reemployment and mental health. *J. Occup. Health Psychol.* **2000**, 5, 32–47.
- 79 HAMILTON, V. L., HOFFMAN, W. S., BROMAN, C. L., RAUMA, D., Unemployment, distress and coping: a panel study of autoworkers. *J. Pers. Soc. Psychol.* **1993**, 65, 234–247.
- 80 WEISSMAN, M. M., Advances in psychiatric epidemiology: rates and risks for major depression. *Am. J. Pub. Health* **1987**, 77, 445–451.
- 81 WHISMAN, M. A., BRUCE, M. L., Marital dissatisfaction and incidence of major depressive episode in a community sample. *J. Abnorm. Psychol.* **1999**, 108, 674–678.
- 82 ADDIS, M. E., JACOBSON, N. S., Reasons for depression and the process and outcome of cognitive-behavioural psychotherapies. *J. Consult. Clin. Psychol.* **1996**, 64, 1417–1424.
- 83 WILHELM, K., PARKER, G., The development of a measure of intimate bonds. *Psych. Med.* **1988**, 18, 225–234.
- 84 BROMBERGER, J. T., WISNER, K. L., HANUSA, B. H., Marital support and remission of treated depression: a prospective pilot study of mothers of infants and toddlers. *J. Nerv. Ment. Dis.* **1994**, 182, 40–44.
- 85 HOOLEY, J. M., TEASDALE, J. D., Predictors of relapse in unipolar depressives: Expressed emotion, marital distress and perceived criticism. *J. Abnorm. Psychol.* **1989**, 98, 229–235.
- 86 WHISMAN, M. A., Marital adjustment and outcome following treatments for depression. *J. Consult. Clin. Psychol.* **2001**, 69, 125–129.
- 87 HICKIE, I., WILHELM, K., PARKER, G., BOYCE, P., HADZI-PAVLOVIC, D., BRODATY, H., MITCHELL, P., Perceived dysfunctional relationships: a specific association with the non-melancholic depressive subtype. *J. Affect. Disord.* **1990**, 19, 99–107.
- 88 BROWN, G. W., HARRIS, T. O., HEPWORTH, C., ROBINSON, R., Clinical and psychological origins of chronic depressive episodes II: a patient enquiry. *Br. J. Psychiatry* **1994**, 165, 457–465.
- 89 DEW, M. A., BROMET, E. J., Effects of depression on social support in a community sample of women. In *The Social Context of Coping*, ECKENRODE, J. (Ed.). Plenum, New York, **1991**.
- 90 VINOKUR, A. D., PRICE, R. H., CAPLAN, R. D., Hard times and hurtful partners: how financial strain affects depression and relationship satisfaction of unemployed persons and their spouses. *Pers. Soc. Psychol.* **1996**, 71, 166–179.
- 91 BAUCOM, D. H., SHOHAM, V., MUESER, K. T., DAUTO, A. D., STICKLE, T. R., Empirically supported couple and family interventions for marital distress and adult mental health problems. *Consult. Clin. Psychol.* **1998**, 66, 53–88.
- 92 PRINCE, M. J., BECKMAN, A. T. F., DEEG, D. J. H., FUHRER, R., KIVELA, S. L., LAWLOR, B. A., Depression symptoms in late life assessed using the EURO-D scale: effect of age, gender and marital status in 14 European centres. *Br. J. Psychiatry* **1999**, 174, 339–345.
- 93 HERZOG, A. R., HOUSE, J. S., MORGAN, J. N., Relation of work to health and well-being in older age. *Psychol. Aging* **1991**, 6, 202–211.
- 94 DEBLE, C., WEISS, R. L., Sex differences in prospective associations between marital quality and depressed mood. *J. Mar. Fam.* **1998**, 60, 1002–1011.
- 95 KIM, J. E., MOEN, P., Retirement transitions, gender, and psychological well-being: a life-course, ecological model. *J. Gerontol. Series B – Psychol. Sc. Soc. Sc.* **2002**, 57, 212–222.
- 96 ROTHERMUND, K., BRANDTSTADTER, J., Depression in later life: cross-sequential patterns and possible determinants. *Psychol. Aging* **2003**, 18, 80–90.
- 97 BALTES, M. M., LANG, F. R., Everyday functioning and successful aging: the impact of resources. *Psychol. Aging* **1997**, 12, 433–443.
- 98 MAIER, H., SMITH, J., Psychological predictors of mortality in old age. *J. Gerontol: Psychol, Sc. Soc. Sc.* **1999**, 54 (B), 44–54.
- 99 BRANDTSTADTER, J., ROTHERMUND, K., The life-course dynamics of goal pursuit and goal adjustment: a two-process framework. *Dev. Rev.* **2002**, 22, 117–150.

3

The Economic Burden of Depression: Societal and Patient Perspectives

Paul E. Greenberg and Howard G. Birnbaum

Abstract

Depressive disorders impose significant costs not only on sufferers but also on their families and caregivers, their employers, and insurers who often pay the resulting medical costs. This chapter summarizes medical and health economics literature that documents the societal economic burden associated with depression, as well as the incremental economic burden of depression patients in comparison with their non-depressed counterparts. Since the first depression cost-of-illness studies in the mid-1980s, several articles have updated these societal estimates, most recently to 2000. The economic burden of depression in the US was estimated to be just over \$83 billion at that time, of which \$26 billion (31%) accounted for direct treatment costs, \$5 billion (7%) suicide-related costs, and \$52 billion (62%) workplace costs. Taken together, this research highlights two important dynamics: (1) managed care has a substantial effect on the economic burden of depression, both in its overall level and its mix of cost components; and, (2) changing general economic conditions have an important influence on the employment rate and treatment rate of depression sufferers. At the patient level, numerous studies have used administrative claims data to assess the excess health care costs associated with treating psychiatric and medical conditions that often co-exist with depression. Such research has found that treatment for depression itself accounts for only 40% of the overall health care and workplace disability costs of depressed patients. Another 40% involves treatment of comorbid physical conditions, and the remaining 20% involves treatment of comorbid psychiatric disorders (other than depression). Claims data research has also provided insight into such economic issues as the workplace burden of depression, the time profile of costs of depression patients relative to the onset of their first episode, the family burden of depression, and the economic role of comorbid painful physical conditions.

3.1

Introduction

Cost-of-illness research in the area of psychiatric disorders dates back to at least the 1950s [1, 2], and burgeoned in the ensuing years [3]. One useful organizational approach to analyzing this body of literature considers the perspective of investigation. At one end of the spectrum, societal burden-of-illness studies frame the issue broadly with respect to the aggregate economic burden, both in terms of explicit resource utilization (e.g. dollars spent visiting the doctor) and the more subtle “opportunity” costs (e.g. the foregone value arising from a missed work day due to illness). This approach attempts to value all types of economic impacts of a disease, with the analytical objective being a full itemization of all those costs that are specific to that illness. For example, in counting up all hospital days in which the primary diagnosis code was depression, the unit of observation is the disease itself.

Individual patient circumstances can also be studied, an approach that lies at the opposite end of the spectrum in terms of aggregation. From this perspective, the nature of costs that accrue for a disease-state can be best understood in terms of the overall medical profile of a sufferer of that illness. Taking this approach, the comorbid medical profile is of great interest in understanding the incremental economic impact of individuals suffering from a common disease. Since the unit of observation is not a particular disease but rather a patient with that specific illness, applying this framework to the example noted above would target all hospital days of depression sufferers no matter what specific diagnosis was the underlying cause of a hospitalization. To the extent that excess hospital days may be identified in comparison with demographically matched non-depression sufferers, the dollar value of those excess days could be included as a cost of illness from a patient perspective. In a similar way, other resource utilization categories could be analyzed with respect to incremental costs over and above what is seen among non-sufferers. Of course, not all these excess costs would necessarily be attributable to depression, as the underlying causal pathway may be other comorbid conditions that predate its onset (e.g. cancer, diabetes, arthritis).

The societal cost of depression is driven primarily by its prevalence rate, its treatment rate, and its debilitating nature. Taken together, these factors explain how widespread the disorder is in the population, the extent to which the illness is addressed in the medical sector, and how impairing the condition is among sufferers. This set of characteristics influences not only the magnitude but also the distribution of costs amongst its various components. Direct costs include spending on medical treatment for such things as inpatient care, outpatient and doctor office visits, prescription pharmaceuticals, and laboratory tests. Indirect costs include the loss of productive capacity due to depression-induced suicides, and the workplace costs due to the symptoms of depression that lead to either missed work (i.e. absenteeism) or at-work productivity impairment (i.e. presenteeism).

Depressive disorders, including major depression, bipolar disorder, and dysthymia, impose significant costs not only on sufferers but also on their families

and caregivers, their employers, as well as the insurance providers who pay their resulting medical costs. Greenberg et al. [4] reported that, at the societal level, the cost of illness in this context was comparable in magnitude to that of widespread physical disorders such as AIDS or coronary heart disease. However, whereas the composition of costs tends to be skewed towards workplace burdens with respect to depression, for a long time, mortality cost was the single largest category in the case of AIDS, while direct medical costs was the dominant category for coronary heart disease [4]. In research by Wells et al. [5], only arthritis was associated with more chronic pain than depression, while only advanced coronary artery disease was found to be more disabling. Furthermore, the Global Burden of Disease study of established market economies in 1990 found that major depression ranked second to ischemic heart disease in terms of leading causes of lost years of healthy life due to premature death or disability. By 2020, major depression is expected to rank first on this particular burden-of-illness metric [6].

The symptoms of depression can result in cognitive, behavioral, and physical impairment, that substantially limit activities of daily living at work, home, or school. At the individual level, among the top decile of beneficiaries in terms of total costs to the typical payer, 40% have been found to suffer from major depression or dysthymia, and are responsible for 25 to 40% of all drug and hospitalization costs [7, 8]. The difficulties faced by depressed individuals often result not only in costly economic outcomes, but also in adverse social outcomes that may be irreversible, including reduced educational attainment, as well as increased likelihood of teenage parenting and marital instability [9–12].

One of the distinguishing characteristics of this illness is that a large proportion of sufferers receive no treatment for any emotional disorder, let alone adequate care specifically for depression. This low treatment rate is likely due to numerous factors, including lack of realization that an individual suffers from depression, financial or insurance-related constraints that limit access to treatment, the stigmatization of mental illness in general, a belief that treatment would not be effective given their particular circumstances, impatience with slow-acting antidepressants and their side-effects, and/or improper dosing of medications by general practice physicians [13–15]. When sufferers do receive depression treatment, it is often inadequate in that it fails to meet minimum standards of care according to best-practice treatment guidelines [16–19].

The objective in the current study is to summarize research findings from the medical and health economics literature documenting either the societal economic burden associated with depression, or the incremental economic burden of patients suffering from depression in comparison with their non-depressed counterparts. While the cost-effectiveness literature comparing the relative merits of specific treatments in this context has burgeoned in recent years [20], it is beyond the scope of this chapter.

3.2

Economic Burden of Illness: Societal Perspective

The first comprehensive societal cost-of-illness study with respect to depression was undertaken by Stoudemire et al. [21] using 1980 population data and focusing on major depression alone. The underlying analysis was based on published information concerning medical resource utilization and wages, and literature-based assumptions concerning the treatment rate of depression as well as the typical duration and profile of depression episodes. The authors estimated the societal burden of illness in the US to be approximately \$16 billion per year, with \$2 billion (13% of the total) accounting for the annual direct costs, \$4 billion (26%) for annual mortality costs, and \$10 billion (61%) for annual workplace costs. With almost two-thirds of the estimated costs borne in the workplace, this study paved the way for much of the subsequent cost-of-illness research in psychiatric disorders in its emphasis on the indirect, opportunity costs associated with depressed workers.

The framework developed by Stoudemire also formed the basis for much subsequent analysis (see Table 3.1). Greenberg et al. [22] broadened the scope of attention within the same basic model to include not only major depression sufferers but also those who experienced bipolar disorder or dysthymia. They also extended the cost categories to include attention to presenteeism while at work. Direct treatment costs were estimated based on patterns of observed medical treatment for depressive disorders in 1990, while lost lifetime earnings were estimated for the 60% of suicides attributed to depression, a ratio supported by numerous studies which found that the majority of all suicides are depression-related [23–27]. Workplace costs were estimated as the wage-based value of workplace impairment.

Table 3.1 Economic burden of depression in the US: a comparative analysis

<i>Reference</i>	<i>Author(s)</i>	<i>Year of estimate</i>	<i>Direct costs (billions of dollars)</i>	<i>mortality (in dollars)</i>	<i>Absenteeism (in billions of dollars)</i>	<i>Presenteeism (in billions of dollars)</i>	<i>Total costs (\$)</i>
21	Stoudemire et al.	1980	2.1	4.2	10.0	N/A	16.3
22	Greenberg et al.	1990	12.4	7.5	11.7	12.1	43.7
31	Rice and Miller	1990	19.2	7.7	2.2*	*	29.1
29	Greenberg et al.	1990	12.4	7.5	24.5	8.5	52.9
33	Greenberg et al.	1990†	19.9	5.6	39.4	12.4	77.4
33	Greenberg et al.	2000	26.1	5.4	36.2	15.3	83.1
44	Stewart et al.	2002	N/A	N/A	4.4	26.6	30.9

* These figures represent total morbidity costs, including both absenteeism and presenteeism costs, based on an estimate of percentage income loss per depressed individual.

† These figures represent the cost estimate from 1990 reported in [4], updated and expressed in 2000 dollars.

This approach distinguished between treated and untreated employees in terms of the number of episodes they experienced while at work, the duration of those episodes, and the number of days spent either in treatment and thus not at work, or at work, but suffering from reduced on-the-job productivity. To the extent that depressed workers, in fact, earn less than their non-depressed counterparts in the labor force, holding all else equal, it was recognized that this approach might overstate the workplace cost to specific employers. Nonetheless, it accurately reflects from a societal perspective the foregone value due to depression-related impairment in productive workplace capacity.

Using this refined model in conjunction with prevalence data from the Epidemiologic Catchment Area survey ("ECA"), the authors estimated the economic burden of depression in 1990 to be approximately \$44 billion, of which \$12 billion (28%) were direct costs, \$8 billion (17%) were suicide-related costs, and \$24 billion (55%) were workplace costs. It is worthwhile to carefully consider the implications of the composition of these cost estimates. The US currently spends over \$1.5 trillion annually on health care of all forms, or almost 15% of the gross domestic product, a staggering total that represents the aggregate direct cost of illness for all diseases [28]. But if only one-quarter of the costs of depression are spent on medical treatment, far more than 15% of all economic activity is likely affected by health-related concerns. Of course, with \$3 of indirect costs for every dollar of direct costs, the economic burden of depression may be especially skewed away from direct medical expenditure, thereby drawing particular attention to workplace costs in this specific instance. But since most illnesses are associated with at least some indirect costs, albeit not necessarily in such an extreme way as is seen with depression, this general framework is highly relevant for broader analysis.

Another important aspect of the findings emphasizes the (possibly unintentional) role of employers in the discussion of depression. Unfortunately, if one were to itemize a set of disease characteristics that would be consistent with a high workplace cost, many of them would be endemic of this particular illness. These characteristics include both the high prevalence of depression among working-age individuals, as well as its debilitating symptoms, such as chronic fatigue, inability to concentrate, moodiness, social withdrawal, inability to become motivated to accomplish even routine tasks, and severe bodily pain. These factors can all contribute to increased absence from work in terms of sporadic sick leave and short- or long-term disability, as well as significant performance impairment while at work. In many cases, the symptoms of depression are not so severe that sufferers withdraw entirely from the labor force, thereby resulting in a very sizable pool of depressed workers at any given time, especially during economic upswings when job opportunities are plentiful. Furthermore, whether the key to success at work primarily requires manual dexterity, physical strength, cognitive capability, or interpersonal skill, the debilitating symptoms of depression are broad enough to have the potential to negatively affect most of those different forms of job performance. In reality, no employer is exempt from the adverse consequences of depression in the workplace, even though some employers continue to behave as if its consequences have no adverse effect on their particular workforce.

The ECA data also underlie a subsequent societal burden of illness analysis undertaken by Rice and Miller [29]. That study reported the total costs of depression to be just over \$30 billion in 1990, with direct treatment costs accounting for approximately \$19 billion (63%) of the total, mortality costs accounting for about \$8 billion (25%), workplace costs represented by just over \$2 billion (7%), and other costs (i.e. related to crime, incarceration, and social welfare administration) estimated to cost around \$1 billion (4%). The largest source of discrepancy between these findings and those reported above concerns the magnitude of the workplace cost component. From a methodological perspective, the approach taken by Rice and Miller was ambitious, as they attempted to isolate the depression-specific impact on earnings using wage equations. Unfortunately, the estimation itself yielded the counter-intuitive result that depressed workers earned a premium wage in the workplace. Since this finding seems implausible (perhaps except in rare cases of artistic creativity coexisting with certain forms of depression), higher estimates of the productivity impact of illness on society reported elsewhere have become more widely accepted.

Subsequent depression prevalence estimates based on the National Comorbidity Survey ("NCS") [30] were much higher than had previously been understood based on the initial reports derived from the ECA data. Given these new epidemiologic data, Greenberg et al. [31] re-estimated the cost of illness using the same framework as before but with NCS data. Given the higher prevalence estimates, the economic burden of depression was calculated to be almost \$53 billion in 1990, with over 60% of the reported costs resulting from increased absenteeism and presenteeism among depressed workers. Underlying this revised cost finding was an estimated adult prevalence rate of depressive disorders of just over 10%, with a relatively young median age of onset compared with that of the most widespread and debilitating physical conditions such as arthritis and heart disease [32]. Because the underlying methodology used to calculate direct medical expenditures was based on identified resource utilization that was depression specific, revisions to the epidemiologic estimates did not affect this cost category. For the same reason, the mortality cost calculation remained unchanged even with the benefit of the NCS data, as these improved prevalence estimates did not change the total number of suicides that were recorded in the US or those that were assumed to be depression-related.

Greenberg et al. updated the earlier cost-of-illness studies based on a similar methodological framework as before, but using the most recent NCS-R prevalence and treatment rate estimates for 2000 [33]. Based on this approach, the economic burden of depression was estimated to be just over \$83 billion in 2000, of which \$26 billion (31%) were direct treatment costs, \$5 billion (7%) were suicide-related costs, and \$52 billion (62%) were workplace costs. In contrast, when the earlier \$53 billion cost estimate reported by Greenberg et al. [31] was expressed in comparable methodological and inflation-adjusted terms for 1990, a cost-of-illness finding of approximately \$77 billion was obtained. Of this total, \$20 billion (26%) was spent on direct costs, \$6 billion (7%) was attributable to suicide-related costs, and \$52 billion (67%) resulted from workplace costs.

Although the total number of depressed people remained relatively stable from 1990 to 2000 at around 18 million people, the number of treated depression sufferers grew substantially from almost 5 million to almost 8 million individuals. Thus, even though the treatment rate of depression increased by over 50% during this time period, the aggregate economic burden of depression changed by less than 10% in real dollars. To the extent that treatment of depression is associated with reduced episode severity and duration in general, this dramatic change over time conferred substantial benefits on society from an economic and quality of life perspective. In fact, the annual direct cost per treated patient decreased from approximately \$4100 in 1990 to \$3300 in 2000, a reduction of almost 20%. However, the quality of that treatment in so many cases was still inadequate.

Two important dynamics were highlighted in this recent societal burden-of-illness study: managed care has had a substantial effect on the economic burden of depression, and the change in general economic conditions has also had an important influence on its workplace cost component. With the widespread penetration of managed care during the 1990s, treatment for depression shifted toward greater utilization of relatively less expensive outpatient, office-based, and pharmaceutical care, and away from relatively more expensive inpatient care. Whereas inpatient care represented two-thirds of the direct costs of depression in 1990 it accounted for only one-third of all direct costs by 2000. Furthermore, the ease of administering and managing patients receiving new types of antidepressant medications made it possible for primary care physicians to provide drug treatment, thus leading to cost shifting from payments for treatment by mental health care specialists (e.g. psychiatrists, psychologists) to the costs of prescription drugs. These findings are consistent with other reported evidence of the effects of managed care on the delivery of health services for depression [34–36]. However, even as greater outreach was made to treat depressed people, quality of care provided in this context was low [37–41] as further evidenced by the enormous gap among treated depression sufferers between a possible treatment adequacy rate of at least 80% cited by National Institute of Mental Health, versus the 42% rate actually found in the NCS-R results for major depression patients [15, 42]. Thus, there remains substantial opportunity for further improvement in the mix of total expenditures in attempting to close the gap between what may be possible under ideal treatment conditions, and what is, in fact, realized in the health care sector.

As the US economy grew in the 1990s, the number of depressed people who were working also increased, and the proportion of those who were unemployed fell substantially. Since so many people obtain health care coverage through their jobs [43], being unemployed would appear to severely limit depression treatment opportunities. In fact, treatment rates varied enormously by employment status, with a far higher treatment rate found among depressed employees than among depressed people who were unemployed. While society is better off when depressed workers are drawn into employment situations, as the opportunity cost of their lost productive capacity is at least partially recaptured through their labor market activity, individual employers tend to incur added private costs as the employment rate of depressed people rises. This tension is just one example of the structural challenges

that remain in making high quality treatment more accessible to the many depression sufferers that lack adequate care without incurring enormous incremental costs to society.

The focus on the workplace costs of depression was analyzed in detail by Stewart et al. They estimated the excess costs of lost work-time among employees with depression totaling \$31 billion, of which \$27 billion (81%) was associated with presenteeism and only \$4 billion (19%) was attributed to absenteeism [44]. It is important to note that Stewart et al.'s calculation excluded bipolar from the set of depressive disorders considered, and did not incorporate the effects of short- or long-term disability leaves, all of which were explicitly factored into the updated estimates reported by Greenberg et al. [33]. These differences in approach may account for the discrepancy not only in magnitude but also in distribution of cost, which was much more heavily weighted towards presenteeism than absenteeism among depressed workers.

3.3

Economic Burden of Illness: Patient Perspective

The depression-related cost-of-illness literature reviewed above does not include explicit attention to the excess health care costs associated with treating psychiatric and medical conditions that often co-exist with depression. Instead, it focuses on the costs of the disease itself, rather than on all the related and (seemingly) unrelated manifestations of excess cost associated with patients suffering from the disease. This distinction highlights the difference between disease management and patient management. Consequently, the economic burden of illness as presented in those analyses is likely to be an understatement of the burden associated with depression sufferers.

Analyses that profile the cost of patients with depression typically use administrative claims data (de-identified to insure patient confidentiality). This payer data, whether it originates with private insurers (e.g. health plan, employer) or public programs (e.g. Medicare, Medicaid), typically contain detailed information on hundreds of thousands or even millions of beneficiaries derived from their underlying medical, drug and, at times, disability utilization records. Because the files are comprehensive with respect to medical encounters requested by those beneficiaries, it is possible to assess the costs of all forms of care that a depressed patient receives, not only for treatment of depression but also for comorbid conditions (e.g. cancer, lower back pain). This profile can then be compared with that of individuals who were not treated for depression. Moreover, since the claims themselves provide dates of treatment and diagnosis codes associated with specific kinds of care, it is possible to "drill down" with respect to various potentially important aspects of those costs (e.g. assess the time pattern of comorbid costs before and after an initial diagnosis of depression).

Based on this approach, depression has been shown to be associated with increased health services utilization as well as cost. For example, using claims data

for a large manufacturer, Birnbaum et al. documented that individuals treated for depression use all types of health care services intensively [45], with total medical (e.g. inpatient, outpatient, office), pharmaceutical, and disability costs estimated to be 4.2 times higher for major depression patients than for those of the typical beneficiary. These findings were further informed by subsequent research showing that the cost differential was especially large among patients with treatment-resistant depression [46].

Several patient-level studies have assessed the costs of a range of depressive disorders. Using a multi-employer claims database, Goetzel et al. [47] found that the most costly mental health condition was bipolar disorder, followed by major depression. Bryant-Comstock et al. compared the costs of patients with bipolar disorder to non-bipolar patients using claims data, and found that costs were three to four times greater for the bipolar group [48]. In addition, Birnbaum et al. [49] found that in the 12 months following initiation of antidepressant treatment, unrecognized bipolar patients incurred monthly medical costs which were almost 50% greater than those of recognized bipolar patients.

Patient studies also provide insight into the role of comorbid conditions among depressed patients. For example, Birnbaum et al. [50] found that reimbursements for depression itself (identified on the basis of *International Classification of Diseases*, Ninth Revision ("ICD-9") codes and National Drug Code ("NDC") codes) accounted for only 40% of their costs, a finding corroborated by the results of the Bryant-Comstock et al.'s study of bipolar patients [48]. Of the 60% of costs that were not directly attributable to depression-specific claims, approximately two-thirds involved comorbid physical conditions and the remaining one-third involved other psychiatric disorders. If those same proportions held in the aggregate, the recent \$83 billion cost-of-illness estimate reported by Greenberg et al. [33] would imply an equivalent amount of costs due to the physical disorders experienced by depressed people, and in excess of \$40 billion more due to their non-depression psychiatric disorders.

The role of comorbid conditions in the cost of depression, as well as the role of depression in the cost of other medical conditions is an increasingly researched topic of investigation. Sheehan compared the per capita annual medical costs of treating patients with and without depression who also suffered one of several common chronic conditions (i.e. heart failure, allergic rhinitis, asthma, migraine, back pain, diabetes, hypertension, or ischemic heart disease), and found that comorbid depression increased the per-patient cost of treating these conditions by a factor of two to four times [51]. Recent data also indicated that when physical symptoms accompanied depression, the economic burden is magnified. One of the most common physical symptoms of depression is pain, and several studies have shown that the economic burden of depression is even greater when it is comorbid with pain. For example, Sheehan found that patients with back pain and depression incurred medical costs that were 2.8 times higher than patients with back pain alone [51]. Similarly, Greenberg et al. reported that the per-employee cost of depressive disorders comorbid with fibromyalgia was 1.2 times greater than that of employees with only depression. Moreover, the difference in the cost between employed depressed patients with and without fibromyalgia was even greater than

the incremental burden associated with an employed patient with fibromyalgia alone [52].

In addition to analyzing the extent of excess costs incurred by depressed health plan beneficiaries, the time path of those incremental costs is also of interest. For example, a recent study by Greenberg et al. analyzed the time profile of the added health care costs of patients treated for depressive disorders compared to persons who were not treated for depression, including attention to both depression treatment costs, as well as those for coexistent medical and psychiatric conditions [53]. Using claims data for seven large US companies, a multivariate regression model was estimated that included controls for patient demographics as well as a number of medical conditions that tend to precede the onset of depressive disorders. The study found a “run up” of costs prior to an initial diagnosis of depression, and a subsequent “run down” in costs after treatment for the condition. Treated depressive disorder patients incurred approximately \$600 per month incremental health care costs during their first depressive disorder episode. Of this amount, approximately one-third was for depression treatment, and two-thirds was for incremental treatment of coexisting conditions. In addition, while the added costs of treating other medical and psychiatric conditions increased in the months prior to the first depression episode, these costs decreased in the months after a final depression episode (see Figure 3.1).

Another strand of depression outcomes research that has garnered substantial attention at the patient level focuses on workplace costs. Simon et al. surveyed the literature in this context and distinguished among the four types of evidence that have been compiled: (1) cross-sectional naturalistic studies, which found substantial

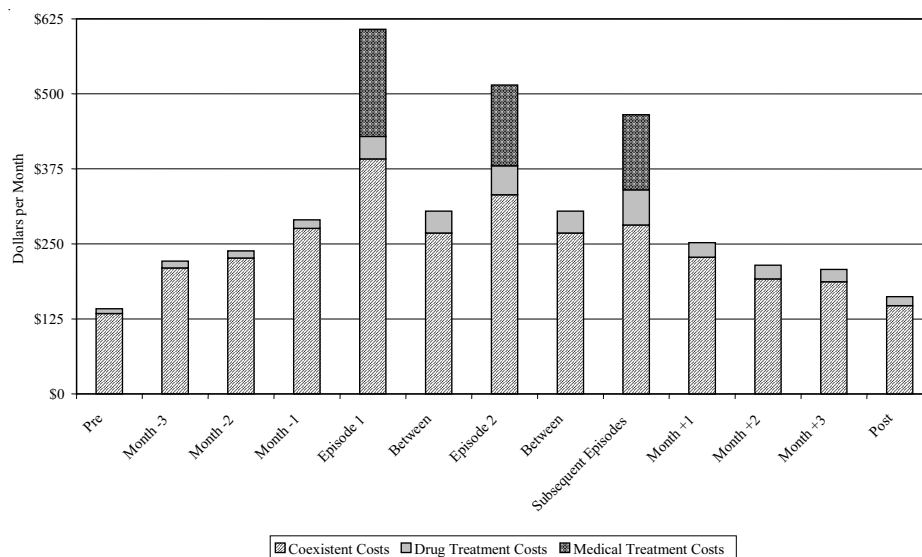


Figure 3.1 Time profile of treatment for depressive disorders patients: per capita incremental health care costs. From Greenberg et al. [55]

impairment among depressed workers on a self-reported basis; (2) longitudinal naturalistic studies, which found a synchrony of change between depression and work impairment; (3) uncontrolled treatment studies, which reported reductions in work impairment with successful treatment; and (4) controlled treatment studies, which tended to find that patients demonstrated work productivity improvement following treatment [54]. To deepen our understanding in this context it would be useful to conduct randomized effectiveness trials that include detailed documentation of patient-specific resource utilization changes with changes in depression status (e.g. incorporating economic instruments within the framework of clinical trial design with attention to costs based a combination of data gathered from the trial itself possibly augmented by administrative claims data obtained for the same patient cohort).

Taken together with findings from societal cost-of-illness studies concerning the magnitude of direct and indirect costs incurred, patient-level results underscore the adverse effect of depression from an economic perspective. Further investigation to better understand the subtle ways in which burdens of illness manifest in this context will likely focus on such issues as the impact of depression in exacerbating comorbid conditions and their attendant costs, the role of caregiver burdens in financial terms, and economic differences in life outcomes depending on age-of-onset. The substantial knowledge base that has been developed by numerous researchers to date will thereby continue to be enhanced as these types of topics continue to occupy the research agenda for many years to come.

References

- 1 MALZBERG, B., Mental illness and the economic value of man. *Mental Hygiene* 1950, 34, 225–227.
- 2 FEIN, R., *Economics and Mental Illness: A Report to the Staff Director*, Jack R. Ewalt. New York, NY: Basic Books, 1958.
- 3 JARVINEN, D., *Cost of Illness Studies: An Annotated Bibliography*. San Francisco, CA: Institute for Health & Aging, University of California, 1988.
- 4 GREENBERG, P. E., STIGLIN, L. E., FINKELSTEIN, S. N., et al., Depression: a neglected major illness. *J. Clin. Psychiatry* 1993, 54 (11), 419–424.
- 5 WELLS, K. B., STEWART, A., HAYS, R. D., et al., The functioning and well-being of depressed patients: results from the medical outcomes study. *JAMA* 1989, 262, 914–919.
- 6 MURRAY, C. J. L., LOPEZ, A. D. (Eds.), *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard University Press, 1996.
- 7 KATON, W., VON KORFF, M., LIN, E., et al., Distressed high utilizers of medical care: DSM-III-R diagnoses and treatment needs. *Gen. Hosp. Psychiatry* 1990, 12, 355–362.
- 8 VON KORFF, M., ORMEL, J., KATON, W., et al., Disability and depression among high utilizers of health care: a longitudinal analysis. *Arch. Gen. Psychiatry* 1992, 49 (2), 91–100.
- 9 GREENBERG, P. E., BIRNBAUM, H. G., The workplace burden of depression: underlying causes, recent empirical findings, and future directions. *TEN* 2000, 2 (6), 37–40.
- 10 KESSLER, R. C., FOSTER, C. L., SAUNDERS, W. B., et al., Social consequences of psychiatric disorders, I: Educational attainment. *Am. J. Psychiatry* 1995, 152 (7), 1026–1032.

- 11 KESSLER, R. C., BERGLUND, P. A., FOSTER, C. L., et al., Social consequences of psychiatric disorders, II: Teenage parenthood. *Am. J. Psychiatry* 1997, 154, 1405–1411.
- 12 KESSLER, R. C., WALTERS, E. E., FORTHOFFER, M. S., The social consequences of psychiatric disorders, III: Probability of marital stability. *Am. J. Psychiatry* 1998, 155, 1092–1096.
- 13 ROST, K., SMITH, G. R., MATTHEWS, D. B., et al., The deliberate misdiagnosis of major depression in primary care. *Arch Fam Med* 1994, 3 (4), 333–337.
- 14 RUBENSTEIN, L. V., JACKSON-TRICHE, M., UNÜTZER, J., et al., Evidence-based care for depression in managed primary care practices. *Health Affairs* 1999, 18 (5), 89–105.
- 15 KESSLER, R. C., BERGLUND, P., DEMLER, O., et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003, 289 (23), 3095–3105.
- 16 CHARBONNEAU, A., ROSEN, A. K., ASH, A. S., et al., Measuring the quality of depression care in a large integrated health system. *Med. Care* 2003, 41, 669–680.
- 17 BRUCE, M. L., WELLS, K. B., MIRANDA, J., et al., Barriers to reducing burden of affective disorder. *Ment. Health Serv. Res.* 2002, 4, 187–197.
- 18 AMERICAN PSYCHIATRIC ASSOCIATION. *Practice Guideline for the Treatment of Patients with Major Depression*, 2nd ed. Washington, DC: American Psychiatric Association Press, 2000. Available at: http://www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm. Accessed January 22, 2004.
- 19 AGENCY FOR HEALTH CARE POLICY AND RESEARCH. *Depression in Primary Care: Vol. 2: Treatment of Major Depression*. Rockville, MD: US Dept of Health and Human Services, 1993. Available at: <http://www.mentalhealth.com/bookah/p44-d2.html>. Accessed January 22, 2004.
- 20 ROSENBAUM, J. F., HYLAN, T. R., Costs of depressive disorders: a review. In: *Depressive Disorders*, MAJ, M., SARTORIUS, N. (Eds.). WPA Series: Evidence and Experience in Psychiatry, 1999, 401–449.
- 21 STOUDEMIRE, A., FRANK, R., HEDEMARK, N., et al., The economic burden of depression. *Gen. Hosp. Psychiatry* 1986, 8, 387–394.
- 22 GREENBERG, P. E., STIGLIN, L. E., FINKELSTEIN, S. N., et al., The economic burden of depression in 1990. *J. Clin. Psychiatry* 1993, 54 (11), 405–418.
- 23 SARTORIUS, N., The economic and social burden of depression. *J. Clin. Psychiatry* 2001, 62 (Suppl. 15), 8–11.
- 24 FOSTER, T., GILLESPIE, K., MCCLELLAND, R., et al., Risk factors for suicide independent of DSM-III-R Axis I disorder. *Br. J. Psychiatry* 1999, 175, 175–179.
- 25 HENRIKSSON, M. M., ARO, H. M., MARTTUNEN, M. J., et al., Mental disorders and comorbidity in suicide. *Am. J. Psychiatry* 1993, 150 (6), 935–940.
- 26 RICH, C. L., YOUNG, D., FOWLER, R. C., San Diego suicide study. I. young vs. old subjects. *Arch. Gen. Psychiatry* 1986, 43, 577–582.
- 27 BARRACLOUGH, B., BUNCH, J., NELSON, B., et al., A hundred cases of suicide: clinical aspects. *Br. J. Psychiatry* 1974, 125, 355–373.
- 28 LEVIT, K., SMITH, C., COWAN, C., et al., Health spending rebound continues in 2002. *Health Affairs* 2004, 23 (1), 147–159.
- 29 RICE, D. P., MILLER, L. S., The economic burden of affective disorders. *Br. J. Psychiatry Suppl.* 1995, 27, 34–42.
- 30 NATIONAL COMORBIDITY SURVEY. Website available at: <http://www.hcp.med.harvard.edu/ncs/index.htm>. Accessed January 22, 2004.
- 31 GREENBERG, P. E., KESSLER, R. C., NELS, T. L., et al., Depression in the workplace: an economic perspective. In: FEIGHNER, J. P., BOYER, W. F. (Eds.). *Selective Serotonin Re-uptake Inhibitors: Advances in Basic Research and Clinical Practice*, Second Edition. New York: John Wiley & Sons Ltd, 1996, 327–363.
- 32 KESSLER, R. C., MCGONAGLE, K. A., ZHAO, S., et al., Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch. Gen. Psychiatry* 1994, 51 (1), 8–19.
- 33 GREENBERG, P. E., KESSLER, R. C., BIRNBAUM, H. G., et al., The economic burden of depression in the united states:

- how did it change between 1990 and 2000? *J. Clin. Psychiatry* 2003, 64 (12), 1465–1474.
- 34 OLFSON, M., MARCUS, S. C., DRUSS, B., et al., National trends in the outpatient treatment of depression. *JAMA* 2002, 287 (2), 203–209.
 - 35 GOFF, V. V., Depression: a decade of progress, more to do. *NHPF Issue Brief* 2002, 786, 1–14.
 - 36 ZUVEKAS, S., Trends in mental health services use and spending, 1987–1996. *Health Affairs* 2001, 20 (2), 214–224.
 - 37 STURM, R., WELLS, K. B., How can care for depression become more cost-effective? *JAMA* 1995, 74 (1), 51–58.
 - 38 WELLS, K. B., STURM, R., Care for depression in a changing environment. *Health Affairs* 1995, 14 (3), 78–89.
 - 39 FRANK, R. G., MCGUIRE, T. G., NORMAND, S.-L., et al., The value of mental health care at the system level: the case of treating depression. *Health Affairs* 1999, 18 (5), 71–88.
 - 40 VALENSTEIN, M., VIJAN, S., ZEBER, J. E., et al., The cost-utility of screening for depression in primary care. *Ann. Intern. Med.* 2001, 134 (5), 345–360.
 - 41 FRANK, R. G., HUSKAMP, H. A., PINCUS, H. A., Aligning incentives in the treatment of depression in primary care with evidence-based practice. *Psychiatr. Serv.* 2003, 54 (5), 682–687.
 - 42 NATIONAL INSTITUTE OF MENTAL HEALTH. *The Effects of Depression in the Workplace*, 2003. Available at: <http://www.nimh.nih.gov/publicat/workplace.cfm>. Accessed January 22, 2004.
 - 43 O'BRIEN, E., Employers' benefit from workers' health insurance. *The Millbank Quart.* 2003, 81 (1), 5–43.
 - 44 STEWART, W. F., RICCI, J. A., CHEE, E., et al., Cost of lost productive work time among US workers with depression. *JAMA* 2003, 289 (3), 3135–3144.
 - 45 BIRNBAUM, H. G., GREENBERG, P. E., KESSLER, R. C., et al., Workplace burden of depression: a case study in social function using employer claims data. *Drug Benefit Trends* 1999, 11 (8), 6–12.
 - 46 COREY-LISLE, P. K., BIRNBAUM, H. G., GREENBERG, P. E., et al., Identification of a claims data “signature” and economic consequences for treatment-resistant depression. *J. Clin. Psychiatry* 2002, 63 (8), 717–726.
 - 47 GOETZEL, R. Z., HAWKINS, K., OZMINKOWSKI, R. J., WANG, S., The health and productivity cost burden of the “top10” physical and mental health conditions affecting Six large US employers in 1999. *J. Occup. Environ. Med.* 2003, 45 (1), 5–14.
 - 48 BRYANT-COMSTOCK, L., STENDER, M., DEVERCELLI, G., Health care utilization and costs among privately insured patients with bipolar I disorder. *Bipolar Disorder* 2002, 4 (6), 398–405.
 - 49 BIRNBAUM, H. G., SHI, L., DIAL, E., et al., Economic Consequences of not recognizing bipolar disorder patients: a cross-sectional descriptive analysis. *J. Clin. Psychiatry* 2003, 64 (10), 1201–1209.
 - 50 BIRNBAUM, H. G., GREENBERG, P. E., BARTON, M., et al., Workplace burden of depression: a case study in social functioning using employer claims data. *Drug Benefit Trends* 1999, 11 (8), 6–12.
 - 51 SHEEHAN, D. V., Establishing the real cost of depression. *Managed Care* 2002, 11 (1), 7–10.
 - 52 GREENBERG, P. E., LEONG, S. A., BIRNBAUM, H. G., ROBINSON, R. L., The economic burden of depression with painful symptoms. *J. Clin. Psychiatry* 2003, 64 (Suppl. 7), 17–23.
 - 53 GREENBERG, P. E., BIRNBAUM, H. G., MOYNEUR, E., et al., The direct health care costs of depressive disorders in the US: a patient time profile. Poster presentation at the European College of Neuropsychopharmacology, 2003, Prague, Czech Republic.
 - 54 SIMON, G. E., BARBER, C., BIRNBAUM, H. G., et al., Depression and work productivity: the comparative costs of treatment versus nontreatment. *J. Occup. Environ. Med.* 2001, 43, 2–9.
 - 55 GREENBERG, P. E., BIRNBAUM, H. G., MOYNEUR, E., et al., The Direct Health Care Costs of Depressive Disorders in the US: A Patient Time Profile. Poster Presented at the International Society for Pharmacoeconomics and Outcomes Research, May, 2004.

4

The Depressive Spectrum: Reconceptualizing the Relationship between Dysthymic, Subthreshold and Major Depressions

Hagop S. Akiskal and Lewis L. Judd

“Not infrequently ... [clinical depression] is preceded by fluctuating nervous disorders and slight irritable or depressive moodiness for years before the more marked morbid phenomena begin ... [the latter] appear only as an increase of a slight morbid state which had always existed”.

E. Kraepelin, 1921 [15]

Abstract

The spectrum of depressive illness has been dichotomized into minor “neurotic” personality-based depressions and “endogenous” biologically-based and more severe. In this chapter, we focus primarily on epidemiological and clinical data to support a new psychobiologic paradigm of depressive illness. The relationship among dysthymia, other subthreshold depressions and major depressive disorder is further strengthened by shared biological finding of neurophysiologic nature. Short-REM latency, neuroendocrine dysregulation in TRH-TSH challenge and electrodermal activity corroborate the notion of a psychobiologic continuum between dysthymia and major depression. Systematic analyses of epidemiological data of the National Institutes of Mental Health (NIMH) Epidemiological Catchment Area Program and of a large clinical cohort being followed prospectively by the NIMH Collaborative Depression Study support the notion that subsyndromal depressive symptoms are a clinically relevant variant of affective disorders. The typical course of unipolar depression is more variable than previously assumed; it is characterized by a significant degree of fluctuation in severity of symptoms, in which the same subject experiences multiple levels of depressive symptom severity as symptoms wax and wane over time.

4.1

Introduction

During much of the past century depressive illness has been dichotomized into minor reactive, atypical, personality disorder-based depressions termed “neurotic” versus more severe, major presumably biologically-based “endogenous” depressions. This confusing legacy [1] has its contemporary adherents [2] who bemoan the loss of the older paradigm, which has not withstood the accumulating evidence against it. This chapter is an account of such evidence in favor of an emerging new paradigm whereby depressive subtypes listed in current classificatory schema lie on a clinical spectrum [3, 4]. The focus of this chapter is largely epidemiologic and clinical; pharmacological and biological findings are briefly mentioned when relevant to the nosologic issues being discussed.

Prospective follow-up of neurotic depressive patients has shown progression over time to major, endogenous, and even psychotic depressive episodes and bipolar transformation [5, 6]. So-called “characterological” or otherwise low-grade chronic neurotic depressives were found to have shortened REM latency [7–9], a well-known biological marker of depressive illness. These depressions were introduced into the *Diagnostic and Statistical Manual of Mental Disorders–III* (DSM-III [10]) under the rubric of “dysthymia”, which represents a variant of major depressive disorder (MDD). Dysthymia is often complicated by MDD, a pattern currently recognized in DSM-IV as “double depression” [11]. Finally, family studies have shown that heritability of MDD is weak if familial cases are limited to strictly-defined major depressive episodes (MDE); it is only when broadly-defined phenotypes including neurotic and minor depressions, are counted as “cases” among the first-degree relatives that robust evidence for heritability can be more confidently demonstrated [12, 13]. All of these studies point to a new psychobiologic paradigm of depressive illness [4, 14] in which depressive symptoms are expressed in a spectrum of severity that ranges from subsyndromal to syndromal levels, in which subthreshold symptoms acquire clinical relevance. This chapter reviews them in historical, conceptual and clinical context.

4.2

Brief History

Long before psychiatry moved to the outpatient arena in the latter part of the 20th century, Kraepelin [15] at the turn of the 19th century, had reported self-limited episodes, and observed milder mood disturbances among the relatives of patients hospitalized for endogenous or psychotic depression or mania. Some were described as sullen, morose, or otherwise moody, but without discrete episodes; others reported self-limited episodes, but often went untreated. Furthermore, Kraepelin envisaged a continuum between premorbid mild affective disturbances and more severe depressive episodes which brought the patient to clinical attention.

With the advent of modern treatments, practitioners are being increasingly consulted by patients presenting with attenuated affective disturbances. Although the relationship of these ambulatory affective dispositions and more classical severe affective states has not been entirely resolved, there is emerging familial–genetic evidence [12–16] that a considerable continuum exists between them. The continuum view represents a “triumph” of the Maudsley continuum model [17] over the Newcastle dichotomous position [18]. Although an Australian author [2] has recently argued for a return to the old dichotomous paradigm of neurotic–endogenous depression, his arguments based largely on cross-sectional psychometric data, neglect the extensive emerging literature on familial–genetic, neurophysiologic and course findings relating subaffective [8] – and so-called “minor” affective states [19] – to mood disorders. Our position on the depressive spectrum does not rule out the likelihood that neurobiological findings in favor of heterogeneity may be uncovered in the future. Our main point here is that such heterogeneity can no longer be supported on the basis of the neurotic–endogenous distinction.

Based on the balance of evidence, current official classification systems such as the ICD-10 [20] and DSM-IV [21], have eventually dropped the neurotic–endogenous dichotomy, and introduced the related rubrics of “dysthymia” and “double depression” in lieu of much of the former terrain of the neurotic category. The new terminology has drawn attention to a large universe of human suffering that had been ignored throughout much of the 20th century, and the conceptualization of dysthymia as a chronic subthreshold variant of mood disorder rather than a neurosis has had a far-reaching impact on the diagnostic and therapeutic habits of clinicians worldwide [22].

Dysthymia, which is commonly observed in psychiatric settings, is not the only subthreshold mood disorder. Subsyndromal, shorter-lasting oligosymptomatic depressions (those with few symptoms) are highly prevalent in epidemiologic [23] and general medical settings [24]. Such subsyndromes can precede (prodromes) or follow (residual states) major depressions, or pursue an intermittent subthreshold course [4, 25]. These subthreshold conditions are obviously of great public health and theoretical and practical significance.

The clinical studies on subthreshold depressions, particularly dysthymia in its relation to major depressions, were initially conducted at the University of Tennessee [26]. Subsequent research expanding on this paradigm and re-conceptualizing the relationship of all subthreshold depressions to major depressions were carried out at the University of California at San Diego [14]. This chapter is an overview of the record of the clinical progress in this field in support of a spectrum concept of depressive illness. This body of work is more extensively represented in previous reviews by the authors [3, 4, 14, 22, 26–29].

4.3

Dysthymia

4.3.1

Terminology

“Temperament” as used herein refers to long-term emotional traits, traditionally believed to have a strong biological component. It is relevant to point out that Kraepelin preferred the concept of “personal disposition”; “temperament” appears in the English translation [15]. It is a dimensional construct, which can be considered to be abnormal in a statistical, and perhaps, in a clinical sense only in its extremes. Thus, where a normal tendency to gloominess merges into dysthymic disorder which manifests in subthreshold depressive symptoms is a matter of clinical convention. The decision when to treat such individuals is even less certain, but the increasing clinical and research attention given to dysthymia is an indication that many such individuals seek psychological and psychiatric help, and mental health professionals should make informed decisions concerning when and how and for how long to treat such individuals [29].

4.3.2

Epidemiology

It is estimated that 3–5% of the general population is suffering from dysthymia [30]. Like major depressive disorder, dysthymia is twice as common in women as in men. Compared with depression in the setting of a severe anxiety disorder like agoraphobia [31], dysthymia is more disabling as far as quality of life in social and personal areas, work, and leisure is concerned. Celibacy too, is common in early onset dysthymia – but not for long: modern successful treatments often lead to change in marital status [29]!

Other research in primary care [24] has focused on depressive symptoms falling short of the major depressive threshold as far as symptom intensity is concerned, as well as falling short of the 2-year duration criterion for dysthymia. Because of the low grade symptoms, 50% of sufferers remain unrecognized by their general practitioners. Yet, given the chronic nature of their complaints, these patients report high degrees of morbidity and impairment in a variety of health domains and quality of life, including “bed days”, i.e. number of days per year they stay bedridden.

In light of the foregoing developments, both the World Psychiatric Association [32] and the World Health Organization [33] have developed programs to address the challenges of educating general practitioners in the proper recognition and treatment of dysthymia. One of the deliberations of the WHO “consensus” was to set the threshold of dysthymia in general medical practice at 6 months of intermittent symptoms. Such revision of the DSM-IV threshold highlights the importance accorded to subthreshold symptoms of depression and their negative impact on comorbid medical and neurological diseases.

4.3.3

Clinical Description

The term “dysthymia” (= “bad mood”) originated in ancient Greece and is still in current use in that country with the same connotation [34]. In the Hippocratic school, it was considered as part of the broader concept of melancholia (= “black bile”). A temperament predisposed to melancholia was also delineated, and referred to individuals who were lethargic, brooding and insecure. The term was re-introduced into medicine in Germany in the early 19th century to describe depressions that pursued a chronic course.

Although he did not use the “dysthymia” rubric, Kraepelin [15] did consider a lifelong depressive disposition as one of the constitutional (“temperamental”) foundations of affective episodes. He provided a compelling portrait of these individuals whom he observed among the “well” relatives of the affectively ill or in the early history of the patients themselves. The condition often began early in life, and by adolescence many had increased sensitivity to life’s sorrows and disappointments. As such individuals grew into adulthood, they experienced “life with its activity [as] a burden which they habitually [bore] with dutiful self-denial without being compensated by the pleasures of existence” ([15] p. 120). In some, these temperamental peculiarities were so marked that they could be considered “morbid without the appearance of more severe, delimited attacks ...” ([15] p. 118), clearly foreshadowing the modern concept of trait dysthymia. In other subjects, recurrent melancholia arose from this substrate without definite boundaries, again anticipating the concept of “double-depression” [11].

Subsequently, Kurt Schneider [35] described a depressive type whose entire existence was entrenched in suffering. Tellenbach [36] has described a melancholic type with a strong sense of duty. Building on these German authors, our research in Memphis [26] led to the operationalization of the core characteristics of such individuals encountered in contemporary practice. They are gloomy, somber and incapable of fun; brooding, self-critical and guilt-prone; lack confidence, are of low self-esteem, and preoccupied with failure; pessimistic, easily discouraged; easy to tire, sluggish and bound to routine; nonassertive, self-denying and devoted; shy and sensitive. These traits have excellent internal consistency and discriminatory ability [37]. Similar concepts have also appeared [38] with particular emphasis on self-critical attitudes and devotion to others.

Until recently, it was believed that affectively ill patients fully recover from their acute episodes with relatively little symptomatic residua and dysfunction. Community psychiatry – which has given renewed visibility to inter-episodic low-grade fluctuating depressive disorders – has challenged this classic view. With the advent of DSM-III [9], such patients are now officially designated as “dysthymic”. In the ICD-10 [20], the low-grade depressive baseline is considered the main pathology; only an occasional mild superimposed depressive episode is permitted. In the latest American Psychiatric Association manual (DSM-IV [21]), at least two patterns have been described: pure dysthymia uncomplicated by major depression, and a more prevalent pattern of dysthymia complicated by major depressive episodes that could

be even moderate or severe in intensity (and which has been dubbed “double-depression” [11]).

Dysthymic individuals at best invest whatever energy they have in work, leaving none for leisure and family or social activities. According to Tellenbach [36], such dedication to work represents an over-compensation against depressive disorganization. Kretschmer [39] had earlier suggested that such persons were the “backbone of society”, devoting their lives to jobs that require dependability and obsessive attachment to work. Excellent contemporary exposition of the foregoing clinical features can be found in the work of Kraus [40] and Possl and von Zerssen [41]. These individuals may seek outpatient counseling and psychotherapy for what some clinicians consider “existential depression”. Such patients complain that their life lacks meaning and joy. Others present clinically because of an intensification of their gloom to the level of clinical depression.

The prototypical dysthymic complains of having been “depressed since birth” [27]. In the eloquent words of Kurt Schneider [35], they view themselves as belonging to an “aristocracy of suffering”. These hyperbolic descriptions of suffering in the absence of more objective signs of depression in the past earned them the label of “characterological depressives” [7]. The description is further reinforced by the fluctuating depressive picture that merges imperceptibly with the patient’s habitual self, leading to the clinical uncertainty as to whether dysthymic disorder belongs to the affective or personality disorder domains. For instance, while classifying “dysthymia” as a subsymptomatic expression of affective pathology on axis I, DSM-IV [21] has introduced into its appendix the concept of “depressive personality disorder” on axis II as a trait characterologic disorder. Such a contemporary split in conceptualization is not new. Although Kraepelin [15] had subsumed individuals manifesting depressive disposition as a subclinical expression of manic-depression, Kurt Schneider [35] considered them as “depressive psychopaths” (i.e. depressive personality). Such a designation underestimates the affective affinities among dysthymics observed in contemporary practice [26, 42]. Table 4.1 summarizes the core features of dysthymia.

One of the most provocative findings in dysthymia arguing against Schneider’s position, is that one out of three dysthymic patients in our research setting – conforming to the double-depressive pattern – switched to hypomania on anti-depressants [43]. Such patients have also been observed in pre-pubertal years, with switches observed in the post-puberty period [44]. Family history is often positive in this dysthymic subgroup which could be considered to be “sub-bipolar” [7, 8, 43].

Table 4.1 The core characteristics of dysthymia in psychiatric settings*

Long-standing subthreshold depression of a fluctuating or persistent nature
Gloomy and joyless disposition
Brooding about the past and guilt-prone
Low drive and lethargy
Low self-esteem and preoccupation with failure
Identifies suffering as part of the habitual self

* Based on Akiskal [26, 27].

They represent a clinical bridge between major depressive disorder and bipolar II. The “complication” of dysthymia by major affective episodes is not due to clinical referral bias – it is also observed in the community [45–49]. The foregoing data are of great significance for preventive public health: juvenile and young adult subjects with dysthymia [44] should be the focus of intervention trials aimed at the prevention of major affective episodes.

Recent 12-year prospective analyses from the NIMH CDS database [50] have shown that patients with major depressive disorder spend 44% of their course in low-grade depression (of which the greater majority are dysthymic weeks) and only 15% of the time in major episodes. These findings indicate that major depression, dysthymia, and briefer subsyndromal depressions constitute somewhat artificial conventions, representing alternative manifestations of the same diathesis [4, 14, 49–51]. In other words, various subthreshold and major depressive conditions must not be viewed as distinct depressive subtypes, but as part of a symptomatic continuum. We will return to these NIMH data in greater detail in subsequent sections of this chapter. At this stage we would like to introduce our model linking the various subthreshold conditions to major depression and their interpersonal sequelae. Figure 4.1 represents diagrammatically these putative relationships within a broad depressive spectrum [52].

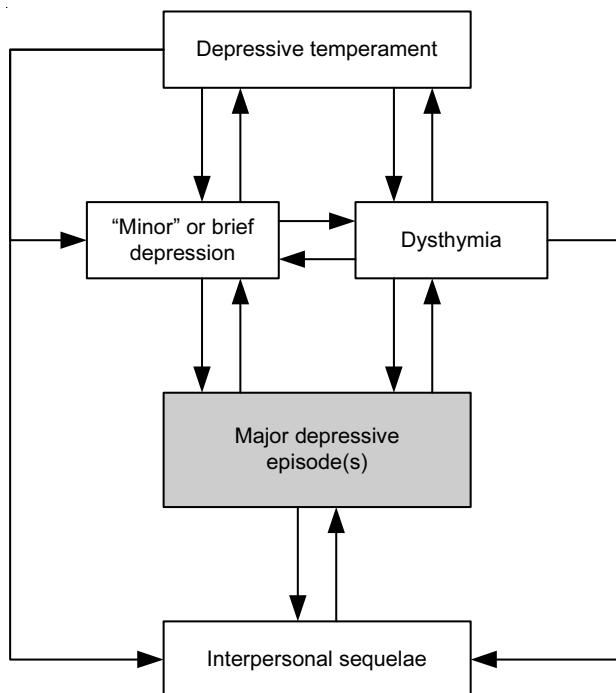


Figure 4.1 Relationship between various depressive conditions supporting a spectrum concept. Reprinted with permission from Akiskal [52]

4.4

Psychobiologic Continuum between Dysthymia and Major Depression

The relationship between dysthymia, other subthreshold depressions and major depressive disorder is strengthened by shared biological findings, which are largely neurophysiologic in nature [4]. It is relevant to point out that dysthymic patients were previously considered to belong to “character neuroses” [5]. In a study of such patients who were not in a state of major depression [7], we reported that REM latency was reduced to < 60 min, and that sleep was redistributed to the early part of the night (which was the reverse of what we observed in chronic anxious patients [53]). Moreover, a family history of major affective illness was significantly high in short-REM latency patients. (The reverse was true for those with familial alcoholism and sociopathy [43]). These findings were so similar to those seen in major depression, that we decided to include our patients in systematic open trials with desipramine and nortriptyline (the best tolerated secondary amine tricyclics at the time) or lithium carbonate if antidepressants had failed (based on the observation of familial bipolar disorder in some). Nearly 40% remitted, of whom one out of three developed brief hypomania. The sleep findings have been replicated in other laboratories (reviewed in [54]), and a Hungarian study [55] has shown that dysthymics experience transient lifting of their mood with sleep deprivation. Another US study [56] has shown high rates of affective illness in a systematic familial investigation of dysthymic probands.

As for neuroendocrine markers (reviewed in [54]), TRH-TSH challenge and electrodermal activity – comparable to those with major depressive disorders – are the main findings; in contrast, DST and catecholamine metabolism are essentially unaltered in dysthymia. Coupled with the REM-latency findings, these data suggest that dysthymia represents trait depression. The family history data further suggests that this traitness is of constitutional origin. It is, therefore, of great theoretical and practical significance that shortened REM latency has been recently reported in the offspring of the affectively ill [57, 58]. The biologic trait in dysthymia is not limited to sleep neurophysiologic abnormalities. Emerging data from several laboratories [58–60] indicate that sophisticated steroidal and/or CRF function indices are abnormal in the offspring of the affectively ill, as well as in those with dysthymia.

There also exist dysthymic patients whose lifelong suffering and discontent appear, in retrospect, a legacy of an unsatisfactory childhood marked by deprivation or abuse at the hands of alcoholic–sociopathic parents or step-parents [7, 43]. Although it is clinically attractive to invoke the notion of “learned helplessness” secondary to such inescapable childhood traumata, an alternative hypothesis is that the pervasive negative cognitive set of these individuals might develop secondary to an inherited diathesis which biases one’s experiences in such a way as to recall life as a series of traumas. Indices of persistent CRF abnormality have also been described in such individuals [61]. As originally formulated in 1973 [62], the offspring of the affectively ill suffer from a double disadvantage – an inherited tendency to affective disorders, and adverse life experiences early in life due to parental assortative mating.

Table 4.2 Similarities of dysthymia to major depressive disorder*

Familial association
Phase advance of REM sleep
Diurnal variation
TRH-TSH
CRF
Major depressive course
Sleep deprivation response
Response to antidepressants
Treatment-emergent hypomania

* Summary of data reviewed in this chapter.

Table 4.2 summarizes the evidence reviewed in linking the phenomenology, course, and biology of dysthymia to major depressive disorders.

4.5

The Relationship of Subthreshold Depressions to MDD

4.5.1

Terminology

There has been increasing interest in the clinical relevance and public health significance of a variety of subthreshold depressions [8, 23, 24, 49, 60]. This terminology is now used broadly to refer not only to dysthymia, but otherwise “minor” and subsyndromal depressive symptoms typically measured in days and weeks. Minor depressions have fewer symptoms than DSM-IV major depression, but this must meet the mood change criterion. Subsyndromal depressive symptoms as defined by our group refer to few depressive symptoms in the absence of mood change [23]. Much of the subthreshold terrain involves intermittent depressive symptoms deemed to be “subclinical”. We have already addressed the fallacy of considering such dysthymia and related disorders as subclinical or otherwise “minor” [19]. We will expand on this thesis in the remainder of this chapter as we proceed with our narrative of the entire spectrum of subthreshold depressions. Henceforth we will refer to subsyndromal and subthreshold depressions generically as “SD”, unless we specifically refer to subsyndromal depressive symptoms (which we will refer to as “SD symptoms”).

4.5.2

SD in the Medical Setting

In their Medical Outcome Survey (MOS), Wells et al. [24], who studied more than 20 000 medical and mental health outpatients, drew attention to the public health importance of SD. The focus of this investigation was to systematically evaluate the psychosocial disability associated with medical and psychiatric diseases, which

had prompted these patients to seek help from the health care system. For the first time, the MOS provided an opportunity to compare self-reported psychosocial impairment associated with MDD, dysthymia, and SD with the impairment associated with other common medical conditions.

Epidemiologists and clinical scientists were intrigued to learn that disability associated with MDD significantly exceeded the disability associated with such common medical illnesses as hypertension, diabetes, arthritis, and gastrointestinal and lung diseases. Only the impairment associated with acute coronary artery disease consistently exceeded or equaled that of MDD. What was even more surprising, however, was the finding that SD – in patients whose depressions fell short of the criteria for major depression or dysthymia – was associated with significant psychosocial dysfunction and impairment in important domains of everyday function, even exceeding the disability associated with certain common medical conditions. This was the first credible empirical evidence indicating that SD was associated with “harmful dysfunction”, the criterion used to define when a condition should be considered as a clinically relevant disorder [63].

4.5.3

SD in the Community

In the early 1990s, other studies extended the MOS findings in community settings. Broadhead et al. [45] analyzed subjects ($n = 2890$) from one data collection site (Durham, NC) of the National Institutes of Mental Health (NIMH) Epidemiological Catchment Area (ECA) Program, a multicenter epidemiologic survey of the national prevalence of mental disorders in the United States. They found that subjects with “minor depression without mood disturbance” (i.e. SD symptoms) accounted for a disproportionate share, or 16% of all the disability days reported by the subjects in the previous month, and that 1.8% of subjects with SD symptoms developed an MDE within the next year. The research group at Columbia University [46], which conducted analyses on the *full* NIMH ECA database ($n = 18\,571$), reported a linear gradient of relative risk for negative outcome that was lowest in subjects with no depressive symptoms, significantly higher in subjects with SD symptoms, and highest among persons with major depressive and dysthymic level symptoms. They also reported that the lifetime prevalence of SD symptoms was substantially higher than the lifetime prevalence of major depression or dysthymia. Based on population-attributable risk, they also found greater service burden and psychosocial impairment to be associated with SD symptoms than with formal depressive disorders, primarily because of the higher prevalence of the SD symptoms. This same research group, again using the ECA data, searched for significant predictors of first onset of MDE within the next year [47]. They found that preexisting dysthymia and the presence of two or more lifetime SD were associated with a 5.5- and 4.4-fold greater risk, respectively, of developing MDD within the next year, compared to subjects with no depressive symptoms.

Analyses conducted at the University of California, San Diego, have confirmed and extended these findings through new analyses of clinical and community-based

samples. In the first study [23], psychosocial impairment was examined in three groups of subjects at the Los Angeles ECA site ($n = 2393$): subjects with major depression, subjects with SD symptoms, and subjects with no depressive disorders or symptoms. The SD group, compared to the no depressive symptoms group, had significantly higher levels of household strain, financial strain, and limitations in physical and job function. The SD group also had more restricted activity days in the prior month, more “bed days” in the previous month, and poorer health status. Given the functional impairment associated with SD symptoms over that of subjects without depressive symptoms, the functional impairment associated with SD symptoms in some cases equals that seen in MDD and underscored the need for additional investigation into the clinical relevance and public health importance of these symptoms.

4.5.4

SD in a Clinical MDD Sample

In a large clinical cohort, we next investigated MDD patients ($n = 373$) being followed in the NIMH Collaborative Depression Study (CDS), an ongoing prospective, naturalistic study of the course of affective disorders during and up to 20 years of follow-up. The goal of these analyses [64] was to examine psychosocial impairment and disability associated with all levels of depressive symptom severity in patients with MDD who had been prospectively followed for a mean of 10 years. Monthly levels of psychosocial functioning were analyzed using a global overall rating of psychosocial function and individual ratings of two important domains of everyday function: work/employment or household duties and relationship with spouse or partner. The results in this clinical cohort confirmed findings based on community respondents that the psychosocial disability associated with depression is pervasive and chronic and affects most areas of everyday function. Indeed psychosocial disability increased linearly in a significant step-wise fashion with each increment in the level of depressive symptom severity during the longitudinal course of illness.

As shown in Figure 4.2, we found that disability in MDD is state dependent, in that when SD was present, disability was always present; however, when patients were symptom-free (asymptomatic), disability decreased significantly and psychosocial function returned to good or very good levels. In other words, it is only when patients are truly asymptomatic that the disability associated with MDD was not detectable in these patients, although in comparison to asymptomatic controls there were small but significant differences in psychosocial function. In the MDD patients, as the severity of depressive symptoms increased, disability increased in parallel and in proportion. These analyses also demonstrated unequivocally that even a few depressive symptoms – below the diagnostic threshold for minor depression, dysthymia, or MDD – were associated with significant decrements involving major domains of psychosocial function, compared to times when the same patients were asymptomatic.

The foregoing analyses in a clinical cohort reinforce those from community settings: SD symptoms are associated with significant increases in psychosocial

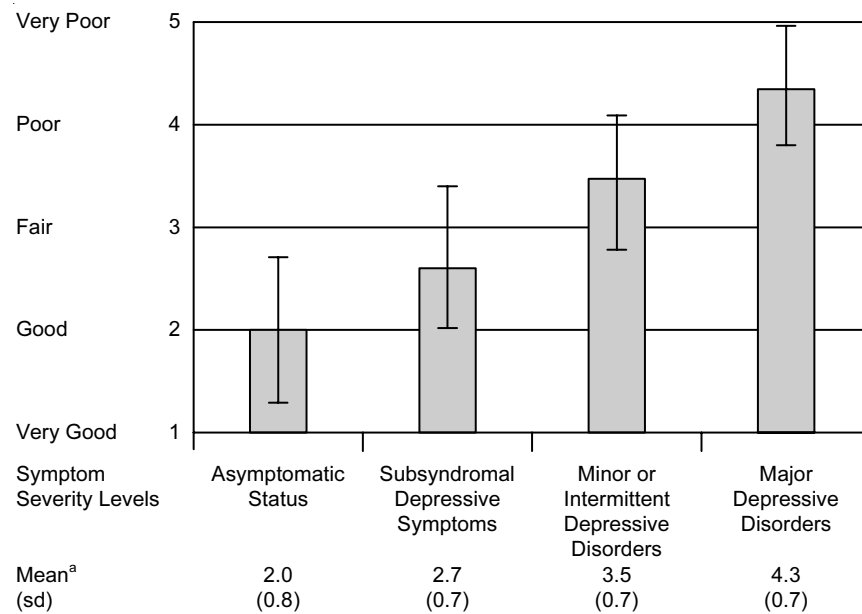


Figure 4.2 Relationship between depressive symptom severity and functional impairment in major depression. Ratings are on a scale where 1 = very good; 2 = good; 3 = fair; 4 = poor; 5 = very poor. Each step-wise increment in depressive symptom severity is associated with a significant increase in functional impairment ($P < 0.001$, two-tailed). Reprinted with permission from Judd et al. [64]

impairment. In the aggregate, these investigations have established that SD symptoms are not just a subclinical condition of interest but also have clinical disorder status, because they are consistently associated with the harmful dysfunction criterion used to define the clinical relevance or caseness of mental disorders.

4.5.5

SD and the Course of MDD

To further understand the clinical relevance of SD, it was necessary to undertake analyses in community subjects from three sites of the NIMH ECA Program ($n = 9160$). To remind the reader, in these analyses [65] SD symptoms were defined as two or more simultaneous symptoms of depression, present for most or all the time for at least 2 weeks, in individuals who did not meet criteria for major or minor depression or dysthymic disorder. Using this definition, it was found that SD symptoms had a 1-year prevalence in the general population of 8.4%, two-thirds of whom were women. The most common symptoms were: insomnia, pervasive fatigue, recurrent thoughts of death and dying, and psychomotor slowing. The total number of the symptoms varied considerably from subject to subject – ranging from two to seven symptoms – but still did not meet the criteria for major

or minor depression. There was a qualitative similarity between the symptoms reported by SD subjects and symptoms reported by subjects with MD, which suggested continuity between SD and MDD. The main difference (by definition) between the two was absence of the “A criterion” symptom of 2 weeks’ depressed mood or anhedonia, which is the “pathognomonic” symptom necessary for the diagnosis of DSM-IV MDD.

In the absence of longitudinal clinical course data, several possible outcomes for SD symptoms were hypothesized. First, SD symptoms may be evanescent and self-limited and remit spontaneously over time. Second, SD symptoms could be a prodrome for future episodes of major depression or dysthymia. Third, SD symptoms may represent an incomplete recovery from fully-fledged clinical episodes of MDD. Fourth, SD symptoms may be relatively stable, existing in a chronic state in which low-grade symptoms smolder over the years and never emerge as syndromal disorders.

In collaboration with Sherbourne et al. [66], another set of analyses was conducted to further examine the clinical relevance of SD symptoms in MOS outpatients. Patients with current MDD or dysthymia were compared to patients with SD symptoms and to a control group of hypertensive patients with and without depression. The SD symptom patients resembled patients with MDD or dysthymic disorder much more closely than they did non-depressed patients; patients with hypertension with SD symptoms were more similar to MDD or dysthymic patients than to non-depressed patients with hypertension. Of the SD symptom patients, 41% had a history of MDD in their families (comparable to MDD patients, of whom 59% had family histories of depression). The two depressive patient groups also had similar types and levels of psychiatric comorbidities, especially anxiety disorders. Treatment rates for SD symptoms in the medical sector were substantially lower than in the mental health sector. The conclusion was that SD symptoms are a clinically relevant variant of affective disorders.

Our group at the University of California subsequently initiated another series of analyses [48] on the NIMH ECA community subjects ($n = 10\,526$) that reported a 1-month point prevalence of depressive disorders and SD symptoms in the general population of 10%, broken down into 2.3% MDD, 2.3% dysthymic disorder, 1.5% minor depressive disorder, and 3.9% SD. There was a higher 1-month point prevalence of SD symptoms in the community than for MDD, dysthymia, or minor depression. There appeared to be two classes of SD symptoms in the community sample: SD symptoms that occurred as an integral component of the ongoing course of MDD and SD symptoms that occurred spontaneously in non-syndromally depressed subjects in the general population. In the first instance, we hypothesized that SD symptoms may be prodromal to episodes of minor or major depression or else residual to resolving syndromal episodes. Subjects with current SD symptoms also had a significantly higher rate of past MDEs. It is worthy of note that SD symptoms were associated with elevated lifetime prevalence of suicide attempts. What was most revealing, however, was that when surveyed diagnostically 1 year later, patients with depressive disorders and symptoms identified at intake into the study, had undergone a great degree of change in depressive diagnoses (Table 4.3).

Table 4.3 Prospective follow-up of depressive subtypes in the community*

At 1 month (%) Depressive disorders at wave I	1-Year incidence (%) of depressive disorders At wave II 1 year later: ECA 3 site sample; (n = 7866)		
	Major depression (n = 201)	Minor depression/ Dysthymia (n = 133)	Sub- syndromal (n = 350)
Major depression (n = 253)	28%	15%	13%
Minor depression (n = 164)	6%	17%	20%
Subsyndromal depressive symptoms (n = 449)	4%	10%	17%

* Reprinted with permission from Judd et al. [48].

Subjects who began the year in one “diagnostic category” of depression frequently ended the follow-up year in another “category”. For example, 5% of the SD symptom subjects met the criteria for minor depression 1 year later, and 3% met the criteria for major depression. Only 28% of the subjects with a diagnosis of MDD at intake continued to meet criteria for MDD by the year’s end, whereas 15% experienced a reduction in their symptoms so that they met criteria for minor depression, and 20% decreased their symptoms to the point where they fell into the SD symptom category. From these data, we concluded that the typical symptomatic course of unipolar MDD is more changeable than previously believed. The course was characterized by a remarkable degree of fluctuation in depressive symptom severity, in which the same subject experiences multiple levels of symptom severity as symptoms wax and wane over time.

These observations were supported and further amplified by a Consensus Conference [3], with the participation of several of the world authorities on the study of depressive illness. The conclusion of the conference was that unipolar MDD is a pleomorphic disorder that consists of a cluster of depressive subtypes which exist in a relatively homogeneous symptomatic clinical continuum, extending from SD symptoms through minor depression to major depression. Unipolar depressive subtypes could thus be conceptualized as alternative forms or levels of depressive symptom severity occurring within the same MDD patient. As Winokur [67] postulated, although MDD might be heterogeneous in etiology, the clinical phenotype seems to be symptomatically homogenous, with patients moving from one subtype or spectrum severity level to another across time. In other words, depression is best conceptualized as a “final common pathway” [62].

At this point, we decided that there was need for a detailed longitudinal study of the course of MDD, because many of the observations regarding SD symptoms had been made in the community and the general medical sector. We again turned to the NIMH CDS. In an investigation [50] of their weekly depressive symptom severity levels during an average of 8.7 years of follow-up, we found that 431 CDS patients with unipolar MDD were symptomatically ill with depressive symptoms

for 59% of the weeks during follow-up. Symptom severity levels changed frequently within the same patient, and most patients experienced symptoms at each level of severity (i.e. major, minor, and subsyndromal depressive symptoms) during their course of illness. It was particularly noteworthy that, in the aggregate, patients experienced symptoms at the MDD level only during 15% of the follow-up weeks, whereas they had symptoms at the minor depressive and dysthymic level during 27% of the follow-up weeks and SD symptoms during 17% of the follow-up weeks. Subthreshold depressions at minor, dysthymic, or subsyndromal levels, taken together, were observed longitudinally three times more frequently (43% of the follow-up weeks) than symptoms at the syndromal MDD level (15% of the follow-up weeks). The frequent fluctuation of the full range of symptom severity levels occurring within the same MDD patient indicates that the symptomatic course of MDD is expressed longitudinally as a dimensional illness, consistent with the views of Kendler and Gardner [68] based on genetic twin data.

Cumulatively, the studies reviewed herein show that MDD is typically expressed over time by fluctuating symptom severity levels, in which the depressive subtypes described in the official diagnostic nomenclature – with the possible exception of the psychotic subtype [69] – do not represent discrete disorders but rather are stages along a dimensional continuum of symptomatic severity [3]. Depressive symptoms at the major, minor, dysthymic, and subsyndromal levels are commonly observed within the same patient followed across time. Such data indicate that all levels of depressive symptom severity are integral components of the longitudinal symptomatic picture of MDD, with each symptom severity level being a different phase of illness intensity, activity, and severity. The symptomatic course of MDD tends to be chronically relapsing, with patients being symptomatic for approximately 60% of the course of their illness, much of this at the subthreshold severity levels. The overall course of MDD consists of symptomatic phases of illness of varying levels of severity, which are interspersed with inactive phases, when MDD patients are asymptomatic and in remission. Sleep EEG studies [4, 7, 70, 71] have confirmed the persistence of shortened REM latency and related neurophysiologic indices of depression across the severity spectrum described herein. This means that the presence of SD symptoms is indicative of ongoing active disease at the biological level.

4.6

Residual Depressive Symptoms as Risk Factors for MDD Relapse

After demonstrating that unipolar MDD is a chronic relapsing disorder rather than an illness with discrete episodes, there was a need to identify risk factors for early episode relapse and to develop new treatment strategies that will prevent relapse or recurrence. In prior studies the authors had observed that SD symptoms were present during prodromal periods before MDE onset, which suggests that the same symptoms could also serve as risk factors associated with relapse after an MDE. To test this hypothesis, we investigated the role of the recovery status (i.e. residual SD

versus asymptomatic recovery) in CDS patients after resolution of their index unipolar MDE [72]. Using survival analysis methods, patients with residual SD symptom recovery ($n = 82$) versus asymptomatic recovery ($n = 155$) were compared during this first well interval on the time to their next episode relapse/recurrence. They were also compared on antidepressant treatment and the presence of comorbid mental disorders during their first well interval. Relapse to an MDE was three times faster in the residual SD recovery group than in the asymptomatic recovery group (median = 68 vs. 231 weeks respectively; $P < 0.001$). Further analyses showed that these striking differences in time to MDE relapse could not be attributed to less intense antidepressant medication treatment or to comorbid mental disorders during the first well interval.

We then compared their relapse risk factor based on level of recovery with another powerful risk factor previously reported in the CDS by Keller et al. [73] namely, past history of more than three recurrent MDEs. In our analyses [72], a history of three or more MDEs was significantly associated with early relapse, but only in the asymptomatic recovery group (median = 79 vs. 224 weeks respectively; $P < 0.0001$). A history of recurrent MDEs had a negligible non-significant effect on time to episode relapse in the residual SD symptom recovery group, in which the survival curves of the two SD recovery groups were virtually identical. Using a Cox Proportional Hazard Model, with which it is possible to quantify the strength of one relapse factor while controlling for the effect of the other, we found that after controlling for the effect of recurrent MDE history, SD recovery patients were 368% more likely to relapse during any given follow-up week than asymptomatic-recovery patients. In contrast, after controlling for the MDE recovery factor, the effect of a history of more than three MDEs increased the likelihood of relapse by only 64%. This finding established that residual SD recovery is one of the most powerful factors associated with early relapse reported to date. The fact that the residual SD symptom recovery is associated with such rapid episode relapse also strongly reinforces the idea that SD symptoms represent a clinically important and active state of MDD illness.

Building on the previous study, we further examined MDD patients who experienced their first lifetime MDE [74]. The first-episode cohort was divided into persons who recovered from the first MDE with residual SD symptoms ($n = 82$) versus asymptomatic recovery ($n = 155$). The number of weeks of the first well interval before relapse to the next subsequent depressive episode of any type (MDE, minor depression, dysthymia) was then subjected to survival analyses. Other course measures were compared, including the percentage of future weeks that patients were symptomatic, percentage of patients who were episode free during follow-up, number and type of future depressive episodes, number of chronic MDEs (> 2 years), and duration of inter-episode well intervals. Time to the next MDE relapse was more than three times faster for the residual SD symptom recovery group versus the asymptomatic recovery patients (103 vs. 384 weeks, respectively; $P = 0.0001$). These results are illustrated in Figure 4.3. The number of weeks to the next depressive episode of any type (i.e. MDE, minor depression, or dysthymia) was more than 12 times greater for SD symptom recovery patients (23 vs. 288 weeks,

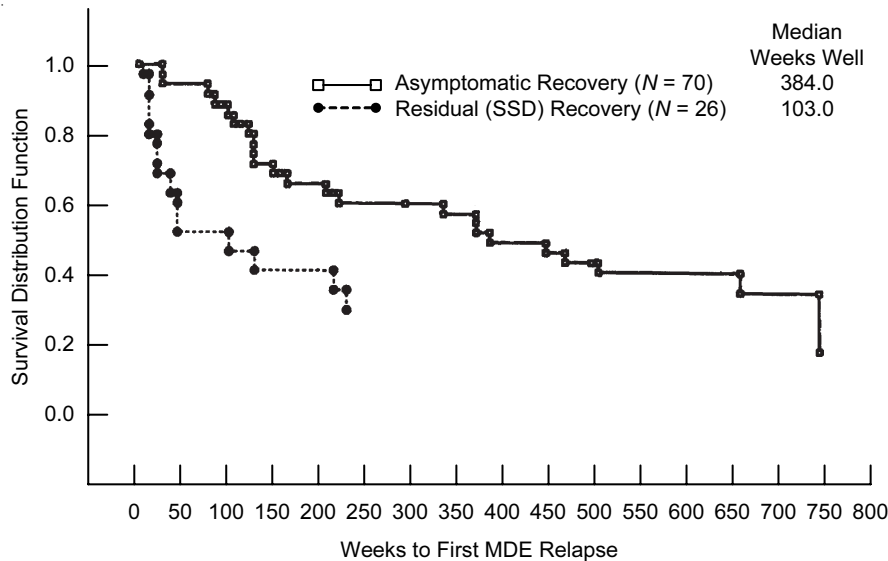


Figure 4.3 Graph showing the relationship between prediction of latency and relapse in the first major depressive episode as a function of residual symptoms. Wilcoxon Chi Square Test of Difference = 16.52; $P = 0.0001$. Odds ratio for risk of major depressive episode relapse/recurrence over all weeks of the follow-up for residual SSD versus asymptomatic recovery groups = 2.3 (95% confidence interval = 1.30–4.26). Reprinted with permission from Judd et al. [74]

respectively; $P = 0.0001$). Overall, SD symptom recovery patients had 2.35-fold higher odds of relapse to some type of depressive episode during any given week of follow-up. The SD recovery patients had significantly fewer asymptomatic weeks (31.8% of follow-up weeks) to the end of follow-up than those with asymptomatic recovery (78.7% of follow-up weeks; $P = 0.001$). More than one-third (34%) of individuals with asymptomatic recovery were episode-free, whereas only 7.7% of individuals with residual SD symptom recovery remained free of any future episodes. Reciprocally, SD symptom recovery was associated with significantly more depressive episodes of all types during the follow-up course, including more minor depressive episodes ($P = 0.005$) and more chronic MDEs (i.e. > 2 years duration; $P = 0.025$). Moreover, the inter-episode well intervals for residual SD recovery subjects were seven times shorter for residual SD than for asymptomatic recovery (median = 22 vs. 154 weeks, respectively; $P = 0.0001$).

The body of work reviewed in this chapter highlights the importance of ongoing residual SD symptoms after MDE recovery by showing that incomplete recovery, even after the first lifetime MDE, is associated not only with faster relapse but also with a more chronic and severe overall prospective course of illness. Early episode relapse associated with SD symptom recovery seems to be the first step leading to a more severe relapsing and chronic course in the future. These findings were not

attributable to a significantly lower antidepressant treatment or to increased comorbidity of mental disorders and substance abuse during the well interval. This means that ongoing SD symptoms after MDE “remission” indicates that the episode has not remitted but rather is still active, has not in reality fully resolved, and that the patient is at risk for early relapse. Such data support the idea that MDE recovery should be defined by the complete abatement of symptoms before an MDE is judged to be fully remitted. Such a conclusion is buttressed by neurophysiologic data [4].

4.7

Concluding Remarks

Epidemiologic and clinical evidence has accumulated during the last quarter century establishing that dysthymic and oligosymptomatic depressions of a subthreshold nature have high prevalence in the general population and in clinically depressed patient cohorts studied in cross-section or followed longitudinally. The clinical relevance and public health importance of these conditions were confirmed by various investigations, including our own at the University of California, San Diego. These subthreshold conditions are associated with a significant impairment of psychosocial function when compared to no depressive symptoms. There is strong evidence that all levels of depressive symptom severity of MDD are associated with high psychosocial impairment, which increases significantly and linearly with each increment in the level of symptom severity. It is only when MDD patients are completely symptom-free that psychosocial function returns to normal. Disability is present when even a few symptoms are detected (i.e. SD symptoms, in the absence of low mood *per se*). There is strong evidence during the long-term course of illness that major, minor, dysthymic, and subsyndromal symptoms wax and wane within the same patient and that these symptomatic periods are interspersed in the overall course with times when patients are remitted and symptom free. The modal longitudinal symptom status of MDD patients involves primarily subthreshold depressive symptoms, which are much more common than symptoms at the syndromal MDE level. The longitudinal systematic examination of the clinical relevance and high prevalence of subthreshold depressive symptoms helped establish the fact that the long-term symptomatic expression of MDD is dimensional, not categorical, in nature. As stated earlier, such a clinical continuum does not rule out the distinct possibility of underlying neurobiological heterogeneity.

The relationship of MDD to bipolar disorder is beyond the scope of this chapter. Given the broadened current definition of bipolarity [75], it is likely that the Depressive Spectrum described in this chapter overlaps with the soft bipolar spectrum [76]. There also exists emerging evidence to indicate that depressive mixed states represent a common thread between unipolar and bipolar II disorders [77]. Some authorities further envision depressive states as the common feature between “unipolar” and “bipolar” disorders [78]. Genetic commonalities between unipolar and bipolar disorders represent a “hot” area of research today [79]. Interestingly, current genetic models involve a spectrum of phenotypes, including “tempera-

ments” among the clinically “well” relatives of probands. This chapter has limited itself to subthreshold conditions distal to temperament in the pathogenetic chain.

Abatement of subthreshold depressive symptoms is of fundamental importance in defining full remission or recovery from MDEs. Ongoing residual symptoms during the recovery periods after an MDE are associated with psychosocial disability, more rapid MDE relapse, and a more severe chronic future course of illness, all of which indicate that when residual symptoms are present the MDE has not fully remitted and the disease is still active. When all depressive symptoms of an MDE abate for a minimum of 8 weeks, then full remission has been achieved. MDE remission defined in this way is associated with significant delay or even prevention of future episode relapse and a less severe, relapsing, and chronic future course. We believe that the research reviewed in this chapter provides a new paradigm in the progression of clinical depression through various overlapping stages of severity, which begin at the seemingly “subclinical” level of depressive symptoms. This conceptualization in turn suggests a public health approach, which emphasizes the treatment of MDD even at the deceptively mild levels of subthreshold symptoms. This approach has already been successfully applied to dysthymic (i.e. chronic subthreshold) depressions [22, 29, 80]. It still remains a challenge for other oligosymptomatic depressions (i.e. those with few intermittent depressive symptoms of subchronic or shorter duration, or those without mood change). Given the persistent risk of chronicity of depressive disorders [81], the paradigm described in this chapter embodies the current recommendation to provide continuous somatic and psychosocial treatments for these disorders.

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References

- 1 KENDALL, R. E., The classification of depressions: a review of contemporary confusion. *Br. J. Psychiatry* **1976**, *129*, 15–28.
- 2 PARKER, G., Classifying depression: should paradigms lost be regained? *Am. J. Psychiatry* **2000**, *157*, 1195–1203.
- 3 JUDD, L. L., Pleomorphic expressions of unipolar depressive disease: summary of the 1996 CINP President’s Workshop. *J. Affect Disord.* **1997**, *45*, 109–116.
- 4 AKISKAL, H. S., JUDD, L. L., GILLIN, J. C., LEMMI, H., Subthreshold depressions: clinical and polysomnographic validation of dysthymic, residual and masked forms. *J. Affect Disord.* **1997**, *45*, 53–63.
- 5 AKISKAL, H. S., BITAR, A. H., PUZANTIAN, V. R., ROSENTHAL, T. L., WALKER, P. W., The nosological status of neurotic depression: a prospective three-to-four year examination in light of the primary–secondary and unipolar–bipolar dichotomies. *Arch. Gen. Psychiatry* **1978**, *35*, 756–766.
- 6 BRONISCH, T., WITTCHEN, H. U., KRIEG, C., RUPP, H. U., VON ZERSSEN, D.,

- Depressive neurosis: a long-term prospective and retrospective follow-up study of former inpatients. *Acta Psychiatr. Scand.* **1985**, *71*, 237–248.
- 7 AKISKAL, H. S., ROSENTHAL, T. L., HAYKAL, R. F., LEMMI, H., ROSENTHAL, R. H., SCOTT-STAUB, A., Characterological depressions: Clinical and sleep EEG findings separating “subaffective dysthymias” from “character-spectrum” disorders. *Arch. Gen. Psychiatry* **1980**, *37*, 777–783.
 - 8 AKISKAL, H. S., Subaffective disorders: dysthymic, cyclothymic, and bipolar II disorders in the “borderline” realm. *Psychiatr. Clin. North Am.* **1981**, *4*, 25–46.
 - 9 BERGER, M., LUND, R., BRONISCH, T., VON ZERSEN, D., REM latency in neurotic and endogenous depression and the cholinergic REM induction test. *Psychiatry Res.* **1983**, *10*, 113–123.
 - 10 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manuals*, 3rd ed. Washington, DC: American Psychiatric Press, **1980**.
 - 11 KELLER, M. B., SHAPIRO, R. W., Double depression: superimposition of acute depressive episodes on chronic depressive disorders. *Am. J. Psychiatry* **1982**, *139*, 438–442.
 - 12 KENDLER, K. S., NEALE, M. C., KESSLER, R. C., et al., A population-based twin study of major depression in women: the impact of varying definitions of illness. *Arch. Gen. Psychiatry* **1992**, *49*, 257–266.
 - 13 MAIER, W., LICHTERMANN, D., MINGES, J., HEUN, R., HALLMAYER, J., The risk of minor depression in families of probands with major depression: sex differences and familiarity. *Eur. Arch. Psychiatry Clin. Neurosci.* **1992**, *242*, 89–92.
 - 14 JUDD, L. L., AKISKAL, H. S., Delineating the longitudinal structure of depressive illness: beyond clinical subtypes and duration thresholds. *Pharmacopsychiatry* **2000**, *33*, 3–7.
 - 15 KRAEPELIN, E., *Manic-depressive Insanity and Paranoia*. Edinburgh: E & S Livingstone, **1921**.
 - 16 WENDER, P. H., KETY, S. S., ROSENTHAL, D., SCHULSINGER, F., ORTMANN, J., LUNDE, I., Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Arch. Gen. Psychiatry* **1986**, *43*, 923–929.
 - 17 LEWIS, A. J., Melancholia: A clinical survey of depressive states. *J. Ment. Sci.* **1934**, *80*, 277–378.
 - 18 ROTH, M., Depressive states and their borderlands: classification, diagnosis and treatment. *Compr. Psychiatry* **1960**, *1*, 135–155.
 - 19 AKISKAL, H. S., WEISE, R. E., The clinical spectrum of so-called “minor” depressions. *Am. J. Psychother.* **1992**, *46*, 9–22.
 - 20 WORLD HEALTH ORGANIZATION. *The ICD-10 Classification of Mental and Behavioural Disorders*. Geneva: World Health Organization, **1992**.
 - 21 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV). Washington, DC: American Psychiatric Association, **2000**.
 - 22 AKISKAL, H. S., CASSANO, G. B. (Eds.), *Dysthymia and the Spectrum of Chronic Depressions*. New York: Guilford Press, **1997**.
 - 23 JUDD, L. L., RAPAPORT, M. H., PAULUS, M. P., BROWN, J. L., Subsyndromal symptomatic depression (SSD), a new mood disorder? *J. Clin. Psychiatry* **1994**, *55* (Suppl.), 18–28.
 - 24 WELLS, K., STEWARD, S., HAYS, R., BURNAM, M. A., ROGERS, W., DANIELS, M., BERRY, S., GREENFIELD, S., WARE, J., The functioning and well being of depressed patients: results from the Medical Outcomes Study. *JAMA* **1989**, *262*, 914–919.
 - 25 FAVA, G. A., KELLNER, R., Prodromal symptoms in affective disorders. *Am. J. Psychiatry* **1991**, *148*, 823–830.
 - 26 AKISKAL, H. S., Dysthymic disorder. Psychopathology of proposed chronic depressive subtypes. *Am. J. Psychiatry* **1983**, *140*, 11–20.
 - 27 AKISKAL, H. S., Dysthymia and cyclothymia in psychiatric practice a century after Kraepelin. *J. Affect Disord.* **2001**, *62*, 17–31.
 - 28 JUDD, L. L., SCHETTLER, P. J., AKISKAL, H. S., The prevalence, clinical relevance, and public health significance of sub-threshold depressions. *Psychiatr. Clin. North Am.* **2002**, *25*, 685–698.

- 29 HAYKAL, R., AKISKAL, H. S., The long-term outcome of dysthymia in private practice: clinical features, temperament, and the art of management. *J. Clin. Psychiatry* **1999**, *60*, 508–518.
- 30 WEISSMAN, M. M., LEAF, P. J., BRUCE, M. L., FLORIO, L., The epidemiology of dysthymia in five communities: rates, risks, comorbidity, and treatment. *Am. J. Psychiatry* **1988**, *145*, 815–819.
- 31 PERUGI, G., AKISKAL, H. S., MUSETTI, L., SIMONINI, E., CASSANO, G. B., Social adjustment in panic-agoraphobic patients reconsidered. *Br. J. Psychiatry* **1994**, *164*, 88–93.
- 32 WPA DYSTHYMIA WORKING GROUP. Dysthymia in clinical practice. *Br. J. Psychiatry* **1995**, *166*, 174–183.
- 33 LICINIO, J., PRILPKO, I., BOLIS, C. L. (Eds.). *Dysthymia in Neurological Disorders*. Proceedings of the WHO Meeting. Geneva: World Health Organization, **1997**.
- 34 BRIEGER, P., MARNEROS, A., Dysthymia and cyclothymia: historical origins and contemporary development. *J. Affect Disord.* **1997**, *45*, 117–126.
- 35 SCHNEIDER, K., *Psychopathic Personalities*. Springfield, IL: Charles, C., Thomas, **1958**.
- 36 TELLENBACH, H., *Melancholia*. Pittsburgh, PA: Duquesne University Press, **1980**.
- 37 PLACIDI, G. F., SIGNORETTA, S., LIGUORI, A., GERVASI, R., MAREMMANI, I., AKISKAL, H. S., The semi-structured affective temperament interview (TEMPS-1), reliability and psychometric properties in 1010 14–26-year-old students. *J. Affect Disord.* **1998**, *47*, 1–10.
- 38 KASAHARA, Y., The practical diagnosis of depression in Japan. In: FEIGHNER, J. P., BOYER, W. F. (Eds.), *The Diagnosis of Depression*. Chichester, UK: Wiley and Sons, **1991**, pp. 163–175.
- 39 KRETSCHMER, E., *Physique and Character*. London, UK: Kegan, Paul, Trench, Trubner and Co. Ltd, **1936**.
- 40 KRAUS, A., Role performance, identity structure and psychosis in melancholic and manic depressive patients. In: Mundt, C. H. (Ed.), *Interpersonal Factors in the Origin and Course of Affective Disorders*. London, UK: Gaskell, **1996**, pp. 31–64.
- 41 POSSL, J., VON ZERSSEN, D., A case history analysis of the “manic type” and the “melancholic type” of premorbid personality in affectively ill patients. *Eur. Arch. Psychiatry Neurol. Sci.* **1990**, *239*, 347–355.
- 42 AKISKAL, H. S., Dysthymia as a temperamental variant of affective disorder. *Eur. Psychiatry* **1996**, *11* (Suppl. 3), 117s–122s.
- 43 ROSENTHAL, T. L., AKISKAL, H. S., SCOTT-STAUB, A., ROSENTHAL, R. H., DAVID, M., Familial and developmental factors in characterological depressions. *J. Affect Disord.* **1981**, *3*, 183–192.
- 44 KOVACS, M., AKISKAL, H. S., GATSONIS, C., PARRONE, P. L., Childhood-onset dysthymic disorder: clinical features and prospective naturalistic outcome. *Arch. Gen. Psychiatry* **1994**, *51*, 365–374.
- 45 BROADHEAD, W. E., BLAZER, D. G., GEORGE, L. K., TSE, C. K., Depression, disability days and days lost from work in a prospective epidemiologic survey. *JAMA* **1990**, *264*, 2524–2528.
- 46 HOWARTH, E., JOHNSON, J., KLERMAN, G. L., WEISSMAN, M. M., Depressive symptoms as relative and attributable risk factors for first-onset major depression. *Arch. Gen. Psychiatry* **1992**, *49*, 817–823.
- 47 JOHNSON, J., WEISSMAN, M. M., KLERMAN, G. L., Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA* **1992**, *267*, 1478–1483.
- 48 JUDD, L. L., AKISKAL, H. S., PAULUS, M. P., The role and clinical significance of subsyndromal depressive symptoms in unipolar major depressions. *J. Affect Disord.* **1997**, *45*, 5–18.
- 49 ANGST, J., MERIKANGAS, K., The relationship between major and subthreshold variants of unipolar depression. *J. Affect Disord.* **1997**, *45*, 31–40.
- 50 JUDD, L. L., AKISKAL, H. S., MASER, J. D., ZELLER, P. J., ENDICOTT, J., CORYELL, W., PAULUS, M. P., KUNOVAC, J. L., LEON, A. C., MUELLER, T. I., RICE, J. A., KELLER, M. B., A prospective 12-year study of subsyndromal and syndromal depressive symptomatology in unipolar major depressive disorders. *Arch. Gen. Psychiatry* **1998**, *55*, 694–700.
- 51 REMICK, R. A., SADOVNICK, A. D., LAM, R. W., ZIS, A. P., YEE, I. M., Major depression, minor depression, and

- double depression: are they distinct clinical entities? *Am. J. Med. Genet.* **1996**, *67*, 347–353.
- 52 AKISKAL, H. S., Dysthymia: clinical and external validity. *Acta Psychiatr. Scand.* **1994**, *89* (Suppl. 383), 19–23.
 - 53 AKISKAL, H. S., LEMMI, H., DICKSON, H., KING, D., YEREVANIAN, B., VAN VALKENBURG, C., Chronic depressions. Part 2. Sleep EEG differentiation of primary dysthymic disorders from anxious depressions. *J. Affect Disord.* **1984**, *6*, 287–295.
 - 54 HOWLAND, R. H., THASE, M. E., Biological studies of dysthymia. *Biol. Psychiatry* **1991**, *30*, 283–304.
 - 55 RIHMER, Z., Dysthymia: a clinician's perspective. In: BURTON, S., AKISKAL, H. S. (Eds.), *Dysthymic Disorder*. London, UK: Royal College of Psychiatrists, **1990**, pp. 112–125.
 - 56 KLEIN, D. N., RISO, L. P., DONALDSON, S. K., SCHWARTZ, J. E., ANDERSON, R. L., OUIMETTE, P. C., LIZARDI, H., ARONSON, T. A., Family study of early-onset dysthymia. Mood and personality disorders in relatives of outpatients with dysthymia and episodic major depression and normal controls. *Arch. Gen. Psychiatry* **1995**, *52*, 487–496.
 - 57 GILES, D. E., KUPFER, D. J., ROFFWARG, H. P., Polysomnographic parameters in first-degree relatives of unipolar probands. *Psychiatr. Res.* **1988**, *27*, 127–136.
 - 58 KRIEG, J. C., LAUER, C. J., SCHREIBER, W., MODELL, S., HOLLSBOER, F., Neuroendocrine, polysomnographic and psychometric observations in healthy subjects at high familial risk for affective disorders: the current state of the "Munich vulnerability study". *J. Affect Disord.* **2001**, *62*, 33–37.
 - 59 CATALAN, R., GALLART, J. M., CASTELLANOS, J. M., GALARD, R., Plasma corticotrophin-releasing factor in depressive disorders. *Biol. Psychiatry* **1998**, *44*, 15–20.
 - 60 AKISKAL, H. S., BOLIS, C. L., CAZZULLO, C., COSTA E SILVA, J. A., GENTIL, V., LECRUBIER, Y., LICINIO, J., LINDEN, M., LOPEZ-IBOR, J. J., NDIAYE, I. P., PANI, L., PRILIPKO, L., ROBERTSON, M. M., ROBINSON, R. G., STARKSTEIN, S. E., THOMAS, P., WANG, Y., WONG, M. L., Dysthymia in neurological disorders. *Mol. Psychiatry* **1996**, *1*, 478–491.
 - 61 HEIM, C., NEWPORT, D. J., HEIT, S., GRAHAM, Y. P., WILCOX, M., BOSALL, R., MILLER, A. H., NEMEROFF, C. B., Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* **2000**, *284*, 592–597.
 - 62 AKISKAL, H. S., MCKINNEY, W. T., Depressive disorders: toward a unified hypothesis. *Science* **1973**, *182*, 20–29.
 - 63 WAKEFIELD, J. C., Disorder as harmful dysfunction: a conceptual critique of DSM-111-R's definition of a mental disorder. *Psychol. Rev.* **1992**, *99*, 232–217.
 - 64 JUDD, L. L., AKISKAL, H. S., ZELLER, P. H., PAULUS, M., LEON, A. C., MASER, J. D., ENDICOTT, J., CORYELL, W., KUNOVAC, J. L., MUELLER, T. I., RICE, J. P., KELLER, M. B., Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch. Gen. Psychiatry* **2000**, *57*, 375–380.
 - 65 JUDD, L. L., PAULUS, M. P., WELLS, K. B., RAPAPORT, M. H., Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *Am. J. Psychiatry* **1996**, *153*, 1411–1417.
 - 66 SHERBOURNE, C. D., WELLS, K. B., HAYS, R. D., ROGERS, W., BURNAM, M. A., JUDD, L. L., Subthreshold depression and depressive disorder: clinical characteristics of general medical and mental health specialty outpatients. *Am. J. Psychiatry* **1994**, *151*, 1777–1784.
 - 67 WINOKUR, G., All roads lead to depression: clinically, homogenous, etiologically heterogeneous. *J. Affect Disord.* **1997**, *45*, 97–108.
 - 68 KENDLER, K. S., GARDNER, C. O. JR., Boundaries of major depression: an evaluation of DSM-IV criteria. *Am. J. Psychiatry* **1998**, *155*, 172–177.
 - 69 CORYELL, W., Do psychotic, minor and intermittent depressive disorders exist on a continuum? *J. Affect Disord.* **1997**, *45*, 75–83.
 - 70 AKISKAL, H. S., LEMMI, H., YEREVANIAN, B., KING, D., BELLUOMINI, J., The utility of the REM latency test in psychiatric diagnosis: a study of 81 depressed outpatients. *Psychiatry Res.* **1982**, *7*, 101–110.

- 71 AKISKAL, H. S., KING, D., ROSENTHAL, T. L., ROBINSON, D., SCOTT-STAUBS, A., Chronic depressions. Part 1. Clinical and familial characteristics in 137 probands. *J. Affect Disord.* **1981**, 3, 297–315.
- 72 JUDD, L. L., AKISKAL, H. S., MASER, J. D., ZELLER, P. J., ENDICOTT, J., CORYELL, W., PAULUS, M. P., KUNOVAC, J. L., LEON, A. C., MUELLER, T. I., RICE, J. A., KELLER, M. B., Major depressive disorder: a prospective study of residual sub-threshold depressive symptoms as predictor of rapid relapse. *J. Affect Disord.* **1998**, 50, 97–108.
- 73 KELLER, M. B., LAVORI, P. W., RICE, J., CORYELL, W., HIRSCHFELD, R. M., The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. *Am. J. Psychiatry* **1986**, 143, 24–28.
- 74 JUDD, L. L., PAULUS, M. P., SCHETTLER, P. J., AKISKAL, H. S., ENDICOTT, J., LEON, A. C., MASER, J. D., MUELLER, T., SOLOMON, D. A., KELLER, M. B., Does incomplete recovery from first lifetime Major Depressive Episode herald a chronic course of illness? *Am. J. Psychiatry* **2000**, 157, 1501–1504.
- 75 AKISKAL, H. S., BOURGEOIS, M. L., ANGST, J., POST, R., MOLLER, H., HIRSCHFELD, R., Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J. Affect Disord.* **2000**, 59 (Suppl. 1), S5–S30.
- 76 AKISKAL, H. S., The bipolar spectrum – the shaping of a new paradigm in psychiatry. *Curr. Psychiatry Rep.* **2002**, 4, 1–3.
- 77 AKISKAL, H. S., BENAZZI, F., Family history validation of the bipolar nature of depressive mixed states. *J. Affect Disord.* **2003**, 73, 113v122.
- 78 JOFFE, R. T., YOUNG, L. T., MACQUEEN, G. M., A two-illness model of bipolar disorder. *Bipolar Disord.* **1999**, 1, 25–30.
- 79 KELSOE, J. R., Arguments for the genetic basis of the bipolar spectrum. *J. Affect Disord.* **2003**, 73, 183–197.
- 80 DE LIMA, M. S., HOTOPH, M., WESSELY, S., The efficacy of drug treatments for dysthymia: a systematic review and meta-analysis. *Psychol. Med.* **1999**, 29, 1273–1289.
- 81 KELLER, M. B., LAVORI, P. W., RICE, J., CORYELL, W., HIRSCHFELD, R. M., The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. *Am. J. Psychiatry* **1986**, 143, 24–28.

5 The Monoamine Hypothesis of Depression

Leslie Iversen

Abstract

The discovery that the first effective antidepressant drugs acted by boosting monoamine function in the brain led to an extensive search for the hypothetical defect in monoamine function that might underlie depression. Measurements of the monoamine metabolites 5-hydroxyindoleacetic acid (from serotonin), 3-methoxy-4-hydroxy-phenylglycol (from noradrenaline) and homovanillic acid (from dopamine) in urine and cerebrospinal fluid (CSF), however, failed to reveal any consistent abnormalities in depression. Nor were there any consistent alterations in the turnover rates of the cerebral monoamines as measured by the probenecid technique, in which the accumulation of metabolites in CSF was measured after blocking their egress with probenecid. Several of these studies did suggest, however, that a subgroup of depressed patients may exhibit abnormally low rates of turnover of serotonin and dopamine. Neurochemical studies of post-mortem brain samples from depressed subjects or imaging studies in live patients failed to reveal significant alterations in monoamines, monoamine transporters or monoamine receptors.

Inhibition of noradrenaline or serotonin biosynthesis in depletion studies did, however, have positive results. Although such procedures failed to cause normal people to become depressed, they had a clear and immediate effect in blocking the effectiveness of antidepressant drugs. Attempts to boost monoamine function by administering precursor amino acids, on the other hand, did not have any obvious antidepressant effect, although there were claims that the serotonin precursor L-tryptophan was effective, particularly when given in conjunction with a monoamine oxidase inhibitor.

Other studies sought to use measurements of monoamine effects on neuroendocrine function or blood platelet monoamines as an indirect means of testing the “monoamine hypothesis”, again without success. Despite these failures, the “monoamine hypothesis” has had heuristic value in guiding drug discovery and has led to the introduction of several series of improved antidepressant drugs during the past 50 years.

5.1

Introduction

The discovery of the first effective antidepressant drugs some 50 years ago and the rapid advances in research which led to the understanding of their mechanisms of action on monoamine systems in the brain, represented the start of the so-called “psychopharmacology revolution” which transformed the practice of psychiatry.

By the 1950s it was known that the drug reserpine, used for a while in the treatment of high blood pressure, tended to cause depression as an unwanted side-effect [1]. Research in Bernard Brodie’s group at the National Institutes of Health showed that reserpine acted to cause a profound depletion of the brain stores of the monoamines serotonin and noradrenaline [2]. The marked depression of behaviour seen in animals treated with reserpine could be reversed by administering the catecholamine precursor L-DOPA [3] which also reversed the depressive symptoms induced by reserpine in human subjects [4]. These findings first suggested a link between brain monoamines and depression.

This was reinforced by the fortuitous discovery that the drug isoniazid, used for the treatment of tuberculosis exerted a mood-elevating effect [5, 6] and the subsequent finding that this drug inhibited monoamine oxidase, an enzyme known to be involved in degrading monoamines in the brain [7].

Experiments performed in Julius Axelrod’s laboratory at the National Institutes of Health with [³H]-adrenaline [8] and later with [³H]-noradrenaline [9] yielded an unexpected result. Although in laboratory animals most of the injected dose of labeled catecholamine was rapidly metabolized a substantial proportion of the injected monoamine (30–40%) was removed from the circulation by a rapid uptake into tissues, where it remained unchanged for some time. A key observation was that the uptake of [³H]-noradrenaline into the heart was virtually eliminated in animals in which the sympathetic innervation had been destroyed by surgical removal of the superior cervical ganglion [10]. This led Hertting and Axelrod [11] to propose that the re-uptake of noradrenaline by the same nerves from which it had been released might represent a novel mechanism for inactivating this neurotransmitter.

The subsequent discovery by the Axelrod group that imipramine potently inhibited the uptake of norepinephrine [12] led to the first understanding of the mechanism of action of this first generation tricyclic antidepressant [13]. A similar uptake system in the brain for serotonin was soon discovered [14], and it became apparent that the classical tricyclic drugs imipramine and amitriptyline were potent inhibitors of both noradrenaline and serotonin uptake. This reinforced the concept of depression as a monoamine deficiency state, and led to the first formulation of the “monoamine hypothesis of depression” as either a noradrenaline [15, 16] or serotonin deficiency state [17–19] in the brain. J. Schildkraut [16] clearly stated the catecholamine version of the hypothesis in 1965:

“The catecholamine hypothesis of affective disorders proposes that some, if not all, depressions are associated with an absolute or relative decrease in catecholamines,

particularly norepinephrine, available at central adrenergic receptor sites. Elation, conversely, may be associated with an excess of such amines."

In North American psychiatry emphasis was placed initially on the noradrenaline version of this hypothesis whereas the serotonin deficiency concept found more favor in Europe. The monoamine hypothesis stimulated much further research in the pharmaceutical industry to discover new inhibitors of monoamine uptake and other means of boosting monoamine function in the brain. The debate as to whether promoting noradrenaline or serotonin was most important in conferring antidepressant efficacy has swung one way and the other over the past 40 years and there is still no definitive answer to this question [20].

The "monoamine hypothesis of depression" initiated a new era of research in "biological psychiatry" and much attention was paid to attempts to find direct support for the hypothesis by measurements of central monoamine function in depressed patients. This search led to many thousands of publications, but to very few firm conclusions – as will be described below. On the other hand, the hypothesis led to the discovery of many important new antidepressant medicines including the discovery of the most important new psychopharmaceutical of the 20th century, fluoxetine (®Prozac), and the process of discovery continues today.

5.2

Attempts to Validate the Monoamine Hypothesis by Direct Measurements of Monoamine Function in Human Subjects

5.2.1

Measurements of Monoamine Metabolites in Body Fluids

Following the formulation of the "monoamine hypothesis of depression" there was a period of intense research activity on both sides of the Atlantic in the 1960s which aimed to detect possible abnormalities of monoamine function in depressed patients. This period of research has been comprehensively reviewed elsewhere [21, 22]. Since the monoamines themselves are rapidly metabolized, attention focused on measurements of the principal metabolites: 5-hydroxyindoleacetic acid (5-HIAA) from serotonin, and 3-methoxy-4-hydroxyphenyl glycol (MHPG) from noradrenaline, formed by the combined actions of the enzymes catechol-O-methyl transferase (COMT) and monoamine oxidase. Although brain dopamine did not feature in the original monoamine hypotheses, measurements of its metabolite homovanillic acid were also included in many such studies. Initial attempts to measure alterations in the excretion of these metabolites in urine failed to yield any consistent findings – but this is hardly surprising as both noradrenaline and serotonin are present not only in the central nervous system but also in various peripheral tissues (noradrenaline in the adrenal medulla and sympathetic nervous system; serotonin in the gut and in blood platelets). Any alterations in brain monoamine function in depressed patients would be obscured by these peripheral monoamine systems.

Only marginally better was the subsequent era of measurements of monoamine metabolites in cerebrospinal fluid (CSF). As nearly all such studies involved measurements in samples of lumbar CSF the contribution of monoamine metabolites of brain origin was again diluted in the case of 5-HIAA and MHPG by those originating locally from the monoaminergic neurons in the spinal cord. Many of the early studies also involved groups containing both untreated patients and those receiving antidepressant medicines. Other variables such as age, mobility, diet and sampling procedures were also often not well controlled. Although some of these studies did show decreased levels of 5-HIAA, MHPG, or homovanillic acid (HVA) there were also numerous studies which failed to show any significant differences between normal and depressed subjects. Post and Goodwin [21] listed seven studies reporting reduced levels of 5-HIAA and another eight that failed to show any differences. For measurements of CSF MHPG they listed three positive and three negative studies, and for HVA two positive studies versus seven negative. The importance of controlling the conditions for CSF sampling was emphasized by the results reported by Post and colleagues [23] who found that patients asked to be physically active for a period of 4 h prior to CSF sampling showed very substantial increases (as much as a doubling) in levels of 5-HIAA and MHPG in lumbar CSF. Motor activity is critical since alterations in this parameter may be associated not only with alterations in amine metabolism but also with changes in CSF mixing. Maintenance of strict bed rest prior to CSF sampling is thus imperative, but it is not clear that this was always required in the various studies reported.

Overall the results obtained from measurements of monoamine metabolites in lumbar CSF proved inconsistent and disappointing. Nevertheless some studies did show statistically significant reductions, particularly in levels of the serotonin metabolite 5-HIAA. The results obtained in some of these positive studies suggested that there might be a bimodal distribution of values in the patient groups, with a subgroup having particularly low 5-HIAA levels, and in one case this was statistically significant [24]. These authors also reported that the subgroup of patients with low 5-HIAA levels had increased suicidal behavior and suicide risk. The association of suicide or increased suicide risk with low levels of 5-HIAA in CSF was confirmed in subsequent studies [25, 26]. But whether this so-called “low serotonin syndrome” [25] is really related to major depression is equivocal; Linnoila et al. [25] suggest that this syndrome is associated with impulsive and aggressive behavior, and a history of early-onset alcohol or drug abuse.

5.2.2

Attempts to Measure the Turnover of Monoamines in Human Brain: The Probenecid Method

The drug probenecid blocks the transport of 5-HIAA and HVA out of the CSF, so measurements of the rate at which these metabolites accumulate in CSF after probenecid administration can be used as a way of estimating the rate of synthesis and turnover of the parent monoamines serotonin and dopamine in brain.

Probenecid does not affect the efflux of MHPG from CSF and so cannot be applied to estimate the rate of turnover of noradrenaline.

This is, however, a complex procedure. Probenecid tends to cause nausea and vomiting and in order to obtain maximum inhibition of monoamine transport it was usually administered in staged doses. Van Praag [22] described his procedure which involved patients spending 4 days in the clinic. After 1 day of rest a baseline lumbar CSF sample was taken on day 2. On day 4 the patient received a total of 5 g of probenecid in 1-g doses given at hourly intervals. After a 4-h interval after the last dose a second CSF sample was taken. Some patients volunteered to undergo the procedure for a second time after remission! It is hard to believe that this complex and invasive test procedure would be considered acceptable nowadays.

Nevertheless, the probenecid procedure did yield results which seemed to reflect accurately changes in cerebral monoamine turnover. For example administration of L-DOPA caused the expected large increases in HVA accumulation, while administration of the serotonin precursor L-tryptophan similarly led to increased accumulation of 5-HIAA [21]. However, the results obtained in depressed patients again proved to be equivocal. Post and Goodwin [21] described six studies that reported significantly reduced rates of 5-HIAA in depressed subjects, but three studies failed to find such differences. Interestingly, a majority of the studies again reported the possible existence of a subgroup of patients with particularly low rates of 5-HIAA accumulation. According to van Praag and colleagues the serotonin deficit as measured by the probenecid technique was not a universal phenomenon in depressed patients, but occurred in only some 40% of cases [22]. Measurement of HVA accumulation after probenecid in depressed patients also reported reduced values in six studies, with only two negative reports [21].

Although the probenecid technique failed to produce unequivocal evidence to support the “monoamine hypothesis” it did generate other valuable data. For example Post and Goodwin [21] reported a clear sex difference in the rates of 5-HIAA and HVA accumulation in depressed patients, with women having significantly higher values than men. A number of laboratories also showed a clear reduction in both baseline and probenecid-induced CSF levels of 5-HIAA in patients studied before and after treatment with the tricyclic antidepressants imipramine or amitriptyline [21]. The eight studies cited all reported this, with reductions in baseline levels of 5-HIAA of the order of 20–30% and reductions in probenecid-induced levels of around 40%.

The latter findings emphasize that the probenecid technique is not one that could have much relevance today – when the treatment of depressed patients with antidepressant drugs is almost universal.

Thus these attempts to find evidence for monoamine malfunction in depression proved largely ineffective. It is possible that the “monoamine hypothesis” applies only to a subgroup of depressed patients, and this could explain the inconsistent results obtained in the studies described above – since there is no way of identifying patients in this hypothetical subgroup by clinical criteria. It is worth remembering that the “monoamine hypothesis” rests heavily on the finding that antidepressant drugs all appear to act through monoaminergic mechanisms – but it is less widely

known that these drugs are effective only in some depressed patients. A meta-analysis of clinical trials of antidepressants [27] suggested that no beneficial response at all was seen in 19–34% of depressed patients treated with antidepressant drugs, whereas there was only a partial response in a further 12–15%. Thus, almost half of all patients treated with antidepressants fail to show a full response.

5.2.3

Measurements in Post-mortem Brain Samples and in Living Brain by Neuroimaging

A number of attempts have been made to find support for the “monoamine hypothesis” from measurements of monoamines and their receptors in post-mortem brain samples. This approach, however, is fraught with difficulties. The near universal use of antidepressant medicines makes such studies almost impossible to interpret nowadays – as any changes observed could be drug-related rather than inherent to the illness.

Nevertheless a number of earlier studies in drug-free patients did report significant reductions in the level of serotonin in whole brain, hypothalamus and amygdala in post-mortem tissue from depressed patients or suicide victims (for reviews see [28–30]). Several studies also found an increased density of 5-HT₂ receptor binding sites in the frontal cortex in depressed patients and suicide victims (for a review see [31]). This could be interpreted as an adaptive response to reduced synaptic serotonin. Imaging studies in the living brain using positron emission tomography (PET) with various radioligands, however, have found significant decreases in the density of 5-HT₂ sites in cortical regions in depressed patients (two studies) or no change (two studies; for a review see [32]). Measurements of other serotonin receptors in post-mortem tissue samples have also yielded inconsistent results. While some studies reported no changes in the density of 5-HT_{1A} receptor binding sites, others found significant increases, notably in prefrontal cortex and raphe nuclei [33]. A PET imaging study, however, found significant decreases in the density of 5-HT_{1A} sites in most cortical regions in a group of drug-free depressed patients [34]. The reduced densities of 5-HT_{1A} receptors were not altered by treatment with the serotonin selective reuptake inhibitor (SSRI), paroxetine [34].

A few studies attempted to measure the density of the 5-HT uptake transporter (5-HTT) in post-mortem tissues, and significant reductions in the binding of [³H]-imipramine were observed in cortex, hypothalamus and hippocampus [35, 36]. Although [³H]-imipramine binds to 5-HTT it may not be a reliably selective ligand. However, the finding of a reduced density of 5-HTT in tissue from depressed patients was confirmed in one study using the more selective ligand [³H]-citalopram [37], although another study using [³H]-paroxetine as the ligand failed to show any changes in 5-HTT binding in raphe or locus coeruleus in tissue from depressed patients [38].

Less attention has been paid to measurements of noradrenergic markers in post-mortem brain. The binding of a ligand for the noradrenaline uptake transporter, [³H]-nisoxetine, was reported to be reduced in locus coeruleus tissue from depressed patients [38]. Such a reduction is also seen in animal brain following the chronic

administration of the tricyclic antidepressant imipramine [39]. An increased density of α_2 adrenoceptor binding sites has been reported in frontal cortex and other brain regions [40] and in locus coeruleus [41] – this could reflect enhanced autoreceptor activity that could dampen noradrenergic synaptic mechanisms, or because these receptors are up-regulated in animals by noradrenaline depletion the changes could reflect a defect in noradrenergic mechanisms in depression [41].

Measurements of monoamine oxidase (MAO) A in post-mortem brain showed no overall differences in depressed patients [42], but one study reported that male suicide victims had a significantly higher amount of an allele associated with high enzyme activity [43].

5.2.4

Measurements of Monoamine Markers in Blood Platelets

Because of the inherent difficulties associated with obtaining human post-mortem brain tissue, attempts were made to find surrogate markers that might reflect CNS monoamine function. For a while the blood platelet appeared to offer such a model. Platelets store and release serotonin in much the same way as serotonin neurons do in the brain. They also possess a 5-HTT apparently identical to that in brain and express several serotonin receptors (for reviews see [44, 45]). Several reports of reduced [3 H]-imipramine binding in platelets from drug-free depressed patients suggested reduced expression of 5-HTT in these cells [46–49]. Some studies went further and suggested that the expression of 5-HTT in platelets might represent a state-dependent marker – as the density of [3 H]-imipramine binding sites increased in patients exhibiting clinical recovery in response to antidepressant drug treatment [50, 51], although others failed to find such changes [52, 53]. Despite early enthusiasm for this approach, however, the model proved unreliable. A large World Health Organization (WHO)-sponsored collaborative study involving data from 154 depressed patients and 130 control subjects found no significant differences in [3 H]-imipramine binding capacity between platelets from depressed subjects versus controls [54]. However, a subsequent study using the more selective 5-HTT ligand [3 H]-paroxetine continued to report a decrease in 5-HTT in platelets from depressed subjects [55].

In terms of noradrenergic function, there have been reports of an increased expression of α_2 adrenoceptors in platelets from depressed patients [56], and antidepressant drug treatment or electroconvulsive therapy (ECT) were associated with a decrease in the expression of these receptors in platelets [57]. Others reported an increase in platelet β -adrenoceptors in depressed patients and their down-regulation in response to successful antidepressant treatment [58].

Overall though there seems little reason to believe that monoamine markers in blood platelets can serve as a reliable guide to the status of monoaminergic synaptic function in the brain, and these studies are now largely out of favor.

5.3

Manipulation of Monoamines by Administration of Precursors or by Depletion Strategies

5.3.1

Rationale

If the underlying pathophysiology of depression is indeed due to a deficiency in one or other central monoamine neurotransmitter as predicted by the “monoamine hypothesis” then experimental alterations in monoamine function should have specific effects on depressive symptoms. Boosting brain monoamine levels by the administration of precursors might be expected to exert an antidepressant effect, while depletion of central monoamine stores would be predicted to exacerbate depression, or even to cause it in otherwise normal healthy subjects. Numerous studies of this type have been undertaken, but as so often in this field the results have largely failed to provide clear-cut support for the “monoamine hypothesis”.

5.3.2

Monoamine Depletion Studies

Inhibition of noradrenaline synthesis can be achieved by administering the compound α -methyl-para-tyrosine (AMT) to inhibit the enzyme tyrosine hydroxylase, which catalyzes the first step in catecholamine biosynthesis. AMT is reasonably well tolerated and doses of 2 g/day can be given [22]. Confirmation that AMT does inhibit catecholamine synthesis in the brain is provided by the finding that CSF levels of the dopamine metabolite HVA are reduced after AMT administration [59], although this also points to the limited usefulness of this approach since the synthesis of both noradrenaline and dopamine are affected. It is also impossible to achieve much more than 50% inhibition of catecholamine synthesis with acceptable doses of AMT [22]. Initial reports in hypertensive patients treated with AMT as a potential antihypertensive agent suggested that the compound did induce sedation and depression of mood [60, 61]. In primates AMT also caused a reduction in behavior [62]. However, subsequent studies in healthy subjects have provided equivocal results – the effects of AMT could be interpreted as sedation and may be largely due to impairment of brain dopamine function rather than noradrenaline. More interesting findings have been obtained by Delgado and colleagues with AMT in depressed patients. In depressed patients not taking medication, administration of AMT did not cause any exacerbation of symptoms (measured by their Hamilton Depression rating scores) [63]. However, in a group of 16 depressed patients who were responding well to the noradrenaline-selective uptake inhibitor (NRI) desipramine, after administration of AMT 81% showed a significant clinical relapse [64]. In contrast only 19% of 21 patients who responded to the serotonin-selective uptake inhibitor (SSRI) fluoxetine showed a relapse in response to AMT.

An inhibitor of tryptophan hydroxylase is available, para-chlorophenylalanine, (PCPA) and was used in some early studies. One report showed that PCPA reversed

the antidepressant actions of imipramine in depressed patients [65]. Because of its toxic side-effects, however, PCPA was not considered safe for human use [22]. Inhibition of serotonin synthesis is most easily achieved by manipulation of levels of the precursor amino acid L-tryptophan. This is usually done by administering a cocktail of amino acids, with L-tryptophan omitted. This stimulates protein synthesis in the liver and leads to a rapid depletion of plasma tryptophan with up to an 80–90% reduction plasma levels within a few hours, without any harmful side-effects [66]. Animal studies in rats [67] and primates [68] confirmed the effectiveness of this approach. Using PET imaging serotonin synthesis was reported to be inhibited by around 90% following tryptophan depletion in this way [69]. In healthy subjects [70–72] and in depressed patients not taking medication [73] this had surprisingly little or no effect on mood or depression scores. However, in a group of 21 depressed patients who responded well to the SSRI fluoxetine, two-thirds suffered a relapse (50% increases in Hamilton Depression scores) within 5–7 h after tryptophan depletion [74, 75]. In contrast, only 20% of depressed patients who responded to the NRI desipramine showed relapse in response to tryptophan depletion [74].

Delgado has summarized the results of these various monoamine depletion studies from his group [76, 77] (Table 5.1). They are of great interest in a number of ways. The results show that acute interference with either noradrenergic or serotonergic synaptic transmission in brain has little or no effect on mood either in normal healthy subjects or in depressed patients not taking medication. Monoamine depletion does have clear effects, however, in reversing the beneficial effects of antidepressant drugs, with noradrenaline depletion being most effective against NRIs and tryptophan depletion most effective against SSRIs. One conclusion that can be made is that these results offer strong support to the hypothesis that inhibition of monoamine uptake represents the mechanism of action of such drugs as antidepressants. One unexplained feature of these experimental findings is that monoamine depletion is capable of reversing antidepressant effects very rapidly – within a few hours in the case of tryptophan depletion. On the other hand it is well known that the antidepressant drugs require several weeks of chronic treatment before the maximum antidepressant effects are seen. The depletion studies in some ways not only offer no support to the “monoamine hypothesis” but in fact seem to contradict it.

Table 5.1 Recurrence of depression as a result of monoamine depletion

Subjects	Serotonin depletion	Noradrenaline depletion
Healthy controls	–	+/-
Untreated depressed	–	–
Recovered taking SSRI	++++	+
Recovered taking NRI	–	++++
Recovered taking NA/5-HT mixed drug	++++	++++

Data from [72–76]. For a review see [78].

5.3.3

Effects of Monoamine Precursors

In contrast to monoamine depletion studies other research aimed to boost monoamine levels in brain by administering precursors for their biosynthesis. For noradrenaline there is no way of doing this selectively. Large doses of the precursor L-DOPA do penetrate into the brain and are converted to both dopamine and noradrenaline, and this is evidenced by large increases (up to two-fold) in CSF levels of the dopamine metabolite HVA [21, 78]. However, there is no evidence that L-DOPA is effective as an antidepressant [79–81]. Indeed in Parkinson's disease patients treated with L-DOPA depression may be among the drug-induced unwanted psychiatric side-effects [82].

By analogy with L-DOPA attempts were made to use the serotonin precursor 5-hydroxytryptophan (5-HTP) to boost brain levels of serotonin [22]. But this compound has toxic side-effects and is also capable of decarboxylation to form serotonin not only in serotonin neurons but also in catecholamine neurons, which also possess the same decarboxylase enzyme. Van Praag and colleagues [83], using the maximum tolerated dose of 5-HTP (3 g) did however, report beneficial antidepressant effects, but only in a subgroup of depressed patients with unusually low serotonin turnover (as measured by the probenecid technique).

A safer and more selective way of elevating brain levels of serotonin is to administer the precursor amino acid L-tryptophan. The biosynthetic enzyme tryptophan hydroxylase is not normally saturated with substrate, so administration of L-tryptophan to animals leads to increased serotonin synthesis, particularly in brain [84]. Unlike 5-HTP, this will occur mainly in serotonin neurons. Administration of L-tryptophan at doses of several grams per day is well tolerated in human subjects, and leads to large increases in the CSF levels of the serotonin metabolite 5-HIAA [85].

The effects of L-tryptophan in depressed patients proved inconsistent. In Europe Coppen and colleagues claimed that the amino acid given alone was an effective antidepressant [86, 87]. While this was confirmed in one similar study [88], other investigators in the United States failed to observe any antidepressant efficacy [89–91]. On the other hand, Coppen's earlier finding that large doses of L-tryptophan (> 10 g) potentiated the antidepressant efficacy of the monoamine oxidase inhibitor tranylcypromine [92] was confirmed by several other independent reports [93–95]. However, the use of monoamine oxidase inhibitors was largely abandoned because of the risk of serious cardiovascular side-effects, so this approach to antidepressant therapy has not been pursued. The finding that the effects of L-tryptophan proved to be more robust when combined with an inhibitor of monoamine oxidase argues in favor of the action being mediated via increased formation of serotonin. However, not all the effects of L-tryptophan can necessarily be explained by increased formation of serotonin [22].

5.4

Neuroendocrine Markers of Monoamine Function in Depressed Patients

5.4.1

Rationale

Since monoamines are implicated in several of the brain mechanisms involved in the neural control of endocrine function, measurements of changes in neuroendocrine function in depressed patients can be used indirectly to detect alterations in monoamine function (for reviews see [96, 97]). However, such studies are hard to control since neuroendocrine function may also be altered profoundly by antidepressant drugs, and can be influenced by such factors as stress, gender, age and by caffeine, alcohol and nicotine [96]. Nevertheless some well-controlled studies are available.

5.4.2

Neuroendocrine Markers in Depression

A substantial proportion of patients (40–50%) with endogenous depression demonstrate a reduced resistance to hypothalamus–pituitary–adrenal (HPA) suppression when challenged with the corticosteroid dexamethasone [96, 97]. Dexamethasone acts to inhibit adrenocorticotrophic hormone (ACTH) secretion from the pituitary and this leads to a reduction in plasma cortisol levels for the following 24 h. In depressed patients this inhibitory mechanism is significantly less effective. Although this finding has been repeated in many laboratories [98–101] the involvement of monoamines is less clear [96]. However, the cortisol response to methamphetamine is blunted in depressed patients [102, 103] and methamphetamine may work through α -adrenoceptors to stimulate ACTH secretion [96]. This suggests a possible impairment of α -adrenoceptor function in depressed patients.

This conclusion is also supported by consistent reports of a blunted growth hormone response to the α_2 -adrenoceptor agonist clonidine in depressed patients [104–106]. The increased density of α_2 -adrenoceptors observed in post-mortem brain samples from depressed patients could also be interpreted as a response to noradrenergic deficiency [40, 41]. (For a review of this and other evidence in favor of a noradrenergic defect see [107]).

5.5

Molecular and Genetic Approaches

More recently attempts to understand the basis of the monoamine hypothesis of depression have focused on studies of the molecular mechanisms that lie downstream of the activation of monoamine receptors in the brain, (for a review see [108]) and on the search for possible genetic risk factors (for a review see [109]).

Many of the monoamine receptors are coupled to changes in the intracellular levels of the second messenger molecule cyclic AMP. A number of molecular systems in animal brain that are regulated by cyclic AMP are up-regulated in response to chronic treatment with antidepressants, notably the cyclic AMP response element protein (CREB), a prominent transcription factor in brain [110]. Another way of increasing levels of cyclic AMP is to inhibit its degradation by phosphodiesterases (PDEs). The compound rolipram is a phosphodiesterase inhibitor and it has been found to have clinical antidepressant activity [111]. Although rolipram is not well tolerated because it causes severe nausea, it is possible that inhibitors with more selectivity for phosphodiesterase subtypes could be of future interest. In animals chronic treatment with SSRIs leads to increased expression of the PDE4A and PDE4B subtypes [112]. Among the many genes that may be regulated by CREB are those encoding neurotrophic factors [113]. An important new finding is that chronic treatment with antidepressants leads to increased expression of the neurotrophic factor BDNF (Brain Derived Neurotrophic Factor) in rat hippocampus, and this may underlie the recent finding that chronic antidepressant treatment causes a proliferation of progenitor cells in the rat hippocampus [114–117]. This led Duman and colleagues to propose that a deficiency in BDNF expression, with an accompanying loss of neurons might be a key feature of depression [115]. Neuroimaging and post-mortem histological studies have reported reductions in neuronal and glial densities in dorsolateral prefrontal cortex in patients with mood disorders [116, 117]. Compounds that targeted neurotrophic factor mechanisms could provide a novel approach to antidepressant drug discovery in the future [118].

There is a belief nowadays that most human diseases have a genetic basis, but to date there has been rather little progress in this respect in studies of genetic risk factors in depression. Although suicidal behavior appears have a strong genetic influence (concordance for monozygotic twins is about 13 vs. 0.7% in dizygotics [119]) and there are similar data for bipolar disorder; this is not the case for major depression.

Attention has focused on certain candidate genes associated with monoamine function both in suicide [119, 120] and bipolar disorder [121]. So far no convincing relationship to a variety of polymorphisms in the serotonin transporter or serotonin receptors [120] or with MAO, COMT or tryptophan hydroxylase [119] has been linked to suicidal behavior. A possible association of polymorphisms in monoamine oxidase A and the serotonin transporter has been described in bipolar disorder [121] and a whole genome positional cloning study revealed a possible association of bipolar disorder with the genes DISC1 (disrupted in schizophrenia-1) and DISC2 [121]. Functional genomics using microarray technology has been used to identify more than 300 genes in animal brain affected by antidepressant drug treatments [109] and this may offer novel insights beyond the “monoamine hypothesis” of antidepressant drug actions. Perhaps the most intriguing recent study was one in which a cohort of young people in New Zealand was followed through to adulthood [122]. It was reported that polymorphisms in the promoter regions of the serotonin transporter gene were found to moderate the influence of stressful life events on depression. Individuals with one or two copies of a short allele of the promoter

region exhibited more depressive symptoms, diagnosable depression and suicidality in response to stressful life events than individuals homozygous for a longer promoter allele [122]. This type of result may ultimately hold the key to understanding the influence of genetics and environment on depressive illness, although it is clear that much more remains to be learned from this approach.

5.6

Conclusions

The “monoamine hypothesis” ushered in a new era of biological psychiatry, although the attempts to extrapolate from this hypothesis about antidepressant drug actions to understand the molecular basis of depression have proved disappointing. Despite a major worldwide research effort there is no convincing evidence to support the hypothesis that a deficiency in monoaminergic function underlies the symptoms of major depression, although this may be true for a subgroup of severely depressed patients with suicidal behavior [21, 22, 123]. On the other hand it is worth pointing out that not all depressed patients respond well to antidepressant drug treatment, with as many as 19–34% showing effectively no response at all [27]. Treatments based on enhancing monoaminergic function thus benefit only a subgroup of patients and one might therefore not expect to see a global defect in monoaminergic function in all depressed subjects. However, there is unfortunately no means as yet of distinguishing and identifying these hypothetical subgroups. Current thinking tends towards an explanation of depression in terms of defects in neurotrophic [115] or neuroendocrine mechanisms [124].

Nevertheless, the “monoamine hypothesis” has proved very successful in guiding new drug discovery, and several new classes of improved and safer antidepressants have been introduced during the past 50 years – and this process continues. The development of monoamine uptake inhibitors has come full circle with the introduction of mixed noradrenaline/serotonin uptake inhibitors [125] which lack the toxicity of the earlier tricyclic antidepressants.

References

- 1 MULLER, J. C., PRYER, W. W., GIBBONS, J. E., et al., *J. Am. Med. Assoc.* **1955**, *159*, 836–839.
- 2 SHORE, P. A., SILVER, S. L., BRODIE, B. B., *Science* **1955**, *122*, 284–285.
- 3 CARLSSON, A., LINDQVIST, M., MAGNUSSON, T., *Nature* **1957**, *180*, 1200.
- 4 DEGWITZ, R., FROWEIN, R., KULEN-KAMPFF, C., et al., *Klin. Wochenschr.* **1960**, *38*, 120–123.
- 5 CRANE, G. E., *Am. J. Psychiatry* **1956**, *112*, 494–501.
- 6 KLINE, N. S., *J. Clin. Exp. Psychopathol.* **1961**, *19* (Suppl. 1), 72–78.
- 7 ZELLER, E. A., BARSKY, J., FOUTS, J. P., et al., *Experientia* **1952**, *8*, 349.
- 8 AXELROD, J., WEIL-MALHERBE, H., TOMCHICK, R., *J. Pharmacol. Exp. Ther.* **1959**, *127*, 251–256.
- 9 WHITBY, L. G., AXELROD, J., WEIL-MALHERBE, H., *J. Pharmacol. Exp. Ther.* **1961**, *132*, 193–201.
- 10 HERTTING, G., AXELROD, J., KOPIN, I. J., WHITBY, L. G., *Nature* **1961**, *189*, 66.

- 11 HERTTING, G., AXELROD, J., *Nature* **1961**, 192, 172–173.
- 12 HERTTING, G., AXELROD, J., WHITBY, L. G., *J. Pharmacol. Exp. Ther.* **1961**, 134, 146–153.
- 13 KUHN, R., *Am. J. Psychiatry* **1958**, 115, 459–464.
- 14 CARLSSON, A., FUXE, K., UNGERSTEDT, U., *J. Pharm. Pharmacol.* **1968**, 20, 150–151.
- 15 BUNNEY, W. E., DAVIS, J. M., *Arch. Gen. Psychiatry* **1965**, 13, 483–494.
- 16 SCHILDKRAUT, J. J., *Am. J. Psychiatry* **1965**, 122, 509–521.
- 17 ASHCROFT, G. W., CRAWFORD, T. B., ECCLESTON, D., et al., *Lancet* **1966**, 2, 1049–1052.
- 18 LAPIN, I. P., OXENKRUG, G. F., *Lancet* **1969**, 1, 132–136.
- 19 COPPEN, A., SHAW, D. M., HERZBERG, B., MAGGS, R., *Lancet* **1967**, 2, 1178–1180.
- 20 IVERSEN, L. L., GLENNON, R. A., In: *Burgers Medicinal Chemistry*, 6th ed., Vol. 5, **2003** (in press).
- 21 POST, R. M., GOODWIN, F. K., In: *Handbook of Psychopharmacology*, Vol. 13, IVERSEN, L. L., IVERSEN, S. D., SNYDER, S. H. (Eds.). Plenum Press: New York, **1976**, 137–186.
- 22 VAN PRAAG, H. M., In: *Handbook of Psychopharmacology*, Vol. 13, IVERSEN, L. L., IVERSEN, S. D., SNYDER, S. H. (Eds.). Plenum Press: New York, **1976**, 187–298.
- 23 POST, R. M., KOTIN, J., GOODWIN, F. K., GORDON, E. K., *Am. J. Psychiatry* **1973**, 130, 67–72.
- 24 ÅSBERG, M., TRÄSKMAN, L., THORÉN, P., *Arch. Gen. Psychiatry* **1976**, 33, 1193–1197.
- 25 LINNOILA, V. M. I., VIRKUNEN, M., *J. Clin. Psychiatry* **1992**, 53, 10 (Suppl.), 46–51.
- 26 ROY, A., DEJONG, J., LINNOILA, M., *Arch. Gen. Psychiatry* **1989**, 46, 609–612.
- 27 FAVA, M., DAVIDSON, K. G., *Psychiatr. Clin. North Am.* **1996**, 19, 179–194.
- 28 VAN PRAAG, H. M., In: *Neurobiology of Mood Disorders*, Vol. 1, POST, R. M., BALLINGER, J. C. (Eds.). Williams & Wilkins: Baltimore, **1984**, 601–618.
- 29 GIBBONS, R. D., DAVIS, J. M., *Acta Psychiatr. Scand.* **1986**, 74, 8–12.
- 30 MELTZER, H. Y., LOWY, M. T., In: *Psychopharmacology: The Third Generation of Progress*, MELTZER, H. Y. (Ed.), Raven Press: New York, **1987**, 513–526.
- 31 OWENS, M. J., NEMEROFF, C. B., *Clin. Chem.* **1994**, 40, 288–295.
- 32 YATHAM, L. N., LIDDLE, P. F., SHIN SHIAH, I., et al., *Arch. Gen. Psychiatry* **2000**, 57, 850–858.
- 33 STOCKMEIER, C. A., SHAPIRO, L. A., DILLEY, G. E., et al., *J. Neurosci.* **1998**, 18, 7394–7401.
- 34 SARGENT, P. A., KJAER, K. H., BENCH, C. J., et al., *Arch. Gen. Psychiatry* **2000**, 57, 174–180.
- 35 STANLEY, M., VIRGILIO, J., GERSHON, S., *Science* **1982**, 216, 1337–1339.
- 36 PERRY, E. K., MARSHALL, E. F., G. BLESSED, et al., *Br. J. Psychiatry* **1983**, 142, 188–192.
- 37 LEAKE, A., FAIRBAIRN, A. F., MCKEITH, I. G., FERRIER, I. N., *Psychiatry Res.* **1991**, 39, 155–165.
- 38 KLIMEK, V., STOCKMEIER, C., OVERHOLSER, J., et al., *J. Neurosci.* **1997**, 17, 8451–8458.
- 39 BAUER, M. E., TEDJANI-BUTT, S. M., *Brain Res.* **1992**, 582, 208–214.
- 40 MEANA, J. J., BARTUREN, F., GARCÍA-SEVILLA, J. A., *Biol. Psychiatry* **1992**, 31, 471–490.
- 41 ORDWAY, G. A., SCHENK, J., STOCKMEIER, C. A., et al., *Biol. Psychiatry* **2003**, 53, 315–323.
- 42 ORDWAY, G. A., FARLEY, J. T., DILLEY, G. E., et al., *Brain Res.* **1999**, 847, 71–79.
- 43 DU, L., FALUDI, G., PALKOVITS, M., et al., *NeuroReport* **2002**, 13, 1195–1198.
- 44 PLETSCHER, A., *Int. J. Cardiol.* **1987**, 14, 177–188.
- 45 DA PRADA, M., CESURA, A. M., LAUNAY, J. M., RICHARDS, J. G., *Experientia* **1988**, 44, 115–126.
- 46 BRILEY, M. S., LANGER, S. Z., RAISMAN, R., et al., *Science* **1980**, 209, 303–305.
- 47 PAUL, S. M., REHAVI, M., SKOLNICK, P., et al., *Arch. Gen. Psychiatry* **1981**, 38, 1315–1317.
- 48 LANGER, S. Z., GALZIN, A. M., *Experientia* **1988**, 44, 127–130.
- 49 NEMEROFF, C. B., KNIGHT, D. L., KRISHNAN, K. R. R., et al., *Arch. Gen. Psychiatry* **1988**, 45, 919–923.
- 50 BERRETTINI, W. H., NURNBERGER, J. I., POST, R. M., GERSHON, E. S., *Psychiatry Res.* **1982**, 7, 215–219.
- 51 LANGER, S. Z., GALZIN, A. M., POIRIER, M. F., et al., *J. Receptor Res.* **1987**, 7, 499–521.

- 52 BARON, M., BARAKAI, A., GRUEN, R., et al., *Am. J. Psychiatry* **1986**, 143, 711–717.
- 53 BARON, M., BARAKAI, A., GRUEN, R., et al., *Neuropsychobiology* **1987**, 17, 182–186.
- 54 WHO COLLABORATIVE STUDY, *Pharmacopsychiatry* **1990**, 23, 113–117.
- 55 NEMEROFF, C. B., KNIGHT, D. L., KRISHNAN, K. R. R., *Soc. Neurosci. Abstr.* **1991**, 17, 586.4.
- 56 GARCÍA A-SEVILLA, J. A., *Br. J. Psychiatry* **1989**, 154 (Suppl. 4), 67–72.
- 57 GARCÍA A-SEVILLA, J. A., PADRO, D., GIRALT, M. T., et al., *Arch. Gen. Psychiatry* **1990**, 47, 125–132.
- 58 LEONARD, B. E., *J. Psychopharmacol.* **1997**, 11 (Suppl. 4), S39–S47.
- 59 BRODIE, H. K. H., MURPHY, D. L., GOODWIN, F. K., BUNNEY, W. E., *Clin. Pharmacol. Ther.* **1971**, 12, 219–224.
- 60 SJOERDSMA, A., ENGELMAN, K., SPECTOR, S., UDENFRIEND, S., *Lancet* **1965**, 2, 1092–1094.
- 61 SCHILDKRAUT, J. J., In: *American Handbook of Psychiatry*, Vol. VI, HAMBERG, D. (Ed.). Basic Books: New York **1975**, 609–672.
- 62 REDMOND, E. E., MAAS, J. W., KLING, A., et al., *Science* **1971**, 174, 428–430.
- 63 MILLER, H. L., DELGADO, P. L., SALOMON, R. M., et al., *Neuropsychopharmacology* **1996**, 14, 151–158.
- 64 MILLER, H. L., DELGADO, P. L., SALOMON, R. M., et al., *Arch. Gen. Psychiatry* **1996**, 53, 117–128.
- 65 SHOPSIN, B., GERSHON, S., GOLDSTEIN, M., et al., *Psychopharmacol. Bull.* **1974**, 10, 521.
- 66 YOUNG, S. N., SMITH, S. E., PIHL, R., et al., *Psychopharmacology* **1985**, 87, 173–177.
- 67 MOJA, E. A., CIPOLLO, P., CASTOLDI, D., et al., *Life Sci.* **1989**, 44, 971–976.
- 68 YOUNG, S. N., ERVIN, F. R., PIHL, R. O., et al., *Psychopharmacology* **1989**, 98, 508–511.
- 69 NISHIZAWA, S., BENKELFAT, C., YOUNG, S. N., et al., *Proc. Natl. Acad. Sci. USA* **1997**, 94, 5308–5313.
- 70 BENKELFAT, C., ELLENBOGEN, M. A., DEAN, P., et al., *Arch. Gen. Psychiatry* **1994**, 51, 687–697.
- 71 MORENO, F. A., DELGADO, P. L., MCKNIGHT, K., et al., *Soc. Neurosci. Abstr.* **1996**, 26, 811.9.
- 72 MORENO, F. A., GELENBERG, A. J., HENINGER, G. R., et al., *Biol. Psychiatry* **1999**, 46, 498–505.
- 73 DELGADO, P. L., PRICE, L. H., MILLER, H. L., et al., *Arch. Gen. Psychiatry* **1994**, 51, 865–874.
- 74 DELGADO, P. L., CHARNEY, D. S., PRICE, L. H., et al., *Arch. Gen. Psychiatr* **1990**, 47, 411–418.
- 75 DELGADO, P. L., MILLER, H. L., SALOMON, R. M., et al., *Biol. Psychiatry* **1999**, 46, 212–220.
- 76 DELGADO, P. L., MORENO, F. A., *J. Clin. Psychiatry* **2000**, 61 (Suppl. 1), 5–12.
- 77 DELGADO, P. L., *J. Clin. Psychiatry* **2000**, 61 (Suppl. 6), 7–11.
- 78 GOODWIN, F. K., POST, R. M., DUNNER, D. L., GORDON, E. K., *Am. J. Psychiatry* **1973**, 130, 73–79.
- 79 GOODWIN, F. K., MURPHY, D. L., BRODIE, H. K., BUNNEY, W. E., *Biol. Psychiatry* **1970**, 2, 341–366.
- 80 MURPHY, D. L., BRODIE, H. K., GOODWIN, F. K., BUNNEY, W. E., *Nature* **1971**, 229, 135–136.
- 81 MENDELS, J., STINNETT, J. L., BURNS, D., FRAZER, A., *Arch. Gen. Psychiatry* **1975**, 32, 22–30.
- 82 GOODWIN, F. K., *J. Am. Med. Assoc.* **1971**, 218, 1915–1920.
- 83 VAN PRAAG, H. M., KORF, J., DOLS, L. C. W., SCHUT, T., *Psychopharmacologia* **1972**, 25, 14–21.
- 84 FERNSTRÖM, J. D., WURTMAN, R. J., *Science* **1972**, 178, 414–416.
- 85 DUNNER, D. L., GOODWIN, F. K., *Arch. Gen. Psychiatry* **1972**, 26, 364–366.
- 86 COPPEN, A., SHAW, D. M., HERZBERG, B., MAGGS, R., *Lancet* **1967**, 2, 1178–1180.
- 87 COPPEN, A., BROOKSBANK, B. W. L., PEET, M., *Lancet* **1972**, 1, 1393.
- 88 JENSEN, K., FRUENSGAARD, K., AHLFORS, U. G., et al., *Lancet* **1975**, 2, 920.
- 89 CARROLL, B. J., MOWBRAY, R. M., DAVIES, B. M., *Lancet* **1970**, 1, 967–969.
- 90 BUNNEY, W. E., BRODIE, H. K., MURPHY, D. L., GOODWIN, F. K., *Am. J. Psychiatry* **1971**, 127, 872–881.
- 91 DUNNER, D. L., FIEVE, R. R., *Am. J. Psychiatry* **1975**, 132, 180–183.
- 92 COPPEN, A., SHAW, D. M., FARRELL, J. P., *Lancet* **1963**, 1, 79–81.
- 93 PARE, C. M. B., *Lancet* **1963**, 2, 527–528.

- 94 GLASSMAN, A., PIATMAN, S. R., *J. Psychiatr. Res.* **1969**, 7, 83–88.
- 95 LOPEZ-IBOR, A. J. J., GUTIERREZ, J. L. L. A., IGLESIAS, M. L. M., *Int. Pharmacopsychiatr.* **1973**, 8, 145–151.
- 96 S. A. CHECKLEY, *Psychol. Med.* **1980**, 10, 35–53.
- 97 NATHAN, K. I., SCHATZBERG, A. F., In: *Review of Psychiatry*, Vol. 13, OLDHAM, J. M., RIBA, M. B. (Eds.). American Psychiatric Press Inc.: Washington DC, **1994**, 171–186.
- 98 CARROLL, B. J., CURTIS, G. C., MENDELS, J., *Arch. Gen. Psychiatry* **1976**, 33, 1039–1044.
- 99 BROWN, W. A., JOHNSON, R., MAYFIELD, D., *Am. J. Psychiatry* **1979**, 136, 543–547.
- 100 RIBIERO, S. C. M., TANDON, R., GRUNHAUS, L., et al., *Am. J. Psychiatry* **1993**, 150, 1618–1629.
- 101 ARANA, G. W., BALDESSARINI, R. J., ORNSTEIN, M., *Arch. Gen. Psychiatry* **1985**, 42, 1193–1204.
- 102 CHECKLEY, S. A., *Psychol. Med.* **1979**, 9, 107–116.
- 103 CHECKLEY, S. A., CRAMMER, J. L., *Br. J. Psychiatry* **1977**, 131, 582–586.
- 104 MATUSSEK, N., ACKENHEIL, M., HIPPIUS, H., et al., *Psychiatr. Res.* **1980**, 2, 25–36.
- 105 SIEVER, L., TRESTMAN, R., COCCARO, E., *Neuropsychopharmacology* **1992**, 6, 165–177.
- 106 SCHATZBERG, A., SCHILDKRAUT, J., In: *Psychopharmacology: The Fourth Generation of Progress*, BLOOM, F., KUPFER, D. (Eds.). Raven Press: New York, **1995**, 911–920.
- 107 RESSLER, K. J., NEMEROFF, C. B., *Biol. Psychiatry* **1999**, 46, 1219–1233.
- 108 COYLE, J. T., DUMAN, R. S., *Neuron* **2003**, 38, 157–160.
- 109 YAMADA, M., HIGUCHI, T., *Eur. Neuro-psychopharmacol.* **2002**, 12, 235–244.
- 110 VAIDYA, V., DUMAN, R., *Br. Med. Bull.* **2001**, 57, 61–79.
- 111 FLEISCHHACKER, W. W., HINTERHUBER, H., BAUER, H., et al., *Neuropsychobiology* **1992**, 26, 59–64.
- 112 TAKAHASHI, M., TERWILLIGER, R., LANE, C., et al., *J. Neurosci.* **1999**, 19, 610–618.
- 113 MAUBACH, K. A., RUPNIAK, N. M. J., KRAMER, M., HILL, R. G., *Curr. Opin. Chem. Biol.* **1999**, 3, 481–488.
- 114 NIVUYA, M., NESTLER, E. J., DUMAN, R. S., *J. Neurosci.* **1996**, 16, 2365–2372.
- 115 DUMAN, R. S., HENINGER, G. R., NESTLER, E. J., *Archiv Gen. Psychiatry* **1997**, 5, 597–606.
- 116 RAJKOWSKA, G., *Biol. Psychiatry* **2000**, 48, 766–777.
- 117 ONGUR, D., DREVETS, W. C., PRICE, J. L., *Proc. Natl. Acad. Sci. USA* **2000**, 95, 13290–13295.
- 118 ALTAR, C. A., *Trends Pharmacol. Sci.* **1999**, 20, 59–61.
- 119 ZALSMAN, G., FRISCH, A., APTER, A., WEIZMAN, A., *Isr. J. Psychiatry* **2002**, 39, 252–261.
- 120 ARANGO, V., HUANG, Y. Y., UNDERWOOD, M. D., MANN, J. J., *J. Psychiatr. Res.* **2003**, 37, 375–386.
- 121 KATO, T., *Neurosci. Res.* **2001**, 40, 105–113.
- 122 CASPI, A., SUGDEN, K., MOFFITT, T. E., et al., *Science* **2003**, 301, 386–389.
- 123 CHARNEY, D. S., *J. Clin. Psychiatry* **1998**, 59, 11–14.
- 124 WOLKOWITZ, O. M., REUS, V. I., *World J. Biol. Psychiatry* **2003**, 4, 98–102.
- 125 TRAN, P. V., BYMASTER, F. P., MCNAMARA, R. K., POTTER, W. Z., *J. Clin. Psychopharmacol.* **2003**, 23, 78–86.

6

Monoaminergic-based Pharmacotherapy for Depression

George I. Papakostas and Maurizio Fava

Abstract

Although recent advances in neuropharmacology, neuroendocrinology, molecular biology, and pharmacogenetics have been instrumental in bringing about potential treatments for depression which are fundamentally unrelated to their predecessors, including substance P antagonists, glutaminergic agents, and corticotropin-releasing factor (CRF) antagonists, nevertheless it was agents that influenced the function of monoamine receptors and transporters that were discovered initially by serendipity and then developed as treatments for depression. The development of such compounds also served as a framework for the understanding of depression as a medical illness affecting brain functioning. As a result of these efforts, our field has gained further understanding of the role of monoamines in depression. In previous chapters, the relevance of monoamines in the underlying pathophysiology of depression was reviewed. In the following chapter we will focus on describing the contemporary role of monoaminergic agents in the treatment of depression.

6.1

Origins of the Monoamine Theory of Depression and the Development of the First Monoamine-Based Antidepressant Families

A number of key observations in the 1950s and 1960s linking the monoamines to mood, perception and cognition were pivotal in the formulation of the monoamine hypothesis of depression, published the same year (1965) by Schildkraut in the *American Journal of Psychiatry* (Schildkraut, 1965) and by Bunney and Davis in the *Archives of General Psychiatry* (Bunney and Davis, 1965; see Chapter 4 for a detailed account of the Monoamine Theory of Depression). The antihypertensive reserpine, which was noted to precipitate depression in some cases (Muller et al., 1955), was also found to decrease urine serotonin (5HT) levels (Shore et al., 1955), an effect reversed by administration of the dopamine and norepinephrine precursor DOPA (Degkewitz et al., 1960).

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These initial observations were followed by the serendipitous discovery of the precursors of two of the major contemporary antidepressant families, the monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants (TCAs). Specifically, the administration of iproniazid, an antimycobacterial agent, was first noted to possess antidepressant effects in depressed patients suffering from tuberculosis (Crane, 1956). Shortly thereafter, iproniazid was found to inhibit the monoamine oxidase enzyme involved in the catabolism of serotonin, norepinephrine and dopamine. In parallel, imipramine was initially developed as an antihistamine, but Kuhn (1958) discovered that of some 500 patients with various psychiatric disorders treated, only those with endogenous depression with mental and motor retardation showed a remarkable improvement after about 1 to 6 weeks of daily imipramine therapy. The same compound was subsequently found to inhibit the reuptake of serotonin and norepinephrine (Gershon et al., 1962; Glowinski and Axelrod, 1964). Thus, it was the discovery of the antidepressant effects of iproniazid and imipramine that led to the development of the MAOIs and TCAs, but also such discovery was instrumental in the formulation of the monoamine theory of depression in 1965. In turn, guided by this theory, the subsequent development of compounds selective for the reuptake of either serotonin or norepinephrine or both was designed, rather than accidental. As a result, over the last few decades, chemical alterations of these first antidepressants have resulted in the creation of a wide variety of monoamine-based antidepressants with a variety of, even opposing (selective serotonin reuptake inhibitors – SSRIs and tianeptine for example), mechanisms of action. In the following paragraphs we will first discuss the use of monoamine precursors for the treatment of depression. We will then categorize monoaminergic agents that have been studied for the treatment of depression as belonging to one of 13 families. We will then continue our discussion of the contemporary role of monoaminergic agents in the treatment of depression with the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) for historic reasons, followed by the SSRIs, serotonin receptor antagonists/agonists, serotonin reuptake enhancers, serotonin norepinephrine reuptake inhibitors (SNRIs), serotonin norepinephrine dopamine reuptake inhibitors (SNDRI), norepinephrine reuptake inhibitors (NRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), α -adrenergic receptor antagonists, dopaminergic drugs, catechol-o-methyltransferase inhibitors, and will conclude with the anti-psychotic agents.

6.2

Monoamine Precursors for the Treatment of Depression

Tryptophan and 5-hydroxytryptophan (5-HTP) are precursors of serotonin, and have been studied for decades as a treatment for depression (Fugh-Bergman and Cott, 1999), although some have proposed that tryptophan itself may be insufficient to boost Central Nervous System (CNS) serotonin levels (van Praag, 1981; van Praag et al., 1986). 5HTP has the advantage of bypassing the conversion of tryptophan

into 5HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in serotonin synthesis. Numerous studies, although mostly small and uncontrolled but also some double-blind studies, have shown positive effects for tryptophan and 5HTP in the treatment of depression (Birdsall, 1998; Fugh-Berman and Cott, 1999; Meyers, 2000). However, the results of a meta-analysis for the use of tryptophan and 5HTP in depression reveal that while tryptophan and 5HTP appear to be more effective than placebo, the present evidence is inconclusive, due to the large number of underpowered studies or studies with methodological limitations (Shaw et al., 2002a,b). In fact, of 108 studies reviewed in that meta-analysis, only two were included.

Tryptophan is no longer available in the United States due the emergence of eosinophilia-myalgia syndrome (EMS) associated with its use, characterized by eosinophilia, fever, abdominal pain, dyspnea, skin rash, and elevated serum concentrations of aminotransferase and aldolase (Hertzman et al., 1990). Cases of EMS with 5HTP have also been reported (Michelson et al., 1994). The role of a β -carboline derivative in the development of EMS, found to contaminate the tryptophan and 5HTP preparations of some of those affected, has been postulated (Fugh-Berman and Cott, 1999; Michelson et al., 1994; Williamson et al., 1998). There are also reports of serotonin syndrome when tryptophan was combined with SSRIs (Steiner and Fontaine, 1986), as well as reports of fatalities when tryptophan was combined with MAOIs (Brennan et al., 1988; Staufenberg and Tantam, 1989).

Tyrosine is the precursor of norepinephrine, and L-phenylalanine is the direct precursor of tyrosine. In a double-blind study reported in 1979, DL-phenylalanine (150–200 mg/day) or imipramine was administered to 40 depressed patients (20 in each group) for 1 month. No statistical difference was found between the two groups using the Hamilton Depression Scale and a self-rating questionnaire, leading to the conclusion that DL-phenylalanine (DLPA) might have antidepressant properties (Beckmann et al., 1979). A subsequent open trial for oral phenylalanine (Sabelli et al., 1986) also reported a decrease of depressive symptoms during treatment for depression. Two small case studies suggested L-tyrosine may have potential as an antidepressant (Gelenberg et al., 1980; Goldberg, 1980). However, a 4-week clinical trial treated 65 outpatients with major depression in a double-blind comparison of L-tyrosine (100 mg/kg/day), imipramine, or placebo and found no evidence that L-tyrosine had antidepressant activity (Gelenberg et al., 1990). The development of phenylalanine derivative compounds as antidepressants is currently underway (Amsterdam et al., 2002).

Levodopa (L-Dopa, Sinemet) is the immediate precursor of dopamine, and is approved by the Food and Drug Administration (FDA) for the treatment of Parkinson's disease. A single controlled trial did not reveal levodopa/carbidopa (Sinemet) to be more effective than placebo in the treatment of seasonal affective disorder (Oren et al., 1994).

6.3

Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants (TCAs), referred to as such because they share a chemical structure with two joined benzene rings, have been in use for almost half a century. With the exception of clomipramine, which has been reported to achieve anywhere from 83 to 100% *in vivo* 5HTT occupancy (20–210 mg daily; Suhara et al., 2003), TCAs inhibit the reuptake of norepinephrine more potently than the reuptake of serotonin. In the case of doxepin, amitriptyline and nortriptyline, they also inhibit glycine uptake by blocking the glycine transporter 1b (GLYT1b) and glycine transporter 2a (GLYT2a) to a similar extent. Amoxapine displays a selective inhibition of GLYT2a behaving as a 10-fold more efficient inhibitor of this isoform than of GLYT1b (Nunez et al., 2000) and is also a dopamine D2 receptor antagonist (Kapur et al., 1999). Interestingly, *in vitro* data suggest that trimipramine and clomipramine have comparable affinity for the dopamine D2 receptor (Richelson and Nelson, 1984). TCAs, to varying degrees, are also fairly potent blockers of histamine H-1 receptors, serotonin 5-HT2 receptors, muscarinic acetylcholine receptors, and α -1 adrenergic receptors (Richelson and Nelson, 1984). Imipramine also appears to act as a neurokinin receptor inhibitor (Iwashita and Shimizu, 1992).

Although their overall efficacy in treating depression is equivalent to that of the SSRIs (Anderson, 2000), they tend to have considerably more side-effects and, due to their ability to block the above-mentioned receptors, as well as sodium (Pancrazio et al., 1998) and potassium channels (Casis et al., 1998; Dreixler et al., 2000; Grunnet et al., 2001; Jo et al., 2000; Teschemacher et al., 1999), TCAs are often arrhythmogenic (Harrigan and Brady, 1999) and epileptogenic (Wedin et al., 1986) when taken in very large (supra-therapeutic) quantities. As a result, they are rarely chosen as first-line agents in the treatment of depression (Petersen et al., 2002a). However, the TCAs are still used in treatment-resistant depression (TRD), either as a “next-step” (switch) strategy in patients with SSRI- (Thase et al., 2002a) or MAOI-resistant depression (McGrath et al., 1993), or for depression resistant to several antidepressants (Nierenberg et al., 2003), but also as an adjunct to the SSRIs (augmentation) in SSRI-resistant depression (Amsterdam et al., 1997a; Eisen, 1989; Fava et al., 1994a, 2002a; Levitt et al., 1999; Montes et al., *in press*; Weilburg et al., 1991; Zajecka et al., 1995). In fact, the results of a small study also suggest that augmenting the SSRIs with the relatively noradrenergic TCA desipramine may also speed the onset of clinical response (Nelson et al., 1991), while the results of a subsequent double-blind study suggest greater remission rates following treatment with combined desipramine and SSRIs than SSRIs alone in MDD (Nelson et al., 2004). There is even anecdotal evidence to support the use of TCAs in electroconvulsive therapy-resistant depression (Lykouras et al., 1995; Shapira et al., 1988).

Furthermore, several studies also suggest TCAs may be more effective than the SSRIs in the treatment of melancholic depression, or in the treatment of depressed patients with certain comorbid medical conditions (Danish University Anti-depressant Group, 1986, 1990; Navarro et al., 2001; Robinson et al., 2000; Roose et al., 1994), although not all studies support this finding (Mulsant et al., 1999;

Sandor et al., 1998). It has recently been proposed that age and gender may influence the likelihood of responding to TCAs versus SSRIs in melancholic depression, with older men preferentially responding to TCAs, while younger women preferentially respond to SSRIs (Joyce et al., 2003a).

In addition, perhaps due to their ability to inhibit the reuptake of both serotonin and norepinephrine, as well as their ability to block sodium channels and potassium channels (Galeotti et al., 1997, 2001), TCAs appear to be more effective in treating neuropathic pain than the SSRIs (Sindrup et al., 1999). In fact, the results of a meta-analysis reveal the TCAs to be superior to the SSRIs in the treatment of a number of somatic/pain disorders often diagnosed in patients with chronic depression, including headaches, fibromyalgia, irritable bowel disorder, idiopathic pain, tinnitus and chronic fatigue (O'Malley et al., 1999). For this reason, TCAs and other agents which combine noradrenergic as well as serotonergic activity have been regarded by some researchers as being more effective than the SSRIs in the treatment of certain somatic symptoms of depression such as pain and headaches, and in the treatment of depression with comorbid medical illness.

Studies looking at genetic markers as predictors of response to the TCAs are few. The results of two clinical trials (Joyce et al., 2003b; Tsapakis et al., 2003) but not a third (Pollock et al., 2000), report a polymorphism for the serotonin transporter to influence the likelihood of responding to nortriptyline in MDD. G protein β -3-subunit genotype was found to influence the likelihood of responding to nortriptyline in one study (Joyce et al., 2003b).

6.3.1

Classification

The TCAs may be subdivided into tertiary amines and secondary amines (their demethylated secondary amine derivatives). In addition, maprotiline (Ludiomil), which is classified as a tetracyclic antidepressant is commonly grouped with the TCAs, due to similarities in dosing, mechanism of action and side-effects.

- **Tertiary Amine TCAs:** Examples of tertiary amine TCAs are as follows: amitriptyline (Elavil, Adepril), imipramine (Tofranil, Antidepril), trimipramine (Surmontil, Herphonal), clomipramine (Anafranil, Clopress), and doxepin (Sinequan, Deptran).
- **Secondary Amine TCAs:** Examples of secondary amine TCAs are as follows: nortriptyline (Pamelor, Aventyl), desipramine (Norpramin, Metylyl), protriptyline (Vivactil, Concordin), amoxapine (Ascendin, Defanyl).

6.3.2

Dosage

There is a wide range of effective doses for TCAs. Typical antidepressant doses are 100–300 mg/day for imipramine. There is evidence to suggest a relationship between serum levels of TCAs and clinical response. Perry et al. (1994) pooled

and analyzed all available studies examining the relationship between TCA blood levels and clinical response with the use of receiver operating characteristics curves. The relationship between clinical response and blood levels for desipramine was linear, with the threshold concentration in plasma for therapeutic response being ≥ 116 ng/ml (response rates: 51 vs. 15% for patients with levels above or below that threshold, respectively). The remaining TCAs exhibited a curvilinear (inverse “U”-shaped curve) relationship between blood level and clinical response. The optimal ranges for nortriptyline, “total” imipramine (imipramine plus desipramine), and “total” amitriptyline (amitriptyline plus nortriptyline; with their corresponding response rates within versus outside the level range) were: 58–148 ng/ml (66 vs. 26%), 175–350 g/ml (67 vs. 39%), and 93–140 ng/ml (50 vs. 30%), respectively.

Genotype may also influence the relationship between dose and TCA levels. Duplication of the CYP (cytochrome P450) 2D6L allele of the CYP2D6 enzyme, for instance, present in 2–7% of Caucasians (Agundez et al., 1995) and up to 9% of Ethiopians and 25% of Tanzanians (Aklilu et al., 1996), has been associated with ultra-rapid metabolism of nortriptyline (Bertilsson et al., 1985), imipramine (Brosen et al., 1986a,b) and desipramine (Spina et al., 1984; Bergman et al., 2001). There is also a single case report of ultra-rapid metabolism of maprotiline not resulting from 2D6 duplication (Vormfelde et al., 1997).

Finally, some TCAs including doxepin (Uhr et al., 2003), amitriptyline (Uhr et al., 2000), and nortriptyline (Roberts et al., 2002), are also substrates for p-glycoprotein (p-GP), which is expressed by the ABC (ATP-binding cassette transporter superfamily genes) b gene in blood–brain barrier cells and acts as an extrusion pump for various xenobiotic compounds (Schinkel et al., 1995, 1996), including some antidepressants. The clinical relevance of these relationships remains unclear, although it is possible that p-GP status may influence the relationship between serum levels and CNS levels of TCAs.

6.3.3

Side-effect Profile

The considerable side-effect burden of TCAs accounts for higher drop-out rates than the SSRIs (Anderson and Tomenson, 1995). Thus, treatment is typically initiated at lower doses (e.g. 10 mg/day for imipramine) in order to minimize the risk of adverse events and premature treatment discontinuation. The side-effect profile of the TCAs can be subcategorized in terms of their relative affinity for a number of monoamine receptors and transporters. Overall, secondary amine TCAs tend to cause fewer anticholinergic, antihistaminergic and anti- α -1 adrenergic receptor-related side-effects than tertiary amine TCAs. Amoxapine is the only TCA with documented, significant dopamine D-2 receptor antagonism (Kapur et al., 1999). There have been case reports of tardive dystonia and dyskinesia associated with amoxapine treatment (Hayashi et al., 2000; Huang, 1986), and amoxapine should be avoided in patients with comorbid depression and Parkinson's disease (Okun and Watts, 2002).

Anticholinergic-related side-effects result from the affinity of TCAs for muscarinic cholinergic receptors and typically include sedation, dry mouth, blurred vision (Oshika, 1995), constipation, urinary hesitancy, tachycardia, memory difficulties, and ejaculatory difficulties. Finally, due to their anticholinergic effects, TCAs should be avoided in patients with narrow angle glaucoma (Oshika, 1995) and prostatic hypertrophy, as symptoms related to these conditions may worsen because of such anticholinergic effects.

Antihistaminergic-related side-effects result from histaminergic H-1 receptor blockade and typically include increased appetite, weight gain, sedation and fatigue. Weight gain with TCAs can be substantial, averaging 1–3 lb per month of treatment (Fava, 2000). As a result, TCAs may complicate the management of diabetes and worsen glycemic control (Lustman et al., 1997; True et al., 1987), and should be avoided whenever possible in diabetics (Goodnick, 2001). TCAs may also have hyperlipidemic effects, thus complicating their long-term use in patients with hyperlipidemia (Olusi and Fido, 1996; Pollock et al., 1994). TCA-induced increases in soluble TNF receptor p75 plasma levels (Hinze-Selch et al., 2000) and leptin levels (Hinze-Selch et al., 2000; Moosa et al., 2003) have recently been proposed as additional mechanisms contributing to TCA-related weight gain.

Xerostomia secondary to anticholinergic and antihistaminergic effects may also increase the risk of oral pathology, particularly dental caries (Peeters et al., 1998). There is anecdotal evidence for the usefulness of cholinergic agents (i.e. bethanechol, pilocarpine) in the management of anticholinergic side-effects during TCA treatment (Everett, 1975; Salah and Cameron, 1996).

Perhaps due to their sedative effects, a positive relationship between TCAs and an increased risk of a motor vehicle accident occurring in the elderly has been suggested by one epidemiologic study (Ray et al., 1992). The sedative potential of various antidepressants is also a serious consideration in younger depressed patients as well, as they may also increase the risk of mortality from automobile accidents. In fact, in one literature review (Ramaekers 2003), sedating antidepressants (dothiepin, amitriptyline, imipramine, doxepine, mianserin) were found to result in driving impairments on a standardized road test comparable to impairments found in drivers with a blood alcohol level of 0.8 mg/ml (considered driving under the influence in most states), while non-sedating antidepressants (moclobemide, fluoxetine, paroxetine, venlafaxine, nefazodone) were not found to affect driving performance. Treatment with TCAs has also been reported to worsen some aspects of memory, including immediate recall (Meyers et al., 1991). Despite these sedative effects and reports of TCA-related ventilatory suppression in patients with chronic obstructive sleep apnea (Chronic Obstructive Pulmonary Disease (COPD); Greenberg et al., 1993), treatment of depression with the TCAs in patients with COPD with baseline hypercapnia appears to be effective (Borson et al., 1992) and does not appear to result in worsening hypercapnia, spirometry or ventilatory control (Gordon et al., 1985). In elderly depressed patients, the presence of allele E4 of the apolipoprotein E (APOE) gene was found to confer an increased risk of developing anticholinergic cognitive side-effects in one study (Pomara et al., 2001).

Orthostatic hypotension and reflex tachycardia may result from α -1 adrenergic receptor antagonism. Nortriptyline is generally thought to be less likely to cause orthostatic hypotension than tertiary amine TCAs such as imipramine (Roose et al., 1987a; Thayssen et al., 1981). However, although the affinity of nortriptyline for the α -1 adrenergic receptor is less than that of most TCAs, it is actually much greater (e.g. more than twice) than the affinity of desipramine and protriptyline (Richelson and Nelson, 1984). In addition, homozygosity for the 3435T allele of the ABCB1 gene, the multi-drug resistance gene that encodes a p-GP, appears to be a risk factor for occurrence of nortriptyline-emergent postural hypotension (Roberts et al., 2002), which may be due to decreased CNS and, therefore, increased peripheral concentrations of the drug. Antidepressant-emergent postural hypotension in the elderly may, in turn, increase the risk of falls (Leipzig et al., 1999) and fractures i.e. hip fractures (Ray et al., 1991). There is anecdotal evidence for midodrine, an α -adrenergic receptor agonist, to produce TCA-emergent orthostasis (Maskall and Lam, 1993). Other monoamine-based treatments for SSRI-related side-effects will be discussed in the following sections of the chapter.

The ability of TCAs to inhibit the sodium channel may also result in electrocardiographic changes in susceptible individuals (for instance in post-myocardial infarction patients, in patients with bi-fascicular heart block, left bundle branch block or a prolonged QT interval), even at therapeutic doses (Nelson et al., 1999) and, given that contemporary psychopharmacologists have access to a multitude of alternative treatment options, should be avoided in these patients. Due to the inhibition of sodium channels and cholinergic receptors, the TCAs also carry a risk of seizure. Maprotiline and clomipramine are considered the TCAs with the greatest risk of seizures (Pisani et al., 2002). This combined risk of seizure and arrhythmia renders the TCAs as the least safe during overdose (Henry et al., 1995).

The TCAs also have variable effects on sleep physiology. Certain TCAs (e.g. amitriptyline, trimipramine) shorten sleep-onset latency, improve sleep efficiency and decrease wake time after sleep onset (WASO), while others (e.g. desipramine or protriptyline) prolong sleep-onset latency, reduce sleep efficiency and increase WASO (Winokur et al., 2001). With the exception of trimipramine, all TCAs suppress rapid eye movement (REM) sleep (Winokur et al., 2001). Adjunct Ginkgo biloba was reported to increase sleep efficiency, decrease the number of night-time awakenings, reduce REM density and enhance non-REM sleep in trimipramine-treated patients in one study (Hemmeter et al., 2001). Patients who received a bedtime-only dose of TCAs reported more frequent nightmares than patients who divided their TCA regimen throughout the day according to two studies (Flemlenbaum, 1976; Strayhorn and Nash, 1978).

The endocrinologic effects of the TCAs are highly variable and, at times, appear contradictory. There are several case reports of TCA-emergent hyponatremia or syndrome of inappropriate antidiuretic hormone secretion (SIADH; Adlakha et al., 1991; Liskin et al., 1984; Madhusoodanan and Osnos, 1981; Parker, 1984). There are also case reports of galactorrhea with imipramine (Klein et al., 1964), and clomipramine (Anand, 1985; Fowlie and Burton, 1987), suggesting that an increase in prolactin levels, due to increased serotonergic turnover, may underly such

phenomenon (Hanna et al., 1991). Amitriptyline or imipramine however, do not appear to increase prolactin levels (Meltzer et al., 1977; Sonntag et al., 1996; Steiger and Holsboer, 1997). Linnoila et al. (1981) found no changes in total T3 or T4 in depressed outpatients treated with amitriptyline, imipramine or desipramine. In a subsequent study, however, although administration of desipramine (up to 300 mg) in 19 major depressive disorder (MDD) patients for 6 weeks did not result in changes in thyroid stimulating hormone (TSH), free thyroxine (T4), triiodothyronine (T3) or thyroid binding globulin levels, desipramine administration was found to result in increased total T4 levels (Shelton et al., 1993). In contrast, administration of amitriptyline in MDD outpatients for 6 weeks was reported to result in decreased T4 and free T4 levels (Kusalic et al., 1993). Finally, administration of imipramine for 4 weeks in MDD patients was not found to result in changes in testosterone levels (Sonntag et al., 1996).

Clomipramine did not appear to alter follicle stimulating hormone (FSH), luteotropic hormone (LH), testosterone, prolactin, estradiol, or gonadotropin-releasing hormone (GnRH) levels in depressed men in one study (Maier and Konig, 1994). Similarly, in a study involving administration of clomipramine or nortriptyline to six healthy volunteers for 6 days, there were no significant changes in TSH, growth hormone (GH) or prolactin levels reported (Widerov et al., 1978). Nordgren and von Scheele (1981) also found no effect of 28 days of nortriptyline therapy on T3, T3 reuptake, T4 or TSH in 20 MDD outpatients. Schlienger et al. (1980), however, reported reductions in T3, free T3 and TSH levels with clomipramine treatment. Treatment of endogenous depressives with nortriptyline for 4 weeks was also found to result in increases in prolactin levels (Nielsen, 1980). Doxepin also appears to increase prolactin levels during treatment (Nielsen, 1980).

Perhaps due to their ability to block norepinephrine reuptake, treatment with the TCAs may also result in tremors (Beasley et al., 2000), and anecdotal evidence suggests that the use of β -blockers alleviates such tremors (Kronfol et al., 1983). There are a number of reports of occult pheochromocytoma “unmasked” by TCAs (Achong and Keane, 1981; Birkebaek and Perrild, 1986; Brown et al., 2003; Ferguson, 1994; Johnson et al., 1979; Korzets et al., 1997; Kuhs, 1998; Mok and Swann, 1978).

Chronic treatment with imipramine has also been reported to result in hyperpigmentation of the face, arms and back of hands (Ming et al., 1999) requiring laser treatment (Atkin and Fitzpatrick, 2000). The TCAs also appear to carry an increased risk of emergence of manic symptoms in the treatment of bipolar depression compared to the SSRI, paroxetine (Nemeroff et al., 2001). Finally, symptoms of gastrointestinal and somatic distress, sleep disturbance, and movement disorders and mania have been temporally linked to abrupt discontinuation of TCAs (Garner et al., 1993).

6.4

Monamine-Oxidase Inhibitors (MAOIs)

MAOIs act by inhibiting MAO, an enzyme found on the outer membrane of mitochondria, where it catabolizes a number of monoamines including dopamine, norepinephrine, and serotonin. After reuptake, norepinephrine, serotonin, and dopamine are either reloaded into vesicles for subsequent release or broken down by the enzyme MAO. MAO is present in two forms (MAO-A and MAO-B), which differ in their substrate preferences, inhibitor specificities, tissue expression, and cell distribution. MAO-A preferentially oxidizes serotonin and is irreversibly inactivated by low concentrations of the acetylenic inhibitor clorgyline. MAO-B preferentially oxidizes phenylethylamine (PEA) and benzylamine and is irreversibly inactivated by low concentrations of pargyline and deprenyl. Dopamine, tyramine, and tryptamine are substrates for both forms of MAO (Fava and Rosenbaum, 1995). In the gastrointestinal (GI) tract and the liver, MAO catabolizes a number of dietary pressor amines, such as dopamine, tyramine, tryptamine and phenylethylamine (Hasan et al., 1988). For this reason, consumption of foods containing high levels of dietary amines while on an MAOI may precipitate an adrenergic crisis, characterized by hypertension, hyperpyrexia, tachycardia, tremulousness and cardiac arrhythmias (Lavin et al., 1993). The same reaction may also occur during co-administration of dopaminergic agents and MAOIs, while the co-administration of MAOIs with other antidepressants that potentiate serotonin could result in serotonin syndromes due to toxic CNS serotonin levels. The serotonin syndrome is characterized by alterations in cognition (disorientation, confusion), behavior (agitation, restlessness), autonomic nervous system function (fever, shivering, diaphoresis, diarrhea), and neuromuscular activity (ataxia, hyperreflexia, myoclonus; Beasley et al., 1993; Feighner et al., 1990; Lane and Baldwin, 1997). Since MAO enzymatic activity requires approximately 14 days to be restored, such food or medications should be avoided for 2 weeks after the discontinuation of an irreversible MAOI ("MAOI washout period"). Serotonergic and dopaminergic antidepressants are typically discontinued 2 weeks before the initiation of an MAOI, with the exception of fluoxetine which needs to be discontinued 5 weeks in advance due to its relatively longer half-life.

Older MAOIs, including phenelzine (Nardil), tranylcypromine (Parnate), and isocarboxazid (Marplan), irreversibly inhibit the enzymatic activity of both MAO-A and MAO-B. Newer MAOIs are relatively selective, such as brofaromine (Consonar) and moclobemide (Manerix), which preferentially inhibit MAO-A, and selegiline (Eldepryl), which, at least at doses of 10 mg daily, selectively inhibits MAO-B (Fowler et al., 2001). In addition, while older MAOIs result in irreversible inhibition of MAO, some newer ones such as moclobemide and brofaromine result in reversible inhibition. Reversible MAO-A-selective inhibitors are designed to minimize the risk of hypertensive crises, and patients on conventional doses of moclobemide do not need to strictly adhere to the low tyramine diet, although at very high doses (i.e. 900 mg/day of moclobemide), inhibition of MAO-B also occurs (Bonnet, 2003). Similarly, transdermal selegiline, at doses that produced maximal MAO-B inhibition,

was reported to also inhibit MAO-A in several brain regions tested (Wecker et al., 2003).

More recently, additional pharmacologic properties for the MAOIs have been revealed. MAOIs, for instance, also appear to inhibit the binding of [3 H] quinpirole, a dopamine agonist with high affinity for D2 and D3 dopamine receptors (Levant and Bancroft, 1998; Levant et al., 1996). To complicate the pharmacology of MAOIs, two of the MAOIs, selegiline and tranylcypromine have methamphetamine and amphetamine as metabolites (Baker et al., 1999; Slawson et al., 2002). Phenelzine also elevates brain γ -aminobutyric acid (GABA) levels, and as yet unidentified metabolites of phenelzine may be responsible for this effect (Baker et al., 1999). R[−] but not S[+] selegiline also appears to induce dopamine release by directly modulating ATP-sensitive potassium channels in the striatum (Neusch et al., 1997). Finally, the (−) enantiomer of tranylcypromine also appears to more potently inhibit catecholamine uptake, while the (+) enantiomer appears to more effectively inhibit MAO (Baker and Prior, 2002).

Although the risk for serotonin syndromes may be lower than with the older MAOIs, and a number of studies suggested the safety of combining moclobemide with SSRIs (Dingemanse et al., 1998; Ebert et al., 1995; Joffe and Bakish, 1994), there have been a number of non-fatal (Dardennes et al., 1998; Hilton et al., 1997) and fatal serotonin syndromes involving the co-administration of moclobemide and SSRIs (Dams et al., 2001; Finge et al., 1997; Hojer et al., 2002; Isbister et al., 2001a; Rogde et al., 1999; Singer and Jones, 1997). For these reasons, the concomitant use of moclobemide and serotonergic agents should be avoided. In addition, the co-ingestion of moclobemide and SSRIs in overdose may result in death, which needs to be taken into account for patients at risk for suicide (Isbister et al., 2001a).

In addition to its oral formulation, selegiline is also available in a transdermal form (patch), designed to minimize the inhibition of the MAO enzymes found in the lining of the GI tract (Mawhinney et al., 2003). For instance, in a recent animal study, the inhibition of MAOs in gastrointestinal tissue with transdermal selegiline appeared to be less than that in brain, and doses that produced maximal MAO-A inhibition in brain inhibited MAO-A in gastrointestinal tissue by only 30–40% (Wecker et al., 2003). Treating major depression with transdermal selegiline appears effective (Amsterdam et al., 2003; Bodkin and Amsterdam, 2002) and also safe, even in the absence of a tyramine-restricted diet (Amsterdam et al., 2003). Transdermal selegiline was also found to be more effective than placebo in the prevention of depressive relapse (Moonsammy et al., 2003). Although rare, serotonin syndrome may occur when oral selegiline is combined with serotonergic agents, particularly the SSRIs (Richard et al., 1997). The risk of such drug interactions with the transdermal formulation of selegiline has not been studied. In addition, it is important to keep in mind that, while relatively selective for the MAO-B enzyme, selegiline is an irreversible inhibitor for that enzyme and there is a lag time between discontinuation of selegiline and recovery in MAO-B activity (Fowler et al., 1994). The transdermal form of selegiline (EmSam) is expected to be approved by the Food and Drug Administration (FDA) for the treatment of depression in 2004.

Although the overall efficacy of MAOIs for the treatment of MDD does not differ from that of other commonly used antidepressants, their use is considerably limited by (1) the risk of potentially lethal adverse events such as hypertensive crises and serotonin syndromes, and (2) the strict dietary restrictions required to minimize such risks. As a result, they are rarely chosen as first-line agents in the treatment of depression (Petersen et al., 2002a); their use mainly limited to the treatment of TRD, either as a “next-step” strategy in TCA-resistant depression (Flint and Rifat, 1996; McGrath et al., 1993, 1987a; Nolen, 1989; Nolen et al., 1993, 1988; Thase et al., 1992;), cognitive-behavior therapy (CBT)-resistant depression (Mercier et al., 1992), or even depression resistant to a number of antidepressant trials (Adli et al., 2002; Georgotas et al., 1983; Hoencamp et al., 1994; Stabl et al., 1995; Sunderland et al., 1994; Volz et al., 1994). High doses of the MAOI tranylcypromine (90–170 mg daily) may also be effective in depressed patients who do not experience sufficient improvement during treatment with lower doses (Amsterdam and Berwisch, 1989). Furthermore, relatively low-doses (300 mg) of the MAO-A selective agent moclobemide have also been reported to be safe and effective as an adjunct to TCAs in acute phase of treatment of TCA-resistant depression (Konig and Woldersdorf, 1997; Pestaloty et al., 2003; Schmauss et al., 1988a), a strategy which also appears safe and effective during longer treatment periods (Berlanga and Ortega-Soto, 1995). On the other hand, the evidence for the safety of this combination is clearly not adequate. Treatment with oral selegiline was reported to result in a decrease in depressive symptoms in one open trial (Ruggieri et al., 1986), and greater reductions in depression severity than placebo in a double-blind trial of outpatients with Parkinson's disease (Allain et al., 1993), and there is also an open trial of oral selegiline in atypical MDD (Quitkin et al., 1984).

In addition, perhaps due to their ability to inhibit the reuptake of dopamine in addition to serotonin and norepinephrine, the MAOIs appear to be more effective than TCAs (Liebowitz et al., 1984, 1988; McGrath et al., 1992, 1993; Quitkin et al., 1989, 1990, 1993; Rothschild et al., 1994; Stewart et al., 1989, 1992; Thase et al., 1992, 1995) in the treatment of patients with atypical depression (characterized by mood reactivity in addition to symptoms such as hypersomnia, hyperphagia, extreme fatigue and rejection sensitivity) or in patients with several symptoms of atypical depression, particularly in those patients with early onset and chronic course of illness (Stewart et al., 2002). However, not all studies support this finding (Davidson and Pelton, 1986; Larsen et al., 1991; Paykel et al., 1982). In addition, the results of one double-blind trial also reports treatment with moclobemide to be more effective than treatment with SSRIs in atypical depression (Lonnqvist et al., 1994), but two subsequent double-blind trials did not support this finding for phenelzine (Pande et al., 1996), or moclobemide (Sogaard et al., 1999). In parallel, while the MAOIs also seem to be effective in the treatment of chronic fatigue syndrome (Hickie et al., 2000; Natelson et al., 1996, 1998), studies do not show any effect of the SSRIs on chronic fatigue syndrome (Vercoulen et al., 1996). Although, to date, there are no double-blind studies comparing the relative efficacy of MAOIs versus the SSRIs or TCAs in the treatment of fatigue in depression, the above studies suggest a potential advantage for MAOIs over SSRIs.

Studies examining genetic markers as predictors of clinical response to the MAOIs in MDD are lacking. To date, there is a single negative study examining the role of MAO-A genotype as a predictor of clinical response to moclobemide (Muller et al., 2002).

6.4.1

Side-effect Profile

The most common side-effects of MAOIs include postural hypotension, insomnia, agitation, and sedation. The risk of hypotension and hypertension was recently estimated for moclobemide. Specifically, in analyses of large prospective studies containing over 20,000 patients (Coulter and Pillans, 1995; Delini-Stula et al., 1999), the risk of hypertension or hypotension with moclobemide was estimated at 0.11 and 0.04–0.05%, respectively. In addition, moclobemide was not found to result in changes in supine or standing blood pressure in one study, while in patients with pre-existing hypertension, no significant increases beyond baseline values occurred (Moll et al., 1994). Salt tablets may be useful in alleviating MAOI-emergent postural hypotension (Munjack, 1984). The MAOIs also do not appear to prolong cardiac conduction (Georgotas et al., 1987; McGrath et al., 1987b; O'Brien et al., 1991).

Sexual dysfunction is also common with the MAOIs, although its incidence is much lower than with the SSRIs (Philipp et al., 2000). There is also anecdotal evidence suggesting switching to moclobemide may alleviate SSRI-emergent sexual dysfunction in depressed outpatients (Ramasubbu, 1999). Phenelzine-emergent sexual dysfunction may respond to treatment with Sildenafil (Viagra; Gupta et al., 1999).

Other side-effects include weight change, dry mouth, constipation, urinary hesitancy (Fava and Rosenbaum, 1995). There are reports of rare but serious hepatotoxicity with phenelzine (Bonkovsky et al., 1986; Gomez-Gil et al., 1996). One case of fatal intrahepatic cholestasis related to the use of moclobemide has also been reported (Timmings and Lamont, 1996). Peripheral neuropathies have also been reported, and may be prevented by concomitant therapy with pyridoxine (Harrison et al., 1983; Stewart et al., 1984). There are also several reports of thrombocytopenia during tranylcypromine abuse or overdose (Chatterjee and Tosyali, 1995; Davids et al., 2000; O'Grady and Carney, 1997; Pennings et al., 1997; Szelenyi and Albrecht, 1998), and a report of phenelzine-related leukopenia (Tipermas et al., 1984). Finally, some cases of MAOI abuse have been reported (Ben-Arie and George, 1979; Brady et al., 1991; Davids et al., 2000; Griffin et al., 1981; Szelenyi and Albrecht, 1998).

The endocrinologic effects of treatment with the MAOIs are less well characterized. Joffe and Singer (1987), found no effect of treatment with phenelzine on T4, free T4, T3, T3 resin uptake, or TSH in 16 MDD outpatients. Moclobemide does not appear to alter GH or prolactin (Markianos et al., 1991; Stefanis et al., 1988; Steiger et al., 1994), LH, FSH levels (Markianos et al., 1991; Steiger et al., 1994), total T4, or free T4 levels (Kusalic et al., 1993). Brofaromide, also, did not

appear to alter prolactin, testosterone, FSH or LH levels in one small, short-term study involving normal volunteers (Steiger et al., 1987). Phenelzine (Stewart and Halbreich, 1989), tranylcypromine, but not selegiline (Murphy et al., 1986) do appear to increase melatonin levels. In addition, in a separate study involving 12 depressed patients who were administered 400–600 mg of moclobemide orally for 4 weeks, significant increases in testosterone levels were reported (Markianos et al., 1991). There is only one case report of MAOI-related SIADH (Peterson et al., 1978). MAOIs must be used with caution in patients with diabetes due to the possibility of worsening of hypoglycemia (Adnitt, 1968; Adnitt et al., 1966; Bressler et al., 1968; Cooper and Ahcroft, 1966; Potter et al., 1969; Rowland et al., 1994).

Similar to the TCAs, the MAOIs have also been shown to alter sleep physiology (Winokur et al., 2001). Irreversible MAOIs, for instance, prolong sleep-onset latency, reduce sleep efficiency, increase WASO, and suppress REM sleep (Landolt et al. 2001; Winokur et al., 2001).

6.4.2

Dietary Restrictions and Drug Interactions

As discussed above, treatment with MAOIs carries a risk of hypertensive crisis. To minimize this risk, patients on MAOIs need to adhere to a strict dietary regimen which excludes foods and beverages that have a high content of dietary amines including: all aged cheeses, sour cream, yogurt, fermented or dried meats (sausages, basderma, pastrami, pepperoni, louza, lingiça, chorizo), offal (liver, sweetbread, kidney, tripe, brains), fava and broad bean pods (lima, lentils, snow-peas), marmite yeast extract, sauerkraut, soy sauce and other soy products, overripe bananas and avocado, eggplant, spinach, pickled, dried or salted fish, caviar, fish-roe (tarama), and foods containing monosodium glutamate (MSG). Patients should also avoid consumption of caffeinated drinks, and most alcoholic beverages, especially tap beer, red wine, but also certain white wines including those that are resinated (retsina), botrytized (sauternes, tokaji aszú, trockenbeerenausle), aged (sherry), and others (riesling, vermouth). Sympathomimetics, both prescribed and over-the-counter (pseudoephedrine, ephedrine, oxymetazoline, dextroamphetamine, methylphenidate), potent noradrenergic and dopaminergic antidepressants, dexamethorphan and meperidine (Demerol) may also precipitate a hypertensive crisis. In addition, as mentioned above, combining MAOIs with potent serotonergic agents such as the TCAs, SSRIs, and others carries a risk of serotonergic syndrome.

6.4.3

Dosage

Optimal dosages vary from agent to agent. Optimal doses for phenelzine range between 45 and 90 mg/day, doses of tranylcypromine and isocarboxazid generally range between 30 and 60 mg/day, while doses for moclobemide range from 300–900 mg daily. For oral selegiline, the minimal reported effective dose is 30 mg/day,

while for transdermal selegiline, the minimal effective dose reported is 20 mg/day. There are also reports of adverse reactions (Absher and Black, 1988; Curtin et al., 2002; Halle and Dilsaver, 1993; Joyce and Walshe, 1983; Palladino, 1983) and worsening of mood and anxiety (Tyrer, 1984) following the abrupt discontinuation of MAOIs.

6.5

Selective Serotonin Reuptake Inhibitors (SSRIs)

The immediate action of the SSRIs is to inhibit the neuronal re-uptake of serotonin by blocking the serotonin transporter (Bolden-Watson and Richelson, 1993; Owens et al., 2001). The SSRIs also appear to have effects at other monoamine receptors that vary from agent to agent, with sertraline demonstrating mild dopaminergic reuptake inhibition and paroxetine demonstrating mild noradrenergic reuptake inhibition (Bolden-Watson and Richelson, 1993; Owens et al., 2001). In addition, fluoxetine, particularly its R stereo-isomer, has mild 5HT_{2A} and 5HT_{2C} antagonist activity, which may explain the increase in norepinephrine and dopamine in the prefrontal cortex of animals treated with fluoxetine (Koch et al., 2002), as well as mild noradrenergic reuptake inhibition (Koch et al., 2002; Owens et al., 2001). Paroxetine also appears to inhibit the enzyme nitric oxide synthase (NOS), resulting in a decrease in nitric oxide and an increase in the metabolic end-products of nitric oxide in humans (Finkel et al., 1996; Lara et al., 2003a). Fluoxetine has also been found to depress glutamate exocytosis in the rat cerebrocortical nerve terminals (synaptosomes) via inhibition of P/Q-type Ca²⁺ channels (Wang et al., 2003). Fluoxetine (Fryer and Lukas, 1999; Maggi et al., 1998), sertraline, and paroxetine also appear to act as non-competitive antagonists of nicotinic acetylcholinergic receptors (Fryer and Lukas, 1999). Finally, fluoxetine (Choi et al., 1999, 2001; Hajdu et al., 2003; Terstappen et al., 2003; Thomas et al., 2002; Yeung et al., 1999), norfluoxetine (Choi et al., 2001), and fluvoxamine (Milnes et al., 2003) have also been reported to inhibit potassium channels, while fluoxetine also appears to be a weak inhibitor of sodium channels in some laboratory studies as well (Pancrazio et al., 1998).

With the exception of paroxetine which is a weak cholinergic receptor antagonist, the SSRIs have minimal or no affinity for the cholinergic receptors (Koch et al., 2002; Owens et al., 2001). The effects of the SSRIs on various histaminergic and α -adrenergic receptors are negligible (Koch et al., 2002; Owens et al., 2001). For these reasons, treatment with the SSRIs is associated with greater improvements in memory and cognitive performance than treatment with the TCAs (Ivkovic et al., 2000; Keegan et al., 1991; Levkovitz et al., 2002). This, in turn, may explain the greater improvement in psychosocial and work functioning in MDD patients treated with SSRIs rather than TCAs (Finkel et al., 1999; Lyliard et al., 1997). Treatment with the SSRIs also appears to be associated with lower rates of gait disturbance than treatment with the TCAs (Lemke and Wendorff, 2000), an important consideration in the elderly or medically ill.

The overall efficacy of the SSRIs in the treatment of depression is equivalent to the other antidepressants, while all six of the SSRIs appear to be relatively equally effective in the treatment of depression (Anderson, 2001; Fava et al., 2002b). Due to their favorable side-effect profile, the SSRIs are used as first-line treatment in the overwhelming majority of cases, with more than 90% of clinicians in one survey indicating SSRIs as their first-line treatment preference (Petersen et al., 2002a). The SSRIs also appear to be effective in the treatment of a number of depressive symptoms in addition to depressed mood, including anxiety (Fava et al., 1998a), anger/hostility (Fava et al., 1993, 1996a,b), and sleep disturbance (Fava et al., 2002b). SSRIs also appear to work equally well in patients who present with a variety of comorbid symptoms and conditions including comorbid anxiety symptoms (Fava et al., 2000b; Rush et al., 2001; Simon et al., 1998), personality disorders (Fava et al., 1994b, 2002c; Hirschfeld et al., 1998), attention deficit hyperactivity disorder (Alpert et al., 1996), mild hypo- or hyperthyroidism (Fava et al., 1995; Iosifescu et al., 2001), neuroticism (Petersen et al., 2002b), hypochondriacal concerns (Demopulos et al., 1996), dysfunctional attitudes (Fava et al., 1994c), or in patients with various degrees of temperament characteristics including harm avoidance, reward dependence or novelty-seeking (Newman et al., 2000). The degree of psychosocial adjustment at baseline also does not appear to influence SSRI response in MDD (Papakostas et al., 2003a). SSRIs also appear to work equally well in patients with melancholia, as in patients with atypical depression or depression with anger attacks (Fava et al., 1997a). In fact, anger and hostility appears to improve before anxiety or depressed mood in MDD (Sonawalla et al., 2001a). Finally, the SSRIs also appear to be effective as a “next step” (switch) treatment in TCA-resistant (Amsterdam et al., 1994a; Beasley et al., 1990; Papakostas et al., 2003b; Thase et al., 2002a), or SSRI-resistant depression (Burke et al., 2003; Joffe et al., 1996; Thase et al., 1997; Zarate et al., 1996), and as an adjunct to TCAs in TCA-resistant depression (Weilburg et al., 1989). There is also a case report of SSRIs as an adjunct to venlafaxine in venlafaxine-resistant depression (Gonul et al., 2003).

Despite the tolerability and widespread efficacy of the SSRIs, there is mounting evidence to suggest that depressed patients with certain characteristics have a poorer response to the SSRIs than those without such characteristics including those with comorbid anxiety disorders (Fava et al., 1997a), hopelessness (Papakostas et al., 2004d), a greater burden of medical illness (Iosifescu et al., 2004), a greater burden of cardiovascular risk factors (Iosifescu et al., 2003), a greater number of somatic symptoms such as pain, headaches and fatigue (Papakostas et al., 2004a), hypercholesterolemia (Papakostas et al., 2004b; Sonawalla et al., 2002), hypofolateemia (Alpert et al., 2003; Fava et al., 1997b; Mischoulon et al., 2003; Papakostas et al., 2003c,d), and even in non-abusing patients who consume moderate amounts of alcohol compared to those who do not (Worthington et al., 1996).

There is also mounting evidence that depressed patients with a certain polymorphism for the serotonin transporter have a poorer response to the SSRIs than those without (Arias et al., 2003; Durham et al., 2003; Joyce et al., 2003b; Perlis et al., 2003; Pollock et al., 2000; Rausch et al., 2002; Serreti et al., 2001a; Smeraldi et al., 1998; Yu et al., 2002a; Zanardi et al., 2000, 2001), although not all studies

support this finding (Ito et al., 2002; Kim et al., 2000a; Yoshida et al., 2002a). Two studies also suggest that patients with a specific polymorphism in the gene coding for the enzyme tryptophan hydroxylase, the rate-limiting step in serotonin synthesis, may show a poorer response to SSRIs than those without such a polymorphism (Serretti et al., 2001a,b); although this was not confirmed by a third study (Yoshida et al., 2002b). Finally, there are reports of poorer response to the SSRIs in patients with specific polymorphisms for the interleukin-1 β gene (Yu et al., 2003), the apolipoprotein E gene (Murphy et al., 2003), or the G-protein $\beta 3$ -gene (Serretti et al., 2003; Zill et al., 2000). In contrast, the presence of certain alleles of genes coding for the methyltetrahydrofolate reductase enzyme (Mischoulon et al., 2003), the methionine synthase enzyme (Mischoulon et al., 2003), the dopamine D-2 and D-4 receptors (Serretti et al., 2001c), the 5HT_{2A} receptor (Cusin et al., 2002), the MAOI enzyme (Cusin et al., 2002; Yoshida et al., 2002b), or brain-derived neurotrophic factor (BDNF; Tsai et al., 2003) were not found to influence the likelihood of responding to SSRIs.

6.5.1

Safety: The Use of SSRIs in Various Medical Conditions

The SSRIs appear to be relatively safe when used in depressed patients with comorbid medical disorders. For example, there have been six studies of fluoxetine at a dose of 60 mg/day pursued up to 12 months which have demonstrated the safety and usefulness of that medication in diabetic patients (Goodnick, 2001) although there have been case reports of hypo- (Deeg and Lipkin, 1996; Pollak et al., 2001) or hyperglycemia (Oswald et al., 2003; Petty 1996; Sansone and Sansone, 2003) during SSRI treatment.

In addition, the results of a large ($n = 369$) randomized clinical trial of sertraline versus placebo for the treatment of MDD in patients hospitalized for an acute myocardial infarction or unstable angina revealed sertraline to be safe and effective, without significant adverse effects on left ventricular ejection fraction, ventricular premature complex (VPC) runs, or QTc interval length (Glassman et al., 2002), and more effective than placebo in restoring psychosocial functioning in depressed patients hospitalized for an acute myocardial infarction or unstable angina (Swenson et al., 2003). Sertraline has also been found to accelerate the rate of autonomic recovery in post-MI depressed patients (McFarlane et al., 2001), while treatment with sertraline in depressed post-acute coronary syndrome patients also appears to be associated with reductions in markers of platelet/endothelial activation (β -thromboglobulin and P-selectin; Serebruany et al., 2003). There is also a case report of SSRIs being useful in the treatment of recurrent syncope due to carotid sinus hypersensitivity resistant to dual chamber cardiac pacing (Grubb et al., 1994).

The use of SSRIs in patients with COPD (Chronic Obstructive Pulmonary Disease) has not been systematically assessed. However, administration of SSRIs to patients with obstructive sleep apnea has been shown to result in various beneficial effects in a number of cases including an increase in the minimum night-time percentage of oxygen saturation (Kopelman et al., 1992), a decrease in the apnea/

hypopnea ratio during non-REM sleep (Kopelman et al., 1992; Kraiczi et al., 1999), a decrease in the number of apneas and hypopneas during non-REM sleep (Hanzel et al., 1991), and an increase in peak genioglossus muscle activity during non-REM sleep (Berry et al., 1999). Due to their REM-suppressing effects (Winokur et al., 2001) the SSRIs may also relieve symptoms of cataplexy in patients with narcolepsy (Frey and Darbonne, 1994; Schachter and Parkes, 1980; Thirumalai and Shubin, 2000).

Fluoxetine was also found to be safe and more effective than placebo in the treatment of post-stroke depression (Wiart et al., 2000). Fluoxetine, more so than placebo, was also found to increase the survival of both depressed and non-depressed stroke patients after a 6-month follow-up (Jorge et al., 2003). Non-depressed patients randomized to sertraline (Rasmussen et al., 2003) or fluoxetine (Narushima et al., 2002) were also less likely to develop depression after a stroke than those randomized to placebo. Studies also support the use of sertraline in the treatment of depression (Mohr et al., 2001a) and fatigue (Mohr et al., 2003) in multiple sclerosis (MS). Sertraline also appears to concomitantly reduce interferon- γ production by peripheral blood mononuclear cells in MS patients (Mohr et al., 2001b). Although some patients with Parkinson's disease may experience a worsening of motor symptoms during SSRI administration, these effects do not appear to be consistent (Ceravolo et al., 2000; Dell'Agnello et al., 2001; Tesei et al., 2000), while the SSRIs appear effective in alleviating depressive symptoms (Ceravolo et al., 2000; Dell'Agnello et al., 2001; Hauser and Zesiewicz, 1997; Tesei et al., 2000), and orthostatic hypotension in Parkinson's disease patients (Montastruc et al., 1998). A small open trial also suggests that treatment with citalopram improves bradykinesia in many patients with Parkinson's disease (Rampello et al., 2002). Finally, the SSRIs also appear to have some anti-convulsant effects *in vitro* (Leander, 1992; Pasini et al., 1992; Prendiville and Gale, 1993), while there is anecdotal evidence for an anticonvulsant role for the SSRIs in epilepsy (Favale et al., 1995, 2003), perhaps related to GABA-ergic effects of some SSRIs (Czlonkowska et al., 2003). Open trials of citalopram support its use in patients with MDD and co-morbid epilepsy (Hovorka et al., 2000; Kuhn et al., 2003).

Treatment of depression in hemodialysis patients with fluoxetine appears safe, yielding fluoxetine and norfluoxetine blood levels comparable to those of patients with normal renal function (Blumenfield et al., 1997; Levy et al., 1996), and more effective than placebo in the treatment of depression (Blumenfield et al., 1997). In fact, the fluoxetine and sertraline may also be beneficial with regard to alleviating postural hypotension in dialysis patients, present in up to 50% of patients with end-stage renal disease (Chin et al., 1996; Yalcin et al., 2002). The use of citalopram for the treatment of depression in patients with hepatitis C also appears not to reduce levels of aspartate aminotransferase, alanine aminotransferase, or γ -glutamyltransferase (Gleason et al., 2002). However, the results of a literature review suggest caution when combining SSRIs with NSAIDs in patients who are at risk of bleeding, i.e. cirrhosis (Weinreb et al., 2003). SSRIs also appear to be useful and safe for the treatment of interferon- α -related depressive disorder (Farah, 2002; Hauser et al., 2002; Kraus et al., 2002a; Levenson and Fallon, 1993; Schramm et al.,

2000), and for the prevention of interferon- α (INF- α)-related depressive disorder (Capuron et al., 2002; Hauser et al., 2000; Musselman et al., 2001), perhaps by attenuating the behavioral consequences of interferon- α -mediated tryptophan depletion (Capuron et al., 2003). On the other hand, nitric oxide has also been implicated in INF- α -related depression (Suzuki et al., 2003).

SSRIs also appear to be safe in the treatment of depression in human immunodeficiency virus-positive (HIV+) patients (Cazzullo et al., 1998; Ferrando et al., 1997, 1999; Grassi et al., 1997; Judd et al., 1995; Rabkin et al., 1999), with no significant reductions in CD4 count (Ferrando et al., 1999), and more effective than placebo in the treatment of depression in HIV+ patients who had received adequate treatment (Elliott et al., 1998; Rabkin et al., 1999; Zisook et al., 1998). There is potential, however, for drug interactions between antiretroviral agents and the SSRIs (DeSilva et al., 2001; Eralp Bellibas, 1999; Ouellet et al., 1998).

There are reports of the use of SSRIs as a treatment for depression in advanced cancer (Fisch et al., 2003; Holland et al., 1998), breast cancer (Pezzella et al., 2001), hematological malignancy (Pae et al., 2004), and for the treatment of hot flushes in women with breast cancer (Weitzner et al., 2002). The results of a placebo-controlled study of paroxetine in cancer patients on chemotherapy also reported a significantly greater reduction in depressive symptoms but not fatigue in the paroxetine group (Morrow et al., 2003). There is also an open-label trial for sertraline for depression in patients treated with gonadotropin-releasing hormone agonists (Warnock et al., 1998). However, there are limited data on the use of the SSRIs in transplant recipients. A single study reporting chart reviews of 13 depressed organ transplant recipients treated with fluoxetine revealed no serious adverse events, and no significant alterations in cyclosporine levels or graft function (Strouse et al., 1996). There is also a case report of depression after cardiac transplant treated with paroxetine and psychotherapy (Miller, 2002).

6.5.2

Side-effect Profile

The most common side-effects of the SSRIs are nausea, tremor, excessive sweating, flushing, headache, insomnia/activation or sedation, jitteriness, dizziness, rash, and dry mouth (Masand and Gupta, 1999). Sedation does not appear to occur more often with any particular SSRI, while the SSRIs appear equally well tolerated and effective in the treatment of depressed patients, regardless of whether they present with insomnia/activation or sedation (Fava et al., 2002b; Simon et al., 1998).

The early recognition and management of SSRI-associated adverse events such as fatigue, jitteriness, nausea and headaches is critical, since these side-effects have been reported as a common cause of discontinuation or switching of treatment (Bull et al., 2002). Adjunctive modafinil (Provigil) may be useful as a short-term (i.e. up to 4 weeks) treatment for fatigue in SSRI-treated patients (DeBattista et al., 2003a; Fava et al., 2003c), a practice which may also result in significant improvement in depressive symptoms in some patients (DeBattista et al., 2004), and speed up the onset of action of the SSRIs (Ninan et al., 2003). Adjunctive zolpidem (Asnis

et al., 1999) or melatonin (Dalton et al., 2000; Dolberg et al., 1998) may improve insomnia in patients treated with SSRIs while adjunctive alprazolam (Xanax) has been reported to be effective in the relief of SSRI-emergent jitteriness (Amsterdam et al., 1994b). In addition to relieving SSRI-induced insomnia and jitteriness, the use of adjunct benzodiazepine may also accelerate the onset of the antidepressant response in SSRI-treated patients (Londborg et al., 2000; Smith et al., 1998). There is also anecdotal evidence for valproate prophylaxis for migraine induced by selective serotonin reuptake inhibitors (Delva et al., 2000). Finally, there is anecdotal evidence for the use of Gorei-san (TJ-17) for the treatment of SSRI-associated nausea (Yamada et al., 1999, 2003a).

The use of SSRIs is also associated with the emergence of sexual dysfunction – including decreased libido, delayed ejaculation, impotence, and anorgasmia, or the worsening of preexisting sexual dysfunction in depression (Fava and Rankin, 2002). These side-effects tend to improve rapidly after temporary (“drug holiday”) discontinuation of the SSRIs, particularly those SSRIs with a shorter half-life (Rothschild, 1995), although prolonging such “drug holidays” carries a risk of withdrawal effects and depressive relapse. Sildenafil (Viagra) is also effective for sexual dysfunction during SSRI treatment (Fava et al., 1998b; Nurnberg et al., 2003; Seidman et al., 2003). Three classes of monoamine-based drugs have primarily been used to counteract the sexual side-effects of SSRIs: serotonin receptor antagonists, α 2-adrenergic receptor antagonists, and dopaminergic agents (Fava and Rankin, 2002), although their efficacy remains to be established. There is also a case report of the use of the histaminic-1 and -2 receptor antagonist loratadine (Claritin) to reverse SSRI-emergent sexual dysfunction (Brubaker, 2002). The results of one open trial support the use of Gingko Bilboa for SSRI-related sexual dysfunction (Cohen and Bartlik, 1998); subsequent open (Ashton et al., 2000) and placebo-controlled trials however, did not support this observation (Kang et al., 2002). Monoamine-based treatments for SSRI-related side-effects will be discussed in the following chapters.

Some patients treated with SSRIs may also experience cognitive symptoms such as mental slowing and decreased attention capability, psychological symptoms such as apathy and emotional blunting (Hoehn-Saric et al., 1990 and 1991; Garland et al. 2001; Opbroek et al. 2002; Ellison and Stanziani, 1993; Bertschy and Vandel, 1993), and motor symptoms such as bruxism, akathisia and extrapyramidal symptoms (Adler and Angrist, 1995; Altshuler et al., 1994; Bauer et al., 1996; Bertschy and Vandel, 1993; Black and Uhde, 1992; Boffa and Lofchy, 2000; Bostwick and Jaffee, 1999; Chelben et al., 2001; Chong, 1995; Chong and Tan, 1996; Dave, 1994; Diler et al., 2002; Dominguez-Moran et al., 2001; Fleischhacker, 1991; Freidman, 1990; George and Trimble, 1993; Gerber and Lynd, 1998; Gill et al., 1997; Hansen, 2003; Klee and Kronig, 1993; Lambert et al., 1998; Lee and Nam, 2000; Lipinski et al., 1989; Lobbezoo et al., 2001; Maany and Dhopes, 1990; Mander et al., 1994; Olivera, 1996, 1997; Opler, 1994; Perucca et al., 1997; Reccoppa et al., 1990; Romanelli et al., 1996; Settle, 1993; Shihabuddin and Rapport, 1994; Spigset, 1999; Stanislav and Childs, 1999; Walker, 2002; Wise, 2001). There are also case reports of the SSRIs worsening motor symptoms in patients with Parkinson’s disease (Leo, 1996; Leo et al., 1995;

Steur 1993), as well as increased requirements of levodopa in Parkinson's patients following initiation of an SSRIs for depression (van de Vijver et al., 2002). Anecdotal evidence supports the use of the anticholinergic agent benztropine (Cogentin) (Diler et al., 2002), and the β -adrenergic antagonist propranolol (Fleischhacker, 1991; Lipinski et al., 1989) to alleviate SSRI-emergent akathisia/jitteriness.

Although SSRI-emergent side-effects appear to be well tolerated by most patients (Papakostas et al., 2003e), for depressed patients who are unable to tolerate one SSRI, switching to another SSRI has been effective and well-tolerated in most cases (Brown and Harrison, 1995; Calabrese et al., 2003; Thase et al., 1997, 2002b). For patients complaining of GI side-effects with paroxetine, the continued release formulation (Paxil-CR), reported to have a lower incidence of nausea early on during the course of treatment, and may be used in place of the standard formulation (Golden et al., 2002). The daily dose range for continued release paroxetine is 25–62.5 mg, with the starting daily dose often being 12.5 mg.

Although there are sporadic case reports of SSRI-associated arrhythmias and ECG changes (Catalano et al., 2001; Graudins et al., 1997; Isbister et al., 2001b; Riddle et al., 1989) or tachycardia (Neely, 1998), a large number of studies support the relative safety of the SSRIs with respect to cardiovascular effects. Fluoxetine does not appear to alter QT variability, or heart period variability (Pohl et al., 2003) in healthy volunteers, or to affect either cardiac conduction in post-MI patients (Strik et al., 2000), or left ventricular ejection fraction (LVEF) in elderly depressed patients (Strik et al., 1998). Roose et al. (1998a) studied fluoxetine in 27 MDD patients with cardiac disease and reported that fluoxetine induced a statistically significant 6% decrease in heart rate, a 2% increase in supine systolic pressure, and a 7% increase in ejection fraction. There was no effect on cardiac conduction, ventricular arrhythmia, or orthostatic blood pressure. Fluvoxamine also does not appear to alter LVEF in elderly depressed patients (Strik et al., 1998) or to alter ECG intervals (Hewer et al., 1995).

Similarly, treatment with sertraline does not appear to result in significant changes in heart rate, blood pressure, cardiac conduction, left ventricular ejection fraction, or ventricular ectopic activity in post-MI MDD patients (Glassman et al., 2002; Shapiro et al., 1999). The use of sertraline also appears to be free of cardiovascular adverse events in children and adolescents (Wilens et al., 1999). Paroxetine also does not appear to significantly alter blood pressure, conduction intervals, heart rate or rhythm, or indexes of heart rate variability in MDD patients with ischemic heart disease (Roose et al., 1998b). No significant changes in heart rate, PR, and QTc intervals or in T-wave height were found after treatment with paroxetine in MDD (Edwards et al., 1989). Citalopram does not appear to alter PQ, QRS or QTc intervals (Rasmussen et al., 1999). Finally, of all antidepressants, the SSRIs appear to possess the lowest toxicity in overdose (Henry et al., 1995).

There have been case reports of SSRI-related seizures, mostly occurring during overdoses (Braitberg and Curry, 1995; Caracci and Decina, 1991; Engebretsen et al., 2003; Fisher et al., 2002; Goldstein et al., 1996; Graudins et al., 1997; Gross et al., 1998; Hargrave et al., 1992; Kim et al., 2000b; Neely, 1998; Oke et al., 2001; Prasher, 1997; Raju et al., 2000; Riddle et al., 1989; Saraf and Schrader, 1999; Spivey and

Wait, 1993; Trabert et al., 1995; Ware and Stewart, 1989), although it was noted in one review that a significant proportion of antidepressant-related seizures occurs in individuals with an identifiable predisposition, such as previous seizures, sedative or alcohol withdrawal symptoms, and concomitant use of multiple medications (Rosenstein et al., 1993). Co-administration of agents that inhibit CYP2D6 enzymatic activity, but not CYP2D6 or CYP2C19 genotype, was also identified as a risk factor for antidepressant-related seizures (Spigset et al., 1997). In one prospective study of 100 patients with partial or generalized epilepsy treated with sertraline for depression or OCD and followed for 12 months, six patients experienced an increase in seizure frequency that was thought to be probably or definitely associated with sertraline treatment (Kanner et al., 2000). In addition, the SSRI citalopram was also found not to alter seizure threshold during ECT in a double-blind, placebo-controlled study (Papakostas et al., 2000). Finally, in one literature review, the SSRIs fluoxetine and fluvoxamine were reported to carry the lowest seizure risk of all antidepressants examined (Pisani et al., 1999).

SSRIs have been associated with abnormal bleeding (e.g. bruising, epistaxis) in children and adults who have unremarkable routine hematologic laboratory results except for abnormal bleeding time or platelet counts (Calhoun and Calhoun, 1996; Humphries et al., 1990; Lake et al., 2000; Pai and Kelly, 1996). Paroxetine has been reported to decrease platelet serotonin storage and platelet function (lowered expression of the platelet activation marker CD63 in response to two different concentrations of thrombin receptor-activating peptide) in humans in one study (Hergovich et al., 2000), but did not affect platelet activation of coagulation endothelium or platelets (did not alter plasma concentrations of prothrombin fragment, von Willebrand factor antigen, circulating P-selectin). There are also reports of an increased risk of upper gastrointestinal (Dalton et al., 2003; van Walraven et al., 2001), or postoperative (Movig et al., 2003), but not central nervous system bleeding with the use of SSRIs (Bak et al., 2002; De Abajo et al., 2000), although not all studies suggest an increased risk of upper GI bleeding (Layton et al., 2001). However, systematic study of this issue has failed to reveal abnormalities in platelet aggregation, hematopoiesis, or coagulation profile in SSRI-treated patients (Alderman et al., 1996). For instance, treatment of MDD with fluoxetine was not found to alter coagulation measures including the international normalized ratio (INR), partial thromboplastin time (PTT), thrombin time, bleeding time, euglobulin lysis time, factor II, V, VII, VIII:C, IX, X, XI, XII levels, fibrinogen levels, protein kinase C levels, antithrombin levels, platelet counts, D dimer levels, lupus inhibitor levels, or platelet sensitivity studies to the following agonists: adenosine diphosphate, epinephrine, collagen, and arachidonic acid (Berk et al., 1995). Sertraline also did not appear to alter bleeding time in MDD patients who were post-MI (Shapiro et al., 1999). More recent studies have shown that the combined use of SSRIs and non-steroidal anti-inflammatory agents (NSAIDs) potentiates the risk of GI adverse events (incidence risk ratio (IRR) of 12.4) more than the use of SSRIs alone (IRR 1.2), or the combination of NSAIDs and non-SSRI antidepressants (IRR 2.5; de Jong et al., 2003). Clearly, the role of the SSRIs in potentiating the adverse GI effects of NSAIDs needs further exploration.

There is also a case report of severe bleeding associated with the use of low molecular weight heparin and selective serotonin reuptake inhibitors (de Maistre et al., 2002), as well as drug interactions between SSRIs and warfarin (Claire et al., 1991; Dent and Orrock, 1997; Limke et al., 2002; Woolfrey et al., 1993; Yap and Low, 1999), although interactions between SSRIs and warfarin do not consistently occur (Ford et al., 1997). The reported interactions between SSRIs and warfarin may be mediated through the CYP450 system (Duncan et al., 1998; Sayal et al., 2000), or protein binding (Apseloff et al., 1997). Citalopram does not appear to alter the pharmacokinetics and pharmacodynamics of racemic warfarin (Priskorn et al., 1997). There are no reports of thrombosis or embolism during SSRI treatment.

There have only been sporadic case reports of SSRI-related agranulocytosis (Trescoli-Serrano and Smith, 1996), aplastic anemia (Bosch and Vera, 1998), or leukopenia (Vilinsky and Lubin, 1997). However, it was reported in one study that treatment of depression with a number of agents, including SSRIs, did not appear to alter the number of red blood cells, hemoglobin and hematocrit concentrations, or reticulocyte count (Maes et al., 1996a).

The endocrinologic effects of the SSRIs are less well characterized. There are several case reports of hyponatremia or SIADH during treatment with the SSRIs (Arinzon et al., 2002; Ayonrinde et al., 1995; Baliga and McHardy 1993; Ball, 1993; Barclay and Lee, 2002; Bouman et al., 1998; Bourgeois et al., 2002; Burke and Franker, 1996a and b; Druckenbrod and Mulsant, 1994; Fisher et al., 2002; Flores et al., 2004; Girault et al., 1997; Hull et al., 2002; Iraqi and Baickle, 2004; Kazal et al., 1993; Levsky and Schwartz, 1998; Liu et al., 1996; Lowenthal, 1999; Marik et al., 1990; Odeh et al., 2001; Schattner and Skurnik, 1996). However, a small study ($n = 8$) of daily fluvoxamine administration in healthy subjects for 4 weeks, did not reveal any changes in serum sodium levels during administration but did reveal a small increase in serum sodium levels (mean increase 1.9 mmol/l) following the discontinuation of fluvoxamine (Spigset and Mjorndal, 1997). A large study reporting chart reviews which was published subsequently, did however, suggest an increased risk of hyponatremia in SSRI- or venlafaxine-treated elderly patients (Kirby et al., 2002). Furthermore, in a prospective study, 12 of the 75 elderly MDD patients developed hyponatremia during a 12-week trial with paroxetine (Fabian et al., 2004).

The mechanism of SSRI-associated hyponatremia is unclear. With regard to treatment with fluoxetine, the results of one study did not reveal any significant changes in afternoon basal arginine vasopressin (AVP) levels (Inder et al., 2001), whilst an earlier study had shown a significant decrease in CSF AVP levels in fluoxetine-treated patients (De Bellis et al., 1993). A separate study also failed to show any effects of repeated fluoxetine administration compared to placebo on AVP release, plasma or urine osmolality following a hyper- or hypo-osmotic fluid challenge (Faull et al., 1991). Similarly, treatment with paroxetine also did not appear to interfere with free water excretion following hyposmotic fluid challenge (Marar et al., 2000). In addition, administration of citalopram versus placebo for 7 days to healthy volunteers did not result in significant differences in renin levels between the two groups (Jezova and Duncko, 2002).

Results from studies on the effect of SSRIs on prolactin secretion in humans are somewhat inconsistent. There are reports of hyperprolactinemia (Meltzer et al., 1979; Peterson, 2001), and galactorrhea (Arya and Taylor, 1995; Peterson, 2001;) during treatment with the fluoxetine, although treatment of depression with fluoxetine (up to 80 mg for 12 weeks) in one study was not found to result in increased prolactin levels (Salzman et al., 1993). Administration of fluoxetine 60 mg for 6 days in six healthy post-menopausal women in a separate study, however, was found to increase mean 24-h prolactin secretion significantly (Urban and Veldhuis, 1991).

There are also reports of galactorrhea occurring with paroxetine administration (Bonin et al., 1997; Davenport and Velamoor, 2002; Gonzalez et al., 2000; Morrison et al., 2001). In addition, in one naturalistic study, the rate of breast enlargement appeared to be higher when patients were treated with paroxetine rather than venlafaxine, whilst the trend for higher rates of breast enlargement was associated with paroxetine rather than the other SSRIs (Amsterdam et al., 1997b). These findings could be attributed both to the greater weight gain, and an increase in prolactin levels associated with paroxetine treatment as reported in that study (Amsterdam et al., 1997b). Estradiol and human chorionic gonadotropin (hCG) levels were not influenced by the SSRIs. Paroxetine also appears to increase prolactin levels in healthy volunteers (Cowen and Sargent, 1997), but not in a second study of healthy volunteers (Schlosser et al., 2000) or in separate studies of depressed patients (Muck-Seler et al., 2002; Salzman et al., 1993). Citalopram was found to increase prolactin levels in one study of healthy volunteers (Laine et al., 1997). There is one report of galactorrhea being associated with fluvoxamine use (Bonin et al., 1994), while a small study of healthy volunteers suggests a weak ($p = 0.05$) effect of daily fluvoxamine for 1 month on prolactin (increased), with a substantial increase in two out of eight subjects (Spigset and Mjorndal, 1997). There are reports of galactorrhea (Bronzo and Stahl, 1993; Lesaca, 1996) and breast enlargement (Hall, 1994) being associated with sertraline treatment, although some studies show no effect of sertraline on prolactin (Gordon et al., 1998; Sagud et al., 2002).

To date, there have been no reports published of amenorrhea during SSRI monotherapy. On the contrary, two female patients with Prader–Willi syndrome (PWS) who had primary amenorrhea developed vaginal bleeding believed to be menses following at least 6 months of treatment with fluoxetine (Warnock et al., 1995). Furthermore, the literature supporting reproductive safety is more extensive for fluoxetine than for any other antidepressant (Nonacs and Cohen, 2003).

There are case reports of abnormalities in thyroid function tests among patients treated with sertraline (Harel et al., 1995; McCowen et al., 1997). Sagud et al. (2002), however, reported no change in TSH or T4 levels in 15 MDD patients treated with sertraline (100 mg) for 4 or 24 weeks. While there was no change in T3 levels the first 4 weeks of treatment in that study, T3 levels were increased after 24 weeks of treatment compared to baseline. Administration of fluoxetine (up to 60 mg) in 20 MDD patients for 6 weeks did not result in changes in TSH, free T4, total T4, T3 or thyroid binding globulin (TBG) levels (Shelton et al., 1993). Similarly, treatment with fluvoxamine for 4 weeks did not alter T3, T4 or TSH levels (Moreau et al., 2000). Administration of paroxetine (20 mg) to 25 MDD patients for 24 weeks did

not result in changes in TSH or T3 levels, but did result in a decrease in T3 levels (Konig et al., 2000).

Even less is known about the effects of SSRIs on the gonadal hormones or melatonin. Daily administration of paroxetine for 4 weeks in healthy volunteers did not seem to alter testosterone or melatonin secretion or growth-hormone (GH) secretion in one study (Schlosser et al., 2000). Treatment of panic disorder with fluvoxamine, however, did appear to increase melatonin levels (Den Boer and Westenberg, 1990) while treatment of seasonal affective disorder with fluoxetine reduced melatonin levels (Childs et al., 1995). However, treatment of obsessive-compulsive disorder (OCD) with fluoxetine did not result in lowered melatonin levels in a second study (Monteleone et al., 1995). In fact, it has been proposed that, of all the SSRIs, only fluvoxamine is a potent inhibitor of peripheral melatonin degradation (Hartter et al., 2001). The potential clinical significance of such a relationship is, however, unclear. The effects of the SSRIs on bone mineral density have not been systematically explored.

The effects of the SSRIs on metabolism are variable. Reports in the literature suggest that short-term fluoxetine is responsible for a decrease in food intake assessed by self-report food diaries (Greeno and Wing, 1996), and this may account for the greater weight loss observed during diet plus fluoxetine treatment compared to placebo in overweight subjects (Visser et al., 1993). There are also some reports that fluoxetine may promote weight loss in overweight or obese subjects (Levine et al., 1987) and that this improvement is dose-dependent (Levine et al., 1989). Many MDD patients (de Jonghe et al., 1991; Michelson et al., 1999; Sussman et al., 2001) may also experience reduced appetite and weight loss during the acute phase of treatment with SSRIs. However, any beneficial effects of the SSRIs with respect to weight loss do not seem to be sustained during the continuation and maintenance phases of treatment (Michelson et al., 1999; Sussman et al., 2001), and one study reveals a greater risk for significant weight gain during long-term treatment with paroxetine but not fluoxetine or sertraline (Fava et al., 2000b). A role for adjunctive topiramate (Topamax) in managing weight gain during treatment with the SSRIs has been proposed, and is supported by an open trial (van Ameringen et al., 2002).

The mechanism of SSRI-related changes in weight is unclear, partly because many of the mechanistic studies focus on the short-term effects of SSRIs on biological factors related to weight. For example, although paroxetine (Hinze-Selch et al., 2000) and fluoxetine (Moosa et al., 2003) did not consistently alter serum leptin levels, there was a positive correlation between leptin levels after treatment with fluoxetine and body mass index in one study of women with depression (Moosa et al., 2003). Citalopram did appear to decrease leptin levels in human subjects (Atmaca et al., 2003a), and sertraline was also reported to decrease cerebrospinal fluid (CSF) hypocretin-1 (orexin-A) levels in MDD (Salomon et al., 2003). Fluoxetine has also been reported to increase metabolism (Bondi et al., 2000), by enhancing thermogenesis (Bondi et al., 2000; Bross et al., 1995; Stinson et al., 1992) in humans.

In obese diabetic patients, fluoxetine has been noted to ameliorate mean blood glucose levels, daily insulin requirements and glycohemoglobin levels (Chiasson

et al., 1989; Gray et al., 1992; Kutnowski et al., 1992; O’Kane et al., 1994; Wise, 1992) by improving insulin sensitivity (Maheux et al., 1997; Potter van Loon, 1992). Similarly, in diabetic patients, treatment with the SSRIs has also been reported to reduce weight, as well as fasting plasma glucose levels and HbA1c levels (Goodnick, 2001). Treatment with the SSRIs did not appear to result in increased cholesterol levels in one study (Bilici et al., 2001). In fact, the SSRIs appear to possess anti-hyperlipidemic effects (Bailey and LeMelledo, 2003; Peter et al., 2000; Sonawalla et al., 2001b). Treatment of depression with SSRIs was reported to decrease the activity of a number of antioxidative enzymes (glutathione reductase, glutathione peroxidase, malondialdehyde, superoxide dismutase) in one study (Bilici et al., 2001). However, a subsequent study of healthy volunteers reported an increase in cholesterol levels after 8 weeks of daily paroxetine (Lara et al., 2003b). Finally, treatment of depression with a number of agents, including SSRIs, did not appear to alter iron levels or transferrin as reported in one study (Maes et al., 1996a).

A growing number of studies are also examining the immunologic effects of the SSRIs. Paroxetine did not appear to alter serum-soluble TNF receptor p75 plasma levels in one study (Hinze-Selch et al., 2000). However, fluoxetine (Kubera et al., 2001) and sertraline (Maes et al., 1999a) have been reported to decrease interleukin-10 (IL-10) levels, and the IL-10/interferon- γ (IFN- γ) ratio in depression. Fluoxetine was reported to decrease (Kubera et al., 2001) and sertraline to increase (Maes et al., 1999a) IFN- γ levels in depression although the results of a subsequent study suggest that sertraline decreases IFN- γ production in depressed patients with multiple sclerosis (Mohr et al., 2001b). Sertraline did not appear to alter the production of interleukin-1 β in dysthymia (Anisman et al., 1999).

There are a few reports of rashes developing during SSRI treatment (Charbonnier et al., 1987; Koran et al., 2003; Sannicandro et al., 2002; Spigset, 1999; Thedenat et al., 2001; Warnock and Azadian, 2002). and there are also case reports of alopecia in patients on SSRIs (Mercke et al., 2000).

A growing number of studies have also begun to identify genetic risk factors for the development of SSRI-related adverse events. The presence of a specific polymorphism in the promoter region of the serotonin transporter, for instance, was found to confer an increased risk of developing agitation or insomnia (Perlis et al., 2003), but not nausea (Takahashi et al., 2002) in MDD patients treated with SSRIs. Patients with a functional polymorphism in the monoamine oxidase A (MAOA-VNTR) were found to be at increased risk for developing nausea during treatment with the SSRIs (Yoshida et al., 2003). However, there was no relationship between the presence of a -1438G/A polymorphism in the promoter region of the 5-HT (2A) gene and the incidence of nausea during SSRI treatment (Yoshida et al., 2003). Finally, a double-blind study reported a greater likelihood of discontinuation due to side-effects in paroxetine- but not mirtazapine-treated patients with the presence of a certain single nucleotide polymorphism allele in the 5HT2A gene (Murphy et al., 2003).

6.5.3

SSRI Discontinuation Syndrome

A number of reports also describe discontinuation-emergent adverse events upon abrupt cessation of SSRIs including dizziness, insomnia, nervousness, irritability, nausea, and agitation (Rosenbaum et al., 1998). The SSRIs prolong sleep-onset latency, reduce sleep efficiency, increase WASO, and they suppress REM sleep and prolong REM latency (Armitage, 2000), and their abrupt discontinuation may result in the emergence of nightmares/vivid dreaming (Pace-Schott et al., 2001). For more severe discontinuation-related adverse events, re-institution of the SSRI and a slow tapering-off of the medication may be necessary to alleviate these symptoms (Rosenbaum and Zajecka, 1997). There is also anecdotal evidence to support the use of ginger root (one or two 550-mg capsules t.i.d.) for disequilibrium and nausea associated with discontinuation of SSRIs (Schechter, 1998).

The risk of such withdrawal-related adverse events occurring seems to be inversely related to the plasma half-life of the SSRI, with two studies reporting that withdrawal of fluoxetine carries a significantly lower risk of adverse side-effects than withdrawal of paroxetine (Michelson et al., 2000a; Rosenbaum et al., 1998;). In fact, when patients with fluoxetine- or paroxetine-remitted MDD underwent placebo substitution of their SSRI for 3 days, there was a greater CNS drug level decrease in the paroxetine-treated group (88% decrease) than in the fluoxetine-treated group (38%), with withdrawal-related adverse events correlating with the CNS drug level in the paroxetine group (Henry et al., 2000). Finally, an increase in plasma insulin-like growth factor-1 (IGF-1) levels during abrupt discontinuation of SSRIs has been reported (Michelson et al., 2000c).

6.5.4

Dosage

Due to their relatively low side-effect burden, the starting dose of SSRIs is often the minimally effective dose: 10 mg for escitalopram (Lexapro), 20 mg for fluoxetine (Prozac), paroxetine (Paxil), citalopram (Celexa), 50 mg for sertraline (Zoloft), and 100 mg for fluvoxamine (Luvox). Starting at lower doses and increasing the dose shortly thereafter (i.e. after 1–2 weeks) may further improve tolerability.

In vivo serotonin transporter occupancy during treatment with low doses of SSRIs have been reported to range between 76% for fluvoxamine (25 mg; Suhara et al., 2003), 83% for paroxetine (20 mg; Meyer et al., 2001), and 77% for citalopram (20 mg; Meyer et al., 2001), with higher doses yielding greater 5HTT occupancy for fluvoxamine (79–93%; 200–400 mg; Suhara et al., 2003) and paroxetine (92–100%; 30–40 mg; Kent et al., 2002).

Although it has been hypothesized that the SSRIs demonstrate a “flat” dose–response curve (i.e. higher SSRI doses do not necessarily improve outcome), a number of patients who do not respond to lower doses of SSRIs appear to respond shortly (2–4 weeks) after the dose is increased (Fava et al., 1992, 1994a, 2002a). Contrary to the TCAs, however, SSRI plasma levels do not appear to be useful in

guiding dosing in clinical practice. Specifically, there appears to be great variability from one patient to the next in terms of SSRI plasma levels for each given dose, while plasma levels also do not appear to correlate with the likelihood of response (Mauri et al., 2002), or relapse (Brunswick et al., 2000). In addition, steady state CNS fluvoxamine levels were found to correlate with plasma levels but not dose in one study (Strauss et al., 1997), although there was a correlation between CNS fluvoxamine levels and dose in a subsequent study by the same group (Strauss et al., 2002).

Several factors may account for the lack of correlation between dose, plasma/CNS SSRI levels and clinical response. SSRIs often take longer to achieve steady state levels in the CNS than in plasma (up to 30 days is reported in the study by Strauss et al. (1997)), while rapid decreases in CNS concentrations ranging from 38% (fluoxetine) to 88% (paroxetine) only 3 days after discontinuation have been reported by Henry et al. (2000). In addition, steady state CNS fluvoxamine levels were found to correlate with plasma levels but were not found to correlate with dose in one study (Strauss et al., 1997), although a positive correlation between CNS fluvoxamine levels and dose was found in a subsequent study by the same group (Strauss et al., 2002). Furthermore, the CNS and plasma elimination half-life may differ for some SSRIs. The CNS elimination half-life for the SSRI fluvoxamine (58–79 h), for instance, was reported to be longer than its respective plasma elimination half-life (26–35 h) in two studies (Bolo et al., 2000; Strauss et al., 1998). However, the CNS elimination half-life of fluoxetine combined with norfluoxetine in the latter study was not statistically different from the plasma elimination half-life (406 h). There is growing evidence to suggest that genotype may also influence the relationship between dose and SSRI levels. For instance, certain mutations of the CYP2C19 (*2, *3) have been associated with decreased fluoxetine (Liu et al., 2001), but not fluvoxamine metabolism (Jan et al., 2002). In parallel, certain mutations of the CYP2D6 (i.e. *5, *10) have been associated with decreased fluvoxamine (Gerstenberg et al., 2003a), paroxetine (Yoon et al., 2000) and fluoxetine metabolism (Yu et al., 2002b; Llerena et al., 2004), although not all studies support this finding (Ohara et al., 2003). However, the CYP2D6 genotype does not appear to influence the likelihood of responding or developing side-effects to fluoxetine in MDD (Gerstenberg et al., 2003b; Roberts et al., 2004). There is also a report of ultra-rapid metabolism of paroxetine in a patient with CYP2D6 gene duplication (Charlier et al., 2003).

Citalopram (Uhr and Grayer, 2003b), paroxetine (Uhr et al., 2003), but not fluoxetine (Uhr et al., 2000) also appear to be substrates for p-GP, although it is unclear how p-GP substrate status influences the relationship between SSRI serum levels and the likelihood of clinical response *in vivo*. Furthermore, sertraline and paroxetine are potent inhibitors, fluoxetine and fluvoxamine intermediate inhibitors, while citalopram is a weak inhibitor of p-glycoprotein activity (Weiss et al., 2003). Finally, variability from patient to patient in the fraction of fluoxetine bound to CNS structures other than the 5HTT transporter (i.e. proteins and lipids) has recently been proposed as an additional factor that may contribute to the lack of correlation between SSRI dose, CNS level and clinical response (Strauss and Dager, 2001).

6.5.5

Drug Interactions

With the exception perhaps of citalopram, and its stereo-isomer escitalopram (Hemeryck and Belpaire, 2002), SSRIs may inhibit cytochrome P450 isoenzymes to varying degrees, potentially causing substrate levels to rise, or reducing conversion of a substrate into its active form. As discussed above, the augmentation and combination of SSRIs with other serotonergic agents, tryptophan, 5HTP, or MAOIs may also result in the serotonin syndrome (Beasley et al., 1993; Feighner et al., 1990; Lane and Baldwin, 1997). Clinicians treating patients with such combinations should be aware of this potential, particularly in patients prescribed SSRIs with a longer half-life such as fluoxetine, and in polypharmacy where the potential for cross-inhibition of the cytochrome p450 isoenzymes is greatly increased.

6.6

Serotonin Receptor Antagonists/Agonists

Both trazodone (Desyrel) and nefazodone (Serzone) are relatively weak inhibitors of serotonin and norepinephrine uptake and they primarily block serotonin 5HT_{2A} receptors (in some cases, demonstrating partial agonist properties; Haria et al., 1994; Hemrick-Luecke et al., 1994; Meyer et al., 1999; Taylor et al., 1995), although the *in vivo* effects of nefazodone at the 5HT_{2A} receptor appear to be modest (39% 5HT₂ occupancy after a single dose of 200 mg, Meyer et al., 1999; less than 50% after 6 weeks of treatment with an average dose of approximately 450 mg, Mischoulon et al., 2002). Trazodone and nefazodone also share an active metabolite, m-chlorophenylpiperazine (mCPP), which acts as a serotonin 5HT_{2C} agonist and appears to be able to release serotonin presynaptically (Rothman and Baumann, 2002), while nefazodone also appears to act as a non-competitive antagonist of nicotinic acetylcholinergic receptors (Fryer and Lukas, 1999). Trazodone also appears to stimulate the μ 1- and μ 2-opioid receptors (Schreiber et al., 2000) and is a potent agonist of the serotonin 5HT_{2C} receptors, which are able, when activated (Marcoli et al., 1998; Maura et al., 2000), to inhibit the N-methyl-D-aspartate (NMDA)-emergent cyclic GMP elevation. Since trazodone is also a weak inhibitor of serotonin reuptake, the overall effect of trazodone appears to be an increase in extracellular levels of serotonin in the brain (Pazzagli et al., 1999). This effect explains the fact that trazodone monotherapy has been associated with the occurrence of serotonin syndromes (Rao, 1998).

Trazodone is also potent blocker of the α -1 adrenergic receptor and is very sedating. In fact, in one controlled trial the incidence of asthenia and/or sedation with trazodone was almost double than that of fluoxetine (42.6 vs. 21.5%; Beasley et al., 1991). For this reason, low-dose trazodone (25–150 mg at bedtime) is commonly (Dording et al., 2002) used in the treatment of insomnia secondary to antidepressant use (Kaynak et al., 2004; Nierenberg et al., 1994a), including MAOI-emergent insomnia (Haffmans and Vos, 1999; Jacobsen, 1990; Nierenberg and Keck, 1989),

a strategy which may also result in improvement in depressive symptoms (Nierenberg et al., 1992; Zetin, 1984). Trazodone may also be effective for insomnia in ECT-treated patients (Krahn et al., 2001). There is also anecdotal evidence for the reversal of SSRI-emergent sexual dysfunction with trazodone use (Michael and O'Donnell, 2000).

Although they seem as effective as the SSRIs in the treatment of depression, these agents are used less commonly as first-line treatment (Petersen et al., 2002a). The results of small trials support the use of trazodone in the treatment of HIV-positive subjects and cancer patients with adjustment disorders (De Wit et al., 1999; Razavi et al., 1999).

The most common side-effects of trazodone are sedation, orthostatic hypotension, and headaches. A rare but serious side-effect of trazodone is that of priapism of both penis and clitoris (Bardin and Krieger, 1990; Thompson et al., 1990), which requires immediate medical attention. Priapism has been attributed to the α -adrenoceptor blocking properties of trazodone by interference with the sympathetic control of penile detumescence (Saenz de Tejada et al., 1991).

Rare cases of hepatotoxicity have been associated with the use of trazodone (Fernandes et al., 2000; Longstreth and Hershman, 1985; Rettman and McClintock, 2001), and fatal cases of trazodone overdose have also been reported (de Meester et al., 2001). There have also been several reports of changes in cardiac conduction and/or arrhythmias in patients taking trazodone (Aronson and Hafez, 1986; Himmelhoch et al., 1984; Irwin and Spar, 1983; Janowsky et al., 1983a,b; Levenson, 1999; Lippmann et al., 1983; McCracken and Kosanin, 1984; Rausch et al., 1984; van de Merwe et al., 1984; Vitullo et al., 1990; Vlay and Friedling, 1983; White and Wong, 1985), which may be due to the ability of trazodone to inhibit potassium channels (Casis and Sanchez-Chapula, 1998). There is also a risk of serotonin syndrome when trazodone is combined with serotonergic agents such as nefazodone (Margolese and Chouinard, 2000), TCAs (Nisijima et al., 1996), SSRIs (George and Godleski, 1996; Reeves and Bullen, 1995), venlafaxine (McCue and Joseph, 2001), and buspirone (Goldberg and Huk, 1992).

Trazodone has been reported to increase prolactin levels (Otani et al., 1995; Roccatagliata et al., 1982). In one review trazodone was reported to carry one of the lowest risks for seizures of all antidepressants examined (Pisani et al., 1999), although there have been reports of hyponatremia and seizure during trazodone overdose (Balestrieri et al., 1992; Vanpee et al., 1999). There are reports of adverse reactions (Menza, 1986; Montalbetti and Zis, 1988; Peabody, 1987) following the abrupt discontinuation of trazodone. Nefazodone, but not trazodone, is an inhibitor of p-glycoprotein activity (Stormer et al., 2001). Finally, the presence of mutations for the CYP2D6 enzyme (Mihara et al., 1997) or the CYP1A2 enzyme (Mihara et al., 2001) do not appear to influence trazodone levels. The minimal effective dose for trazodone is usually 300 mg daily, and 600 mg daily is the optimal dose.

Nefazodone has less affinity for the α -1 adrenergic receptor and is, therefore, less sedating. Common side-effects include somnolence, dizziness, dry mouth, nausea, constipation, headache and amblyopia and blurred vision (Cyr and Brown, 1996). Treatment with nefazodone has the advantage of a lower risk of long-term

weight-gain as compared to treatment with the SSRIs or TCAs (Sussman et al., 2001), perhaps because of the appetite-reducing effects of mCPP (Sargent et al., 1997). Nefazodone also has the advantage of a lower risk of sexual side-effects than the SSRIs (Clayton et al., 2002; Ferguson et al., 2001; Montejo et al., 2001). There is also anecdotal evidence to support the use of nefazodone for SSRI-emergent anorgasmia (Michael et al., 1999; Reynolds, 1997). Although small open trials provide preliminary support for the use of nefazodone in patients with treatment-resistant depression (Mischoulon et al., 2000a; Taylor and Prather, 2003), larger controlled studies are lacking. A small double-blind study reported nefazodone to be as effective as fluoxetine in the treatment of depression in outpatients with Parkinson's disease, with perhaps fewer motor side-effects (Avila et al., 2003). There are also open trials of nefazodone for the treatment of depression in HIV+ patients (Elliott et al., 1999), patients with congestive heart failure (Lesperance et al., 2003), and chronic headaches (Saper et al., 2001). There is one case report of remission of cancer chemotherapy-induced emesis during treatment of depression with nefazodone (Khouzam et al., 1998).

Unlike the TCAs, MAOIs and SSRIs, nefazodone does not appear to suppress REM sleep (Rush et al., 1998). In fact, a recent 8-week study comparing the effects of nefazodone and fluoxetine on sleep disturbances in outpatients with non-psychotic depression and insomnia found that fluoxetine was associated with approximately a 30% increase in the number of nocturnal awakenings, whereas nefazodone was associated with about a 15% decrease, a net difference of 45% (Rush et al., 1998).

A rare but serious side-effect of is priapism of both penis and clitoris (Brodie-Meijer et al., 1999; Toofanny and Maddens, 2002), which requires immediate medical attention. In addition, an increasing number of reports suggest treatment with nefazodone may be associated with hepatotoxicity (approximately 29 cases per 100,000 patient years; Carvajal et al., 2002), often severe (more than 80% of cases), and often appearing during the first 6 months of treatment (Stewart, 2002). To date, there has even been one published reported death due to such hepatotoxicity (Ehrentauf et al., 2002). As a result, nefazodone was removed from the market in Canada on 27 November 2003 (Choi, 2003). Nefazodone should be avoided in patients with current or past history of liver abnormalities, while liver enzymes should be checked periodically in patients on nefazodone. There is also a report of nefazodone-emergent hypoglycemia in a patient with diabetes and MDD (Warnock and Biggs, 1997), and a single case report of nefazodone-associated torsade de pointes (Siddiqui and Khan, 2004). The combination of nefazodone with the SSRIs may result in serotonin syndrome (John et al., 1997; Smith and Wenegrat, 2000). Nefazodone has also been reported to inhibit CYP3A4 (DeVane et al., 2004), and co-administration of nefazodone with 3A4-metabolized drugs has been reported to result in increased drug level (DeVane et al., 2004; Lam et al., 2003). Finally, the abrupt discontinuation of nefazodone has been reported to result in adverse reactions (Benazzi, 1998a; Kotlyar et al., 1999; Lauber, 1999; Rajagopalan and Little, 1999; Tamam and Ozpoyraz, 2003). The minimal effective dose for nefazodone is usually 300 mg daily, and the optimal dose is 600 mg daily.

Ritanserin, a serotonin 5HT_{2A} and 5HT_{2C} antagonist, is not FDA-approved, but is available in Europe. One placebo-controlled study revealed ritanserin to be effective in the treatment of dysthymic disorder (Bersani et al., 1991), although a second study found imipramine to be more effective than ritanserin for this condition (Bakish et al., 1994). In a separate study, ritanserin was reported to be as effective as amitriptyline in patients suffering from depression and chronic headaches (Nappi et al., 1990). Ritanserin appears to be effective for depression at doses above 5 mg.

Agomelatine, a newer agent, is a selective 5HT_{2C} antagonist and also an agonist at various melatonergic receptors. The 5HT_{2C} antagonism properties of agomelatine are thought to be responsible for increases in frontocortical dopaminergic and adrenergic activity in animals (Millan et al., 2003). A single placebo-controlled trial found agomelatine (25 mg) to be effective in the treatment of MDD (Loo et al., 2002). The results of one study also suggest that rapid discontinuation of agomelatine is well tolerated, with no discontinuation symptoms reported (Montgomery, 2003). Agomelatine is in the early stages of development and is not available for prescription.

Buspirone (Buspar) and gepirone (Ariza) act as full agonists at serotonin 5HT_{1A} autoreceptors and are generally, but not exclusively, partial agonists at postsynaptic serotonin 5HT_{1A} receptors (Blier and Ward, 2003). Buspirone and gepirone show weak α -1 adrenoceptor affinity but significant and selective α -1 adrenoceptor intrinsic efficacy, which was expressed in a tissue- and species-dependent manner (Rimele et al., 1987), and they also show weak dopamine D-2 antagonism properties (Piercey et al., 1994). The latter effect is thought to lead to excitation of noradrenergic cell firing (Piercey et al., 1994), antagonizing primarily presynaptic inhibitory dopamine D₂ autoreceptors at dopaminergic neurons (Lechin et al., 1998). Buspirone also has potent α -2-adrenoceptor antagonist properties via its principal metabolite, 1-(2-pyrimidinyl)-piperazine (Astier et al., 2003; Gobert et al., 1999).

Buspirone is far more commonly encountered as a treatment for anxiety than depression, while gepirone has not yet been FDA-approved. Nevertheless, a number of double-blind trials report buspirone (Fabre, 1990; Rickels et al., 1990, 1991; Robinson et al., 1990) and gepirone (Feiger, 1996; Feiger et al., 2003; Jenkins et al., 1990; McGrath et al., 1994; Thase et al., 2003a; Wilcox et al., 1996) to be more effective than placebo in the treatment of major depressive disorder, gepirone to be more effective than placebo in the treatment of anxious depression (Alpert et al., 2003), and gepirone to be more effective than placebo in the prevention of depressive relapse (Amsterdam et al., 2004). In addition, case reports (Bouwer and Stein, 1997; Fischer et al., 1998; Jacobsen, 1991), and open trials (Dimitriou and Dimitriou, 1998; Joffe and Schuller, 1993) support a potential role for adjunct buspirone in the treatment of SSRI-resistant depression, although placebo-controlled studies report mixed findings (Appelberg et al., 2001; Landen et al., 1998). The use of adjunct buspirone was also reported to accelerate the antidepressant effects of the SSRIs in one study (Appelberg et al., 2001). Buspirone administration was reported to potentiate fluoxetine-induced dopamine and noradrenaline release in the frontal cortex of rats in one study (Gobert et al., 1997).

One advantage of gepirone and perhaps buspirone is that their use does not appear to be related to a greater incidence of weight-gain or sexual side-effects than placebo, at least during the acute phase of treatment of depression (Feiger et al., 2003). In addition, buspirone augmentation of SSRIs has also been reported to be more effective than placebo in improving libido and sexual dysfunction in depressed outpatients (Landen et al., 1999). However, in a subsequent study, buspirone augmentation of SSRIs in women who had responded to SSRIs but were experiencing sexual dysfunction was not found to be more effective than placebo in alleviating sexual dysfunction or residual depressive symptoms (Michelson et al., 2000b). There are also anecdotal reports of buspirone being effective in alleviating bruxism (Bostwick and Jaffee, 1999; Ellison and Stanziani, 1993; Jaffee and Bostwick, 2000; Romanelli et al., 1996) associated with the use of SSRIs or venlafaxine. Effective daily doses for buspirone and gepirone for depression range between 30–90 mg and 20–80 mg, respectively. Side-effects are similar for these two agents and include headache, dizziness, light-headedness, nausea, and insomnia (Feiger et al., 2003; Newton et al., 1986).

Tandospirone (Sediel) is another serotonin 5HT_{1A} partial agonist available in Japan for the treatment of depression and anxiety. The use of adjunct tandospirone was not found to significantly accelerate the antidepressant effects of clomipramine in one study (Yamada et al., 2003b), although the dosages used in that study were not found to achieve significant 5HT_{1A}-receptor occupancy *in vivo* (Nakayama et al., 2002). Similar to buspirone, tandospirone administration was reported to potentiate fluoxetine-induced dopamine release in the frontal cortex of rats (Yoshino et al., 2002).

Other newer 5HT_{1A} agonists are also being developed; ipsapirone (Stahl et al., 1998) and zalospirone (Rickels et al., 1996) are reported to have greater effectiveness than placebo in controlled trials, while a second trial of iprapirone showed greater efficacy over placebo only for core depressive symptoms (Lapierre et al., 1998). For the serotonin 5HT_{1A} partial agonist flesinoxan, only a small open trial in patients with treatment-resistant depression has been reported (Grof et al., 1993). Flibanserin is a 5HT_{1A} agonist, DRD₄ partial agonist, and 5HT_{2A} antagonist and is in early stages of development (Borsini et al., 2002). There is also at least one 5HT_{1B} inverse agonist (Roberts et al., 2001), one 5HT_{1A} agonist/5HT_{2A} antagonist (Pullar et al., 2000), one 5HT₇ receptor antagonist (Pouzet, 2002), one 5HT_{2C}-selective antagonist (Blackburn et al., 2002), and one 5HT_{2C}-selective agonist (Scriabine, 2003) in the pre-clinical stages of development.

Pindolol (Barbloc, Vypen Viskin in the US), a β -adrenergic receptor antagonist and serotonin 5HT_{1A}-receptor antagonist (Andree et al., 1999), is FDA-approved for hypertension. Due to its 5HT_{1A} agonist activity, it has been hypothesized that pindolol may accelerate the onset of antidepressant action when co-administered with SSRIs (Blier, 2001) while, similar to the 5HT_{1A} agonists, it has been reported that pindolol co-administration potentiates SSRI-induced frontal cortex dopamine release in the rat (Gobert and Millan, 1999). To date, several placebo-controlled studies have reported pindolol to accelerate the therapeutic effects of antidepressants (Bordet et al., 1998; Isaac et al., 2003; Perez et al., 1997; Tome et al., 1997; Zanardi

et al., 1997) while others have not (Berman et al., 1999, 1997; Geretsegger et al., 2002; Maes et al., 1996b, 1999b; Magyaros and Haraszti, 2002). A single placebo-controlled trial also suggests that pindolol may accelerate the therapeutic effects of ECT (Shiah et al., 2000). Only a subset of these studies, however, report greater efficacy at endpoint during treatment with pindolol than placebo (Zanardi et al., 1997; Perez et al., 1997). Finally, the results of a placebo-controlled trial do not support the use of adjunctive pindolol in antidepressant-resistant depression (Perez et al., 1999). The results of a recent meta-analysis concluded that pindolol augmentation appears to be more effective than placebo at 2, but not 6 weeks (Ballestros and Callado, 2004). Although administration of pindolol controlled-release (CR) formulation 7.5 mg daily for 1 week was reported to result in significant 5HT_{1A} receptor occupancy in the dorsal raphe (38–40%) and cortex (12–18%) of healthy volunteers (Martinez et al., 2001), a positron emission tomography (PET) study has shown that augmenting SSRIs or venlafaxine with a 5-mg t.i.d. regimen achieved modest (19%) but significant occupancy of the 5HT_{1A} autoreceptor, while augmentation with the regimen used in the vast majority of clinical trials (2.5 mg t.i.d.) did not achieve significant occupancy (Rabiner et al., 2001). In parallel, microdialysis studies in paroxetine-treated animals administered intravenous pindolol revealed that at plasma levels observed in patients after a 2.5-mg t.i.d. dose (approximately 60 nmol/l), pindolol did not augment the SSRI-induced increase in 5HT in guinea pig hippocampus or raphe (Cremers et al., 2001). NAD-299 which is in the early stages of development is a 5HT_{1A}-selective antagonist with minimal affinity for the β -adrenergic receptor (Johansson et al., 1997). 5HT_{1A} occupancy of 62–85% in the raphe and 68–75% in the neocortex after a single 10-mg dose of NAD-299 in healthy male subjects has been reported (Andree et al., 2003). Although, contrary to initial hypotheses, β -adrenergic receptor antagonism does not appear to worsen mood (Ko et al., 2002), the development of 5HT_{1A}-selective antagonists may lead to the development of treatment strategies that would accelerate the antidepressant response.

Fenfluramine (Pondimin) and dexfenfluramine (Redux) are substituted amphetamines that, in a manner similar to mCPP, act to release 5HT presynaptically (Rothman and Baumann, 2002). Metabolites of these two agents also act as 5HT_{2C} agonists which might explain their anorectic effect, as well as 5HT_{2B} receptor agonists which may explain their adverse valvular effects (Rothman and Baumann, 2002). Initially developed and FDA-approved as anti-obesity drugs, a number of double-blind studies reported greater reductions in depressive symptoms among fenfluramine- or dexfenfluramine-treated than among placebo-treated patients (Blouin et al., 1988; Brzezinski et al., 1990; Galletly et al., 1996; O'Rourke et al., 1989), although a single-open trial did not support the use of fenfluramine as an adjunct to TCAs in TCA-resistant MDD (Price et al., 1990). Both fenfluramine and dexfenfluramine were withdrawn from the market by the FDA in September of 1997 due to reports of cardiac valvulopathy, estimated to occur in as many as one in eight patients who had been treated for at least 90 days (Sachdev et al., 2002). The use of these agents was also linked to the development of primary pulmonary hypertension and serotonergic neurotoxicity (Rothman and Baumann, 2002).

To date, there has been no evidence to support the use of selective 5HT₃-receptor antagonists in depression, these drugs have been FDA-approved for the prevention of nausea and vomiting and include ondansetron (Zofran), granisetron (Kytril), and tropisetron (Navoban; Morrow et al., 1995), although there is preliminary evidence to support the use of ondansetron for the treatment of anxiety (Freeman et al., 1997; Hewlett et al., 2003; Schneier et al., 1996). A single case report also exists for granisetron in SSRI-emergent sexual dysfunction (Nelson et al., 1997), and bupropion-emergent nausea (Lara et al., 2001). A subsequent placebo-controlled trial, however, did not support the use of granisetron in SSRI-emergent sexual dysfunction (Nelson et al., 2001).

There is also no evidence to support the use of selective 5HT_{1D}-receptor agonists in the treatment of depression, these drugs have been FDA-approved for the acute treatment of migraines, and are exemplified by sumatriptan (Imitrex), rizatriptan (Maxalt), almotriptan (Axert), eletriptan (Revmax), naratriptan (Amerge), zolmitriptan (Zomig), frovatriptan (Frova; Ferrari et al., 2002), although treatment of headaches with the triptans in one study was shown to result in a concomitant reduction in depressive symptoms in outpatients with comorbid migraines and depression (Miranda et al., 2001).

Several anecdotal reports suggest the utility of cyproheptadine (Periactin), an antihistamine and 5HT₂ antagonist, for the treatment of SSRI-emergent sexual dysfunction (Aizenberg et al., 1995; Arnott and Nutt, 1994; Cohen, 1992; Keller Ashton et al., 1997; Lauerma, 1996; McComick et al., 1990) and TCA- (Steele and Howell, 1986) or SSRI-emergent yawning (Cohen, 1992), as well as for the treatment of serotonin syndrome (Graudins et al., 1998). Cyproheptadine is FDA-approved for the treatment of allergic conditions.

Finally, there is no evidence to support the use of the 5HT₄-selective agonist and cholinergic enhancers cisapride (Propulsid) or mosapride (available only in Austria as Mosaro and Japan as Gasmotin) in depression, although there is anecdotal evidence to support the use of cisapride to alleviate venlafaxine-emergent nausea and vomiting (Russell, 1996), and mosapride to alleviate fluvoxamine-emergent nausea (Ueda et al., 2001). The use of cisapride carries a high risk for potentially lethal drug-interactions with a number of pharmacologic agents, including many antidepressants (Michalets and Williams, 2000), and is no longer available due to its potential for arrhythmogenesis (Wysowski et al., 2001). However, approval of newer and safer 5HT₄-selective agonists for the treatment of GI conditions, including tegaserod (Zelnorm; Wagstaff et al., 2003), could potentially help alleviate antidepressant-emergent nausea and upper-GI upset, the most commonly reported adverse effect of SSRIs, which has been reported to occur in as many as one in four patients treated with 20 mg of fluoxetine (Papakostas et al., 2003e). Tegaserod is commonly used at doses of 2.6 mg b.i.d. for the treatment of GI conditions. Side-effects include diarrhea, abdominal pain, flatulence, headaches and fatigue.

6.7

Serotonin Reuptake Enhancers

Tianeptine (Stablon) acts to *increase* rather than decrease the reuptake of serotonin and is typically considered to be a serotonin reuptake enhancer (De Simoni et al., 1992; Wilde and Benfield, 1995). Tianeptine targets the phosphorylation-state of glutamate receptors at the CA3 commissural association synapse (Kole et al., 2002), and has neuroprotective effects against hypoxia in tissue culture and against the deleterious effects of cytokines in cortex and white matter (Plaisant et al., 2003). Tianeptine is available in Europe for the treatment of depression. Open trials have suggested its efficacy (Sonawalla et al., 2003), and double-blind trials have demonstrated tianeptine to be superior to placebo (Costa e Silva et al., 1997) and equivalent to the SSRIs (Lepine et al., 2001; Loo et al., 1999, 2001; Novotny and Faltus, 2002; Oral et al., 2001; Waintraub et al., 2002) and the TCAs (Invernizzi et al., 1994) in the treatment of depression, and superior to placebo in preventing depressive relapses (Dalery et al., 2001). Tianeptine also appears to result in earlier improvement in levels of concentration than fluoxetine (Novotny and Faltus, 2003). Treatment with tianeptine may also result in a lower incidence of sexual side-effects than the SSRIs or TCAs (Bonierbale et al., 2003), and switching to tianeptine is effective in alleviating antidepressant-emergent sexual dysfunction in many patients (Atmaca et al., 2003b). Common side-effects include dry mouth, constipation, dizziness, drowsiness, postural hypotension, insomnia and nightmares (Costa e Silva et al., 1997). Tianeptine does not appear to prolong cardiac conduction (Delalleau et al., 1988). The daily dose most commonly found effective is 37.5 mg, given in t.i.d. dosing.

6.8

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

Venlafaxine, duloxetine and milnacipram share the property of being relatively potent reuptake inhibitors of serotonin and norepinephrine and are therefore considered to be SNRIs.

Venlafaxine (Effexor) was the first SNRI to gain FDA approval for the treatment of depression. At daily doses greater than 150 mg (Sanchez and Hytell, 1999), venlafaxine inhibits the reuptake of both serotonin and norepinephrine, while mostly inhibiting the reuptake of serotonin at lower doses (Harvey et al., 2000; Roseboom and Kalin, 2000). Venlafaxine also appears to act as a non-competitive antagonist of nicotinic acetylcholinergic receptors (Fryer and Lukas, 1999). Venlafaxine is generally effective at daily doses of 150 mg or more, and is often started at 75 mg or even 37.5 mg, typically in its extended release (XR) formulation (Wellington and Perry, 2001).

Venlafaxine, along with the SSRIs and bupropion, is also commonly chosen as a first-line treatment for depression (Petersen et al., 2002a). Venlafaxine is also used in TRD as a “next-step” strategy (de Montigny et al., 1999; Kaplan, 2002; Mbaya,

2002; Mitchell et al., 2000; Montes et al., 2004; Nierenberg et al., 1994b; Poirier and Boyer, 1999; Reynaert et al., 2000; Saiz-Ruiz et al., 2002; Schweitzer et al., 2001), and in one large survey of clinicians was reported to be the most popular switch strategy for refractory depression (Kornbluh et al., 2001). There is also anecdotal evidence for the use of venlafaxine as an adjunct in the treatment of resistant depression (Gomez Gomez and Teixido Perramon, 2000), although toxicity may occur when venlafaxine is added to SSRIs since it is a substrate for CYP-450-2D6 (Benazzi, 1997), and for the use of venlafaxine as monotherapy in patients with MDD and co-morbid ADHD (Hornig-Rohan and Amsterdam, 2002). In addition, preliminary reports suggest that improvement in depressive symptoms may occur at an earlier stage of treatment when venlafaxine is administered rather than an SSRI (Davidson et al., 2002; De Nayer et al., 2000; Entsuah et al., 2001) with the exception of mirtazapine (Guelfi et al., 2001), a phenomenon some ascribe to the dual effects of venlafaxine on the serotonergic as well as the noradrenergic system although, contrary to this argument, treatment with venlafaxine was also found to result in earlier improvement than treatment with the TCA imipramine (Benkert et al., 1996). However, to date, controlled, prospectively designed studies revealing an advantage for venlafaxine over the SSRIs in terms of the rapidity of improvement in depressive symptoms are lacking. Venlafaxine has been found to treat the somatic symptoms of depression (Bradley et al., 2003) more effectively than the SSRIs (Entsuah, 2003) and is also effective in the treatment of fatigue (Mallick and Zhuang, 2003), and melancholic depression (Cantillon et al., 2001). In a similar manner to the SSRIs, venlafaxine increases wake time after sleep onset and suppresses REM sleep (Salin-Pascual et al., 1997).

Common side-effects of venlafaxine include nausea, insomnia, sedation, sexual dysfunction, headache, sweating, tremor, palpitations and dizziness (Nelson, 1997). Venlafaxine appears to be less sedating than the TCAs (Shrivastava et al., 1994) or trazodone (Cunningham et al., 1994), while the potential for sexual dysfunction appears to be comparable to the SSRIs (Clayton et al., 2002; Montejo et al., 2001). The incidence of gastrointestinal side-effects and dizziness appears to be lower with the use of the extended release (XR) formulation than the immediate release formulation (Entsuah and Chitra, 1997). Nearly 2–6% of patients may also experience an increase in diastolic blood pressure (Feighner, 1995; Rudolph and Derivan, 1996), which appears to be dose-related (Thase, 1998). Venlafaxine does not appear to alter TNF- α , soluble TNF- α receptor p55 and p75 levels, or leptin levels in MDD (Kraus et al., 2002b).

There are case reports of venlafaxine-emergent hyponatremia (Gupta and Saravay, 1997; Meynaar et al., 1997; Ranieri et al., 1997), galactorrhea (Sternbach, 2003), and hypogonadism (Bell and Shipman, 2000). A large chart review also suggested an increased risk of hyponatremia in venlafaxine- and SSRI-treated elderly patients (Kirby et al., 2002). In one naturalistic study, the rate of breast enlargement reported was lower for patients treated with venlafaxine than with the SSRIs, while venlafaxine did not appear to alter serum prolactin, estradiol or hCG levels (Amsterdam et al., 1997b).

As with the SSRIs, patients treated with venlafaxine may also experience bruxism (Brown and Hong, 1999; Jaffee and Bostwick, 2000) which has been reported to

resolve after administration of gabapentin (Neurontin; Brown and Hong 1999). Benztropine has been reported to be useful in relieving venlafaxine-emergent sweating in a few case studies (Garber and Gregory, 1997; Pierre and Guze, 2000). There are also reports of abnormal bleeding or bruising (Kohn and Labbate, 1997; Linnebur et al., 2002), as well as alopecia during treatment with venlafaxine (Pitchot and Ansseau, 2001).

The abrupt discontinuation of venlafaxine, an antidepressant with a half-life of only a few hours, also carries a risk of withdrawal-related adverse events similar to those described for the SSRIs (Fava et al., 1997c). There are also reports of serotonin syndrome in patients treated with venlafaxine alone (Kolecki, 1997a; Pan and Shen, 2003), or with a combination of venlafaxine and trazodone (McCue and Joseph, 2001), SSRIs (Bhatara et al., 1998), mirtazapine (Dimellis, 2002), TCAs (Dougherty et al., 2002; Perry, 2000), dextroamphetamine (Prior et al., 2002), MAOIs (Brubacher et al., 1996; Diamond et al., 1998; Gitlin, 1997; Heisler et al., 1996; Hodgman et al., 1997; Kolecki, 1997b; Roxanas and Machado, 1998; Weiner et al., 1998), or lithium (Mekler and Woggon, 1997). Finally, in one uncontrolled study, four of 13 patients treated with venlafaxine during ECT experienced asystole (Gonzalez-Pinto et al., 2002). Although the authors noted that this serious adverse event only occurred in patients on daily doses of venlafaxine greater than 300 mg and in patients anesthetized with propofol, in the absence of further data the use of venlafaxine in patients requiring ECT and perhaps even general anesthesia should be avoided. Venlafaxine did appear to have some ability to block myocardial sodium channels in one animal study (Khalifa et al., 1999), while there is one report of conduction abnormalities in a venlafaxine-treated patient (Combes et al., 2001). Venlafaxine appears to be a substrate for p-GP (Uhr et al., 2003a), and is a weak inhibitor of p-GP activity (Weiss et al., 2003). Finally, certain mutations of the CYP2D6 (*10) gene associated with decreased enzyme expression and affinity for venlafaxine (Fukuda et al., 2000a) have been related to increased venlafaxine levels (Fukuda et al., 2002b), as have mutations of the CYP2C19 enzyme (*2, *3; Fukuda et al., 2000b). There is also a report of ultra-rapid metabolism of venlafaxine in patients with CYP2D6 gene duplication (Veefkind et al., 2000). Venlafaxine is marketed as a racemate of both enantiomers, with S(–) venlafaxine being a more potent inhibitor of CYP2D6 *in vitro* than the R(+) isomer (Otton et al., 1996). The results of a small, unreplicated study suggest that higher venlafaxine + O-desmethylvenlafaxine levels and a lower R(+)/R(–) venlafaxine plasma ratio predominate in early sustained (first 2 weeks) versus late sustained responders to venlafaxine (Gex-Fabry et al., 2004).

Duloxetine (Cymbalta) also inhibits the reuptake of serotonin and norepinephrine (Bymaster et al., 2001) and to a greater extent than its negative enantiomer (LY248685 –; Wong et al., 1993). It is commonly used at daily doses of 60–120 mg, and is often started at a dose of 30 mg. To date, duloxetine has not been approved by the FDA for the treatment of depression, but is expected to be given approval in 2004. Double-blind studies reveal duloxetine to be superior to placebo (Detke et al., 2002a,b; Goldstein et al., 2002), and as effective as the SSRIs (Goldstein et al., 2002) in the treatment of MDD. Duloxetine was also found to be more effective than

placebo in increasing the time to depressive relapse (Detke et al., 2003). In addition, again perhaps due to its ability to simultaneously increase synaptic serotonin and norepinephrine, treatment with duloxetine was found to be superior to placebo in reducing the severity of depression as early as week 1 (Brannan et al., 2003). Duloxetine also appears to be particularly effective in the treatment of somatic symptoms of depression such as pain (Detke et al., 2002a,b; Goldstein et al., 2004; Wolhreich et al., 2003), as well as diabetic neuropathy with no alterations in glycosylated hemoglobin, cholesterol or triglyceride levels (Iyengar et al., 2003). In fact, the successful treatment of somatic symptoms of depression was reported to lead to higher remission rates in MDD patients treated with duloxetine (Fava et al., 2003d). Common side-effects associated with duloxetine include dry mouth, headache, nausea, somnolence, sweating, insomnia, and fatigue (Goldstein et al., 2002). Duloxetine does not appear to cause hypertension (Goldstein et al., 2002; Raskin et al., 2003). In addition, one study reported that in an open-label treatment with duloxetine for up to 52 weeks there were no statistically significant changes in body weight, or QTc interval (Raskin et al., 2003).

A number of studies also show that the norepinephrine- and serotonin-reuptake inhibitor milnacipran (Dalcipran; Mochizuki et al., 2002) is equivalent to the SSRIs (Annseau et al., 1994; Clerc et al., 2001; Guelfi et al., 1998), and the TCAs (Annseau et al., 1989; Steen and den Boer, 1997; Tignol et al., 1998; Van Amerongen et al., 2002; Von Frenckell et al., 1990), and superior to placebo in the treatment of depression (Lecrubier et al., 1996; Macher et al., 1989), as well as superior to placebo in the prevention of depressive relapses (Rouillon et al., 2000a). Treatment with milnacipran was also found to result in a faster onset of clinical response, as early as day 7, than fluvoxamine in MDD (Clerc et al., 2001). Common side-effects reported during treatment with milnacipran include headaches, dry mouth, dysuria, tremor, tachycardia, weight gain and sedation, although the incidence of weight gain and sedation with is lower than that associated with the TCAs (Annseau et al., 1989). Milnacipran is available in Europe for the treatment of depression but does not have FDA approval. Daily doses range from 50 to 200 mg, often divided in b.i.d. dosing.

6.9

Serotonin, Norepinephrine and Dopamine Reuptake Inhibitors (SNDRIs)

Sibutramine (Meridia) is a triple-acting, serotonin-, dopamine-, and norepinephrine-reuptake inhibitor (Glick et al., 2000; Heal et al., 1998) that is FDA-approved for the treatment of obesity. The antidepressant potential of sibutramine is suggested by its activity in animal models for depression (Glick et al., 2000) but there are no published placebo-controlled studies in humans. However, the results of a small open trial of sibutramine in obese patients with binge-eating disorder indicate a significant reduction in depressive symptoms during treatment (Appolonario et al., 2002). Doses commonly use for the treatment of obesity are 10–20 mg. The most commonly reported adverse effects of sibutramine are headache, constipation and

nausea. Dizziness, dry mouth and insomnia, have also been frequently reported by patients receiving sibutramine. Increases in blood pressure and heart rate require regular monitoring, especially in obese hypertensive patients. Neither left-sided cardiac valve disease nor primary pulmonary hypertension has been associated with the use of sibutramine (Nisoli and Carruba, 2003). Sibutramine does appear to decrease serum and CSF leptin levels (Gokcel et al., 2002; Rodrigues et al., 2002), and in one study, the decrease in leptin levels during treatment with sibutramine was reported to be proportional to the reduction in total body fat (Rodrigues et al., 2002).

6.10

α -2 Adrenergic Receptor Antagonists

Mirtazapine (Remeron), particularly its (+) isomer (de Boer et al., 1988) is an antagonist of the inhibitory α -2 adrenergic auto- and hetero-receptor (de Boer, 1996; Sambunaris et al., 1997). For this reason, it is thought that the acute administration of mirtazapine produces a rapid increase in both noradrenaline and 5-HT neurotransmission, resulting in enhanced tonic activation of postsynaptic 5-HT receptors (Haddjeri et al., 1995). Mirtazapine was the first α -2 adrenergic receptor antagonist to be approved by the FDA for depression. Since mirtazapine appears to block the serotonin 5HT₂ and 5HT₃ receptors as well, it is thought to enhance the release of norepinephrine and also 5HT_{1A}-mediated serotonergic transmission (Antilla et al., 2001). Mirtazapine is also a potent histaminergic H-1 receptor antagonist, and is more sedating than the SSRIs (Den Braber et al., 2003; Hong et al., 2003; Wade et al., 2003). Perhaps for this reason, treatment with mirtazapine but not fluoxetine was found to result in decreased sleep latency, increased sleep time, increased sleep efficiency (total time asleep/total time in bed), and decreased wake time after sleep onset in a small double-blind trial of MDD patients suffering with insomnia (Winokur et al., 2003). However, mirtazapine appears to have no effect on REM sleep (Winokur et al., 2000).

Mirtazapine is associated with more weight gain than the SSRIs (Benkert et al., 2000; Den Braber et al., 2003; Hong et al., 2003; Leinonen et al., 1999; Wheatley et al., 1998), and the results of a small trial report increased TNF- α , soluble TNF- α receptors p55 and p75, and increased leptin levels during treatment of MDD patients with mirtazapine (Kraus et al., 2002b). Mirtazapine also appears to increase cholesterol levels (Nicholas et al., 2003).

Although the widespread use of mirtazapine as a first-line agent in depression is limited by its sedative and weight gain effects, a number of studies support the use of mirtazapine either as an adjunct to (Carpenter et al., 1999, 2002; Debonnel et al., 2000) or as an alternative to the SSRIs in SSRI-resistant depression (Fava et al., 2001; Wan et al., 2003), although the results of a large double-blind trial of mirtazapine versus sertraline for SSRI-resistant MDD did not reveal any differences in response rates between the two agents (Thase et al., 2001).

Similar to other dual serotonergic/noradrenergic antidepressants, mirtazapine has also been reported to result in an earlier onset of antidepressant action than

the SSRIs (Behnke et al., 2003; Benkert et al., 2000; Leinonen et al., 1999; Nierenberg et al., 2000; Schatzberg et al., 2002; Schutte and Vester-Blokland, 2003; Thase et al., 2001; Wade et al., 2003). In a comparison of mirtazapine versus placebo, antidepressant effects were observed as early as week 1 in the mirtazapine group (Bech, 2001). In fact, a recent study suggested that MDD patients with the apolipoproteinE-4 gene polymorphism may have a quicker response to mirtazapine than those without the polymorphism (Murphy et al., 2003). Preliminary results from a double-blind study also suggest that combining mirtazapine with fluoxetine, venlafaxine or bupropion may also result in a quicker onset of antidepressant response than with fluoxetine alone, while, in the same study, the combination of mirtazapine and venlafaxine was reported to result in the most robust improvement in depression severity at endpoint (week 6) than the other combinations or fluoxetine alone (Blier et al., 2003). To date, there is at least one combined α -2 adrenergic antagonist, serotonin and norepinephrine reuptake inhibitor (S35966) in development (Gobert et al., 2002).

There are also encouraging preliminary reports of mirtazapine being effective in the treatment of somatic symptoms of depression (Fava et al., 2001), and more effective than the SSRIs in the treatment of somatic anxiety (Schatzberg et al., 2002). Furthermore, although mirtazapine is a potent histaminergic H-1 receptor antagonist, treatment of depression with mirtazapine results in improvements in cognitive functioning in many patients (Borkowska et al., 2001). The results of small open trials also support the use of mirtazapine in depressed patients with ischemic heart disease (Smulevich et al., 2001), epilepsy (Kuhn et al., 2003), or HIV (Blanch et al., 2001), and in menopausal women with depression that is unresponsive to estrogen replacement therapy (Joffe et al., 2001). There is also anecdotal evidence to support the use of mirtazapine in the treatment of interferon-associated depression (Russo et al., 2003).

In addition to sedation and weight gain, common side-effects associated with mirtazapine include dizziness, dry mouth, constipation and orthostatic hypotension. Due to blockade of the 5HT₂ and 5HT₃ receptors, mirtazapine is associated with a lower risk of headaches (Den Braber et al., 2003; Hong et al., 2003), and nausea (Benkert et al., 2000; Den Braber et al., 2003; Hong et al., 2003; Leinonen et al., 1999; Wade et al., 2003) than the SSRIs. Treatment with mirtazapine is also associated with a lower incidence of sexual dysfunction than treatment with the SSRIs (Behnke et al., 2003; Montejo et al., 2001; Van der Flier and Vester-Blokland, 2003). In addition, while the treatment of SSRI-emergent sexual side-effects with adjunct mirtazapine is not supported by one double-blind trial (Michelson et al., 2002), switching to mirtazapine may alleviate SSRI-emergent sexual dysfunction in SSRI-remitters (Gelenberg et al., 2000). Mirtazapine was also found to be effective in the treatment of depression in patients who discontinued SSRIs due to sexual dysfunction (Koutouvidis et al., 1999). Switching directly from an SSRI to mirtazapine without a period of tapering the dosage also seems to carry a low risk of SSRI withdrawal-related adverse events (Fava et al., 2001). There are also reports of mirtazapine-emergent hyponatremia (Roxanas, 2003), akathisia (Girishchandra et al., 2002), dystonia (Lu et al., 2002), restless leg syndrome (Bonin et al., 2000),

pancreatitis (Sommer et al., 2001), and serotonin syndrome (Hernandez et al., 2002; Ubogu and Katirji, 2003), as well as serotonin syndrome when mirtazapine was combined with SSRIs (Benazzi, 1998b; Demers and Malone, 2001), venlafaxine (Dimellis, 2002) or 5HT₃ antagonists (Turkel et al., 2001). Finally, thrombocytopenia has also been reported to occur during treatment with mirtazapine, and is thought to be a result of the formation of autoantibodies to a glycoprotein complex (IIb/IIIa; Liu and Sahud, 2003), as well as neutropenia (Anghelescu et al., 2002; Ahmed, 2002; Kasper et al., 1997) and bone marrow suppression (Biswas et al., 2003; Hutchison, 2001). Mirtazapine does not appear to be a substrate for p-GP (Uhr et al., 2003). Effective daily doses range between 30 and 60 mg/day, the starting daily dose often being 15 mg, but can potentially be as low as 7.5 mg in the elderly.

Mianserin (Lantanon), which is also an α -2 noradrenergic receptor antagonist and a serotonin 5HT₂ antagonist, is available in Europe but is not FDA approved. Similar to mirtazapine, the (+) isomer appears to be more potent (six-fold) at inhibiting the α -2 receptors than the (–) isomer (de Boer et al., 1988). Double-blind studies have reported the efficacy of mianserin in the treatment of MDD to be equivalent to that of the TCAs (Moller et al., 1991, 1995; Wilcox et al., 1994). Separate double-blind trials also reveal mianserin to be effective as an adjunct to the SSRIs in the treatment of MDD (Dam et al., 1998; Maes et al., 1999b), as an adjunct to the SSRIs in SSRI-resistant MDD (Ferrerri et al., 2001), and as an adjunct to TCAs in TCA-resistant MDD (Lauritzen et al., 1992). However, a large, double-blind study failed to replicate such findings in SSRI-resistant MDD (Licht and Quitzau, 2002). The results of an open trial also suggest mianserin augmentation of TCAs to be effective in the treatment of post-stroke depression (Lauritzen et al., 1994). Mianserin augmentation of SSRIs may also relieve SSRI-emergent sexual dysfunction (Dolberg et al., 2002), and SSRI-emergent akathisia (Poyurovsky et al., 1997). The most common side-effects include somnolence, weight gain, dry mouth, sleep problems, tremor, and headaches (Licht and Quitzau, 2002). Effective daily doses for mianserin range from 30 to 60 mg, usually given at bedtime.

Similar to mirtazapine and mianserin, the immediate action of yohimbine is to block the α -2 adrenergic inhibitory autoreceptor. Unlike the former two agents, yohimbine does not have any affinity for the serotonin 5HT₂ or 5HT₃ receptors. Yohimbine (Yocon) is FDA-approved for the treatment of sexual impotence, and does not have a depression indication. The results of an open-label trial (Schmauss et al., 1988b) and a placebo-controlled study (Charney et al., 1986) do not reveal any antidepressant effect for yohimbine when used as an adjunct to the TCAs. Yohimbine, however, has been found to be effective in alleviating certain TCA-emergent symptoms including xerostomia (Bagheri et al., 1992; Rispail et al., 1990), and orthostasis (Charney et al., 1986; Hyatt and Messer, 1986; Lacomblez et al., 1989; Lecrubier et al., 1981; Seibyl et al., 1989;). There are also case reports of yohimbine alleviating TCA-emergent anorgasmia (Price and Grunhaus, 1990), and SSRI-emergent sexual dysfunction (Balon, 1993; Hollander and McCarley, 1992). A small open trial further supports the role of yohimbine in the treatment of SSRI-emergent sexual dysfunction (Jacobsen, 1992), but a subsequent double-blind trial did not show any advantage over placebo of using higher doses of adjunct yohimbine

(5.4 mg t.i.d.) in the treatment of SSRI-emergent sexual dysfunction (Michelson et al., 2002). Common daily doses found effective for the treatment of xerostomia, orthostasis or sexual dysfunction range from 5.4 mg q.d. to 5.4 mg t.i.d.

Guanfacine (Tenex) also inhibits the α -2 adrenergic autoreceptor (Sorkin and Heel, 1986), while having no affinity for the serotonergic receptors. Guanfacine is FDA-approved for the treatment of hypertension. To date, there is no evidence to support the use of guanfacine in depression, although both guanfacine (Taylor and Russo, 2001) and yohimbine (Connor et al., 1999) appear to be effective for the treatment of ADHD. Common daily doses for ADHD range between 0.25 and 2 mg. A single open trial reported decreases in depressive symptoms during treatment with the α -2 selective *agonist* clonidine (Catapres) in outpatients with comorbid MDD and post-traumatic stress disorder (PTSD; Kinzie and Leung, 1989).

6.11

Norepinephrine Reuptake Inhibitors (NRIs)

Reboxetine (Edronax; Wong et al., 2000) selectively inhibits the norepinephrine transporter, thereby increasing synaptic norepinephrine levels, and also appears to act as an antagonist of nicotinic acetylcholinergic receptors (Miller et al., 2002a). Reboxetine is available in Europe for the treatment of depression but has not received FDA approval for this indication. Double-blind, placebo-controlled trials suggest reboxetine to be more effective than placebo (Andreoli et al., 2002; Massana, 1998; Montgomery et al., 2003; Versiani et al., 2000), and as effective as fluoxetine (Andreoli et al., 2002) and venlafaxine (Schwartz et al., 2002) in the treatment of major depressive disorder, and more effective than placebo in the prevention of depressive relapses (Versiani et al., 1999). Reboxetine also appears to be effective in the treatment of SSRI-resistant depression (Devarajan and Dursun, 2000; Fava et al., 2003a; Hawley et al., 2000; Rapaport et al., 2002; Rubio et al., 2004; Tavormina et al., 2002). Controlled studies also suggest that reboxetine may be particularly effective in the treatment of cognitive disturbance in depression (Fabre et al., 1983), and more effective than the SSRIs in the treatment of deficits in cognition and attention in depression (Ferguson et al., 2002, 2003). Reboxetine also appears to be more effective than the SSRIs in improving psychosocial functioning in depression (Dubini et al., 1997; Massana, 1998; Massana et al., 1999). There are also open trials supporting the use of reboxetine in patients with co-morbid depression and Parkinson's disease (Lemke, 2002), co-morbid depression and epilepsy (Kuhn et al., 2003), and co-morbid depression and HIV (Carvalho et al., 2003). The starting daily dose is usually 8 mg but can be as low as 4 mg, with effective daily doses ranging between 8 and 10 mg given in divided doses (twice a day). Common side-effects include insomnia, headache, dry mouth, diaphoresis, urinary hesitancy and constipation (Andreoli et al., 2002). The incidence of nausea, headache, fatigue (Andreoli et al., 2002), and sexual dysfunction (Clayton et al., 2003) appears to be more common during treatment with the SSRIs than with reboxetine. There are case reports of the use of α -1 adrenoceptor antagonists (i.e. tamsulosin, doxazosin)

for the treatment of reboxetine-emergent urinary hesitancy (Demyttenaere and Huygens, 2002; Demyttenaere et al., 2001; Kasper, 2002; Kasper and Wolf, 2002; Szabadi, 1998). In addition, long-term treatment with reboxetine does not appear to result in greater weight gain than treatment with placebo (Thase and Bartlett, 2001). Although there are also reports of hyponatremia during treatment with reboxetine (Abdelrahman et al., 2003; Ranieri et al., 2000), it does not appear to alter cardiac conduction (Fleishaker et al., 2001). Treatment with reboxetine may result in increased blood pressure in some patients. In fact, a genetic variant of the norepinephrine transporter (SCL6A2) has been found to confer an increased risk of developing elevated blood pressure during treatment with reboxetine (Ono et al., 2003). Reboxetine possesses intermediate potency for p-GP inhibition (Weiss et al., 2003). It has two chiral centers and is available in a form containing two of its four enantiomers, but there is a paucity of information available regarding the individual properties of its isomers (Baker and Prior, 2002).

Atomoxetine (Strattera) also selectively inhibits the reuptake of norepinephrine (Preti, 2002). While atomoxetine is an FDA-approved treatment for ADHD, controlled depression trials have yet to be published; there is only a single open trial of atomoxetine in depression involving 10 patients, with daily doses ranging from 40 to 70 mg (Chouinard et al., 1984). Common side-effects so far reported include decreased appetite, insomnia, and elevated blood pressure (Wernicke and Kratochvil, 2002). Although atomoxetine does appear to increase blood pressure in some patients, it does not seem to alter QTc (Wernicke et al., 2003). A halogenated analog of atomoxetine (LY303926; particularly the R-isomer) has been reported to be a more potent inhibitor of the NET and less potent as an inhibitor of 5HTT (5HTT/NET inhibition ratio 0.007) than its parent compound, atomoxetine (Gehlert et al., 1995).

6.12

Norepinephrine Dopamine Reuptake Inhibitors

The mechanism of action of bupropion (Wellbutrin) has not been fully elucidated, although it appears to primarily block the reuptake of both dopamine and norepinephrine (Ascher et al., 1995). Bupropion and its metabolites have been shown to inhibit striatal uptake of the selective DAT-binding radioligand (11)C-βCIT-FE *in vivo* achieving DAT occupancy ranging from approximately 14% (Meyer et al., 2002) to 26% (Learned Coughlin et al., 2003; Szabo et al., 2003) at therapeutic doses. This degree of DAT occupancy appears to be equivalent to that achieved after a single oral dose of methylphenidate 5–10 mg in human volunteers (Volkow et al., 1998). However, when comparable methylphenidate doses were given intravenously to healthy volunteers (0.025–0.1 mg/kg), no significant increases in synaptic DA were observed (Volkow et al., 1999, 2003), suggesting that additional mechanisms other than DAT inhibition may be involved. Bupropion has also been reported to have mild affinity for the norepinephrine transporter (Foley and Cozzi, 2002) although some researchers have argued that the effect of bupropion on nor-

epinephrine is primarily through an increase in presynaptic norepinephrine release (Dong and Blier, 2001). Regardless of the exact mechanism, the overall effect of bupropion appears to be a dose-dependent increase in brain extracellular dopamine and norepinephrine concentrations (Li et al., 2002; Nomikos et al., 1989). In addition, bupropion also appears to inhibit the $\alpha 3\beta 2$, $\alpha 3\beta 4$, and $\alpha 4\beta 2$ -nicotinic acetylcholinergic receptors by a non-competitive mechanism *in vitro* (Bondarev et al., 2003; Fryer and Lucas, 1999; Miller et al., 2002b; Slemmer et al., 2000) and at least four stereoisomers of the two major metabolites of bupropion (S,S-, R,R-hydroxybupropion, R,R-threohydrobupropion) were also reported to inhibit $\alpha 3\beta 4$ -nicotinic acetylcholinergic receptors by a non-competitive mechanism *in vitro*, although not as potently as bupropion (Bondarev et al., 2003).

Bupropion is commercially available as a racemate, but there is a paucity of information available about the individual properties of its enantiomers (Baker and Prior, 2002). Bupropion has two major (hydroxybupropion and threohydrobupropion) and one minor metabolite (erythohydrobupropion; Bondarev et al., 2003) and at steady state, the plasma levels of hydroxybupropion are approximately 45–50 times higher than that of the parent compound bupropion, while plasma levels of erythro- and threohydrobupropion have been reported to be 3.5–6 and 18–26 times higher than the levels of the parent compound respectively (Cooper et al., 1984; Golden et al., 1988; Learned-Coughlin et al., 2003; Meyer et al., 2002). Although these three compounds each have four stereoisomers, only a subset of these potential compounds are detectable in human plasma after treatment with bupropion (Bondarev et al., 2003). In addition, of the four stereoisomers of its two major metabolites tested in one study (S,S-, R,R-threohydrobupropion; S,S-, R,R-hydroxybupropion), only one (S,S-hydroxybupropion) had an affinity for DAT comparable to that of bupropion ($K_i = 1295$ versus 1020 nM, respectively; Bondarev et al., 2003). However, in humans, at steady state 96% of hydroxybupropion is predominantly in the R,R-isomer form, with only the remaining 4% in the S,S-form (Suckow et al., 1997).

Bupropion appears to be as effective as the SSRIs in the treatment of mood (Bolden-Watson et al., 2002; Thase et al., 2003b) as well as anxiety symptoms of depression (Trivedi et al., 2001). In fact, bupropion is effective in the treatment of mood and anxiety symptoms of depression regardless of the degree of anxiety and/or insomnia present at baseline (Rush et al., 2001, 2003). Bupropion is often used as a first-line treatment for major depression, and also as an adjunct in SSRI-resistant depression (Bodkin et al., 1997; DeBattista et al., 2003b; Spier 1998), a popular strategy among clinicians (Mischoulon et al., 2000b). In fact, combining bupropion with SSRIs has been reported to potentiate bupropion-induced norepinephrine and dopamine release (Li et al., 2002). Bupropion also appears to be an effective “next-step” strategy in SSRI- (Fava et al., 2003b; Kennedy et al., 2002) or TCA- (Ferguson et al., 1994; Stern et al., 1983) resistant depression. Switching from SSRIs to bupropion may also be effective in the treatment of depressive relapses (McGrath et al., 2002).

Due to its dual noradrenergic and dopaminergic activity, preliminary evidence suggests bupropion may be particularly effective in the treatment of certain

symptoms of depression, including cognitive disturbance and fatigue. In one large placebo-controlled trial, for depression for instance, bupropion was noted to be particularly effective for the symptoms of cognitive disturbance, somatic anxiety, and psychomotor retardation (Fabre et al., 1983). Bupropion has also been reported to be effective for treating SSRI-emergent fatigue (Green, 1997), and SSRI-resistant chronic fatigue syndrome (Goodnick et al., 1992). However, prospective, controlled trials are needed to confirm the potential advantage for bupropion in the treatment of cognitive and somatic symptoms of depression. A number of studies also support the use of bupropion (Zyban) in smoking cessation (Hughes et al., 2003) while, in an open trial, augmenting SSRIs with bupropion in SSRI-remitted depressed patients led to cessation of smoking in a number of patients (Chengappa et al., 2001). In a small open trial, bupropion was found to alleviate depressive symptoms in five of 12 patients with Parkinson's disease (Goetz et al., 1984). An open trial of bupropion for the treatment of depression in HIV+ patients has also been published (Currier et al., 2003).

One advantage of treatment with bupropion compared to the SSRIs is the lower risk of sexual dysfunction (Clayton et al., 2002; Coleman et al., 1999, 2001; Croft et al., 1999; Kavoussi et al., 1997; Modell et al., 1997; Montejo et al., 2001; Segraves et al., 2000). In fact, a number of open trials suggest bupropion to be effective in the treatment of SSRI-emergent sexual dysfunction (Ashton and Rosen, 1998; Chengappa et al., 2001; Clayton et al., 2001a; Gitlin et al., 2002; Labbate et al., 1994, 1997; Walker et al., 1993), a popular strategy among clinicians (Dording et al., 2002). While a small, underpowered, double-blind study did not support the use of bupropion in the treatment of SSRI-emergent sexual dysfunction (Masand et al., 2001) a subsequent placebo-controlled study reported a positive outcome (Clayton et al., 2001b).

Treatment with bupropion is also associated with a lower incidence of gastrointestinal side-effects (e.g. nausea, diarrhea; Croft et al., 1999; Kavoussi et al., 1997), and sedation (Croft et al., 1999; Trivedi et al., 2001) than that with the SSRIs. An additional advantage of bupropion is that it appears to decrease weight more than placebo during the acute phase of treatment for depression (Settle et al., 1999), and obesity (Gadde et al., 2001; Jain et al., 2002). The anti-obesity effects of bupropion also appear to be sustained over longer periods of treatment (48–52 weeks; Anderson et al., 2002; Croft et al., 2002). Although, a difference in terms of weight changes in bupropion- and SSRI-treated depressed patients is not immediately apparent during the acute phase of treatment in randomized trials (Coleman et al., 1999; Croft et al., 1999; Feighner et al., 1991; Kavoussi et al., 1997; Settle et al., 1999; Weihs et al., 2000), there is evidence to suggest that any beneficial effects of SSRIs in terms of weight reduction during the acute phase are not sustained during the continuation and maintenance phases (Michelson et al., 1999; Sussman et al., 2001). In fact, long-term treatment with some SSRIs may also result in long-term weight gain (Fava et al., 2000a). Thus, long-term treatment with bupropion may carry a lower risk of weight gain than long-term treatment with the SSRIs. Unlike sertraline, bupropion does not alter CSF hypocretin-1 (Orexin-A) levels in depression (Salomon et al., 2003).

The dose range for the sustained release formulation of bupropion (Wellbutrin SR) is 150–450 mg in a b.i.d. or t.i.d. regimen, with 100 or 150 mg being a common starting dose. A once-daily dose formulation (Wellbutrin XL), available in 150 and 300 mg doses, was introduced in 2003. Plasma levels derived for each respective dose of bupropion at steady state have been reported to vary as much as 10-fold between patients (Preskorn, 1983). The results of a small, unreplicated study suggest poor response to bupropion (immediate release IR formulation) for patients with trough levels less than 25 ng/ml (Preskorn, 1983). CYP2B6 appears to be primarily responsible for the hydroxylation of bupropion (Hesse et al., 2000), although elevated plasma level/dose ratios for hydroxybupropion but not bupropion or its other two metabolites have been reported in patients who are poor metabolizers of 2D6 (Pollock et al., 1996). Paroxetine appears to inhibit 2B6 *in vitro*, more effectively than fluvoxamine, sertraline/desmethylsertraline, norfluoxetine/fluoxetine, or nefazodone (Hesse et al., 2000). On the other hand venlafaxine and citalopram do not appear to inhibit 2B6 *in vitro* (Hesse et al., 2000). Recently, an allele coding for the CYP2B6 enzyme (*4) has been associated with the increased clearance of bupropion (i.e. increased hydroxybupropion concentrations; Kirchheiner et al., 2003).

Common side-effects of bupropion include agitation, insomnia, weight loss, dry mouth, headache, constipation, and tremor (Settle et al., 1999). There is also a report of bupropion-emergent dystonia (Detweiler and Harpold, 2002). Although bupropion may elevate blood pressure in some patients (Kiev et al., 1994; Roose et al., 1991), it does not appear to do so consistently, even among hypertensive patients (Thase et al., 2003c). Several studies have failed to show an effect of bupropion on cardiac conduction (Kiev et al., 1994; Roose et al., 1991; Wenger et al., 1983), orthostatic blood pressure (Kiev et al., 1994; Roose et al., 1991) or left ventricular ejection fraction in patients with congestive heart failure (Roose et al., 1987b), although conduction delays may occur in patients who overdose on bupropion (Isbister and Balit, 2003; Paris and Saucier, 1998).

Caution is warranted when combining bupropion and paroxetine in the elderly, especially in those with memory impairments and orthostasis, as combining these two agents in the elderly was found to increase the risk of falls (Joo et al., 2002). Treatment with bupropion does not appear to affect prolactin or growth hormone levels (Whiteman et al., 1982, 1983), or bone mineral density (Gadde et al., 2001) and short-term administration did not appear to affect the control of diabetes (Rowland et al., 1997).

The major medically-important adverse event associated with bupropion is seizure. With the immediate-release formulation the rate is 0.4% (4/1000) at doses of up to 450 mg/day. SSRI antidepressants are also associated with seizure at a similar rate of approximately 0.1% (Wellbutrin SR Prescribing Information). Patients should only be administered bupropion with extreme caution if they already have a predisposition to seizure. For this reason, the maximum daily dose for bupropion SR and bupropion XL is 450 mg, with no single dose above 200 mg for the SR formulation. In addition, bupropion may be more likely to induce seizures in patients with bulimia nervosa and histories of head trauma and should therefore

not be used in these patients. Since the risk of seizure appears to be related to dose as well as to the peak plasma concentrations of bupropion, the SR and XL formulations are thought to be associated with a somewhat lower seizure risk, estimated at 0.1% for daily doses lower than 450 mg (Dunner et al., 1998). There are also several reports of bupropion-related hypersensitivity reactions (Bagshaw et al., 2003; Benson, 2001; Chiaverini et al., 2003; Conners et al., 1996; Davis et al., 2001; De Santiago Hernando et al., 2002; Fabre et al., 1983; Fays et al., 2003; Glod et al., 2003; Knowles et al., 2003; Lineberry et al., 2001; Loo et al., 2003; Malesker et al., 1995; McCollom et al., 2000; Peloso and Baillie, 1999; Tripathi and Greenberger, 1999; Woollorton, 2002; Yolles et al., 1999).

Unlike most other antidepressants (Winokur et al., 2001), bupropion appears to *increase* rather than decrease REM sleep (Nofzinger et al., 1995), which may explain reports of somnambulism (Khazaal et al., 2003) or nightmares and vivid dreams (Becker and Dufresne, 1982) during treatment. There have been no reports of worsening cataplexy or of new-onset cataplexy with bupropion, and only a single case report of reduction in sleepiness and REM-sleep propensity in a woman with atypical depression and co-morbid narcolepsy who had been treated with bupropion (Rye et al., 1998). In double-blind trials (Griffith et al., 1983; Miller and Griffith, 1983), substance abusers were unable to distinguish bupropion from placebo, but were able to discriminate between amphetamine but not bupropion, and placebo suggesting low abuse potential; it has been suggested that a minimum of 47% DAT occupancy is required for cocaine to produce euphoric effects (Volkow et al., 1997), which is much lower than the DAT occupancy resulting from therapeutic doses of bupropion.

Nomifensine (Merital) is a tricyclic antidepressant derivative which blocks the reuptake of norepinephrine (Kinney, 1985) and dopamine (Mercuri et al., 1992). Although nomifensine is no longer available for the treatment of depression due to the risk of hemolytic anemia (Giers et al., 1991), reviewing studies of nomifensine in depression can further our insight into the potential advantages for agents with combined noradrenergic and dopaminergic activity in depression. While nomifensine appeared to be equally effective in the overall treatment of depression as the MAOIs (Schiwy et al., 1989), serotonin 5HT₂ antagonists (Granier et al., 1985), and TCAs (Bremner et al., 1984; Fann et al., 1984; Goldstein et al., 1982; Levin, 1982; Lopez-Ibor Alino et al., 1982; Meredith et al., 1984; Ong and Lee, 1981; Poldinger and Streichenwein, 1982; Wistedt et al., 1983), it appeared to work faster than the TCAs (Cohn et al., 1984). Thus, these studies suggest that antidepressants with dopaminergic activity may hasten the onset of clinical improvement in depression.

6.13

Dopaminergic Agents

Piribedil (Trivastal, Trivastan) is a non-ergot dopamine D2/D3 receptor agonist with a significant antagonist action on α 2A and α 2C adrenergic receptor subtypes (Ziegler et al., 2003). Amantadine is a non-competitive antagonist of NMDA receptors (Rogoz et al., 2003a), an action thought to result in increased function of the dopamine receptors and transporter (Peeters et al., 2003). Bromocriptine, cabergoline and pergolide are dopamine receptor agonists. Piribedil is not FDA approved, but is available in Europe for the treatment of Parkinson's disease. Bromocriptine (Parlodel) is FDA-approved for the treatment of Parkinson's disease, hyperprolactinemia, and acromegaly, while amantadine (Symmetrel), and pergolide (Permax) are FDA-approved for the treatment of Parkinson's disease. Cabergoline (Dostinex, Cabaser) is FDA approved for the treatment of hyperprolactinemia.

The use of older dopaminergic agents such as piribedil, amantadine, pergolide, bromocriptine, and cabergoline in depression is limited due to three principal reasons: (1) the paucity of supporting data, (2) the high incidence of side-effects, particularly nausea (with the exception of amantadine), and (3) the development of newer dopaminergic agents discussed in later sections. Nevertheless, given the limited number of dopamine-selective agents available, studies focusing on the treatment of depression with these older agents are important in that they suggest an antidepressant role for dopamine that is independent of serotonin or norepinephrine. Specifically, open trials suggest monotherapy with the dopaminergic agent piribedil (Post et al., 1978), and the D2-receptor agonist bromocriptine (Nordin et al., 1981) to be effective in alleviating depression. Open trials also suggest the utility of adjunct (to TCAs) treatment with the dopamine agonist pergolide (Bouckoms and Mangini, 1993; Izumi et al., 2000) and bromocriptine (Inoue et al., 1996), while three double-blind studies show bromocriptine to be as effective as TCAs in the treatment of depression (Bouras and Bridges, 1982; Theohar et al., 1982; Waehrens and Gerlach, 1981). Bromocriptine also appears to decrease depressive symptoms in patients with Parkinson's disease (Jouvent et al., 1983), and hyperprolactinemia (Mattox et al., 1986). Treatment of hyperprolactinemia (Mattox et al., 1986) and Parkinson's disease (Rektorova et al., 2003) with pergolide also appears to result in a decrease in depressive symptoms. There is also anecdotal evidence to suggest a potential antidepressant role for amantadine when used in conjunction with standard antidepressants in MDD (Rogóz et al., 2003b; Stryjer et al., 2003), and case reports of amantadine used to alleviate SSRI-emergent sexual dysfunction (Balogh et al., 1992; Shrivastava et al., 1995). A double-blind study revealed greater improvement than with placebo in residual fatigue but not sexual dysfunction when amantadine was added to the SSRI regimen of women with MDD who had responded to SSRIs (Michelson et al., 2000b). Two open trials also suggest an antidepressant effect for amantadine in depressed patients with Borna virus infection (Dietrich et al., 2000; Ferszt et al., 1999). Only anecdotal evidence supports the use of cabergoline in depression (Takahashi et al., 2003).

Amineptine (Survector) is a TCA-derivative that predominantly inhibits dopaminergic reuptake, with minimal noradrenergic activity and no serotonergic activity (Garattini, 1997; Garattini and Mennini, 1989). Although amineptine is no longer in use due to its abuse potential, reviewing studies of amineptine in depression is useful for two reasons: (1) such studies further establish an antidepressant role for dopamine and (2) such studies may provide further insights into the potential advantages for agents with predominantly dopaminergic activity in depression. The use of amineptine as an antidepressant is supported by a number of open trials (Boral and Shah, 1989; Paes de Sousa and Tropa, 1989; Scarzella et al., 1985), as well as placebo-controlled trials (Alevizos et al., 1989; Boyer et al., 1999). Amineptine also appears to be as effective as the TCAs (Bornstein, 1979; Lemoine et al., 1981; Mendis et al., 1989; Rampello et al., 1995; Van Amerongen, 1979; Vauterin and Bazot, 1979), the MAOIs (Macher et al., 1992), and the SSRIs (Dalery et al., 1997) in the treatment of depression, and more effective than placebo in preventing depressive relapses (Ferrerri et al., 1997).

Furthermore, similar to the MAOIs, several studies suggest the dopaminergic agent amineptine to be particularly effective in the treatment of fatigue and psychomotor retardation. Rampello et al. (1991) reported amineptine to be more effective than minaprine, clomipramine or placebo in patients affected by “retarded depression” who they described as exhibiting anergia, but also other symptoms including hypokinesia, reduction of speech, hypersomnia, reduced sexual activity, psychomotor slowness, hypomimia, and drowsiness. Dalery et al. (1997) found amineptine to be equally effective as fluoxetine in the treatment of MDD overall, but superior to fluoxetine on the retardation pole of the mood, anxiety, retardation, danger scale.

The psychostimulants dextroamphetamine, pemoline, and methylphenidate have been traditionally regarded as presynaptic releasers of dopamine and as blockers of dopamine reuptake (Cardenas et al., 2004; Saunders et al., 2000; Volkow et al., 2002). Dextroamphetamine (Dexedrine) is FDA approved for the treatment of ADHD, narcolepsy and exogenous obesity. Pemoline (Cylert) is FDA approved for ADHD, and methylphenidate (Ritalin, Concerta) is FDA approved for the treatment of ADHD and narcolepsy.

The use of dexedrine (Kaufmann et al., 1984; Little, 1993; Olin and Masand, 1996; Woods et al., 1986) and methylphenidate (Askinazi et al., 1986; El-Mallakh, 2000; Kaufmann et al., 1984; Lazarus et al., 1992, 1994; Lingam et al., 1988; Little, 1993; Masand et al., 1991a,b; Pickett et al., 1990; Rothenhausler et al., 2000; Stoll et al., 1996; Woods et al., 1986) in depression, particularly in depressed patients with comorbid medical illness, is supported by large chart reviews and small open trials cumulatively containing hundreds of patients. There is also anecdotal evidence to support the use of adjunct stimulants to the TCAs (Feighner et al., 1985), SSRIs (Lavretsky and Kumar, 2001; Lavretsky et al., 2003; Masand et al., 1998) and MAOIs (Fawcett et al., 1991; Feighner et al., 1985) for the treatment of MDD. However, controlled, prospective studies are limited. Wagner and Rabkin (2000), for instance, reported significant improvement in mood and energy among HIV + depressed patients treated with double-blind dexedrine but with not placebo. Similarly, methylphenidate was found to be as effective as desipramine in the treatment of

MDD in HIV + patients in one double-blind trial (Fernandez et al., 1995), while both methylphenidate and pemoline were found to be more effective than placebo for the treatment of depression and fatigue in HIV + patients (Breitbart et al., 2001). A small placebo-controlled trial also found pemoline to be more effective than placebo in the treatment of some symptoms of depression, including depressed mood, fatigue, concentration and memory (Elizur et al., 1979). The results of open trials also suggested that methylphenidate may also hasten the onset of the antidepressant response to TCAs (Gwirstman et al., 1994) or SSRIs (Lavretsky and Kumar, 2001; Lavretsky et al., 2003) in MDD. Finally, there is anecdotal evidence supporting the use of adjunct dextroamphetamine and methylphenidate for the treatment of SSRI-related sexual dysfunction (Bartlik et al., 1995; Gitlin, 1995), and adjunct psychostimulants for the treatment of co-morbid ADHD in MDD patients treated with SSRIs (Findling, 1996). In summary, although promising, the widespread use of these agents is limited by their abuse potential (Drug Enforcement Agency Schedule II drugs) and paucity of supporting data from controlled trials.

Pramipexole (Mirapex) and ropinirole (Requip) are selective dopamine D2 and D3 receptor agonists (Gerlach et al., 2003; Maggio et al., 2003; Piercey, 1998), FDA-approved for the treatment of Parkinson's disease. Small case-series support the use of pramipexole in unipolar (Sporn et al., 2000) and of both pramipexole and ropinirole in bipolar depression (Perugi et al., 2001; Sporn et al., 2000). An open-label study also suggests adjunct (to SSRIs and TCAs) pramipexole to be effective in the treatment of unipolar and bipolar depression (Lattanzi et al., 2002). A double-blind study found pramipexole to be more effective than placebo in the treatment of MDD (Longborn et al., 1999). Finally a large ($n = 174$) double-blind study comparing pramipexole to fluoxetine to placebo found pramipexole to be as effective as fluoxetine and more effective than placebo (Corrigan et al., 2000). There are also anecdotal reports suggesting a useful role for pramipexole and ropinirole in the treatment of SSRI-emergent sexual dysfunction (Sporn et al., 2000; Worthington et al., 2002). Treatment of Parkinson's disease with pramipexole also appears to result in decreases in depression severity (Lemke et al., 2002; Rektorova et al., 2003) and anhedonia (Lemke et al., 2002; Reichmann et al., 2003) in some patients. The usual daily dose range for pramipexole is 0.5–3 mg, given in divided doses (two or three times a day). The usual daily dose range for ropinirole is 0.75–3 mg, given in divided doses (two or three times a day).

6.14

The Catechol-O-Methyltransferase (COMT) Inhibitors

The COMT enzyme is found throughout the human body and, similar to MAO, is involved in the catabolism of the monoamines. Inhibitors of the COMT enzyme have shown activity in animal models of depression, while administration of COMT inhibitors in humans has been reported to result in decreased COMT activity *in vivo* (Ceravolo et al., 2002). These compounds have been primarily developed as adjunctive treatments for Parkinson's disease. Tolcapone (Tasmar) and entacapone

(Comtan) are two inhibitors of the COMT enzyme that have been approved by the FDA for the treatment of Parkinson's disease. While the results of a single open trial of the tolcapone in MDD suggested a potential antidepressant role for this compound, treatment with tolcapone was associated with diarrhea and elevated liver function tests in a large proportion of the patients treated (Fava et al., 1999), thereby making its off-label use in MDD unfeasible. Future compounds with COMT-inhibiting activity and adequate ability to cross the blood–brain barrier may be investigated as potential treatments for depression.

6.15

Antipsychotic Agents

6.15.1

Older Antipsychotic Agents: Amisulpride (Solian) and Molindone (Moban)

The antipsychotic amisulpride (Solian), a selective antagonist for D2 and D3 dopamine receptors, acts preferentially on presynaptic receptors, increasing dopaminergic transmission at low doses (Boyer et al., 1999). Although amisulpride has not been FDA approved, it is available in Europe for the treatment of psychotic disorders, a number of studies suggest it may have antidepressant effects. Amisulpride was first reported to result in greater improvements in anergia and loss of interest in non-psychotic/non-depressed outpatients with chronic anergia and loss of interest (Lecrubier et al., 1988). The antidepressant potential of amisulpride has subsequently been suggested in open (Rocca et al., 2002a), and placebo-controlled trials (Boyer et al., 1999; Lecrubier et al., 1997). Amisulpride also appears to be as effective as the TCAs (Lecrubier et al., 1997), and the SSRIs (Amore et al., 2001; Cassano et al., 2002; Smeraldi, 1998) in the treatment of depression. Finally, while amisulpride augmentation of paroxetine was not found to be more effective than paroxetine alone in an open-label trial of paroxetine-resistant MDD, patients treated with amisulpride did fare significantly better with respect to psychosocial functioning after treatment than patients treated with paroxetine alone (Rocca et al., 2002b). Doses of 50 mg and above are commonly used for depression. The antipsychotic molindone (Moban), FDA approved for the treatment of psychotic disorders, is a dopamine D2 receptor antagonist (Seeman and Tallerico, 1998) which was reported to be more effective than tranylcypromine in the treatment of refractory depression in one small single-blind trial (Small et al., 1981). Doses used in that study ranged from 10 to 30 mg.

The newer atypical antipsychotic agents, due to their unique receptor-affinity profile, may be particularly useful when used in conjunction with standard antidepressants in the treatment of non-psychotic refractory depression. Specifically, in addition to inhibiting D2 receptors, the atypical antipsychotics also act as antagonists at the serotonin 5HT2 receptor, as well as having various effects, which differ from agent to agent, on other serotonergic receptors including the 5HT1A receptor (Richelson and Souder, 2000). It has been hypothesized that these complex

pharmacological actions are responsible for an enhancement of the CNS noradrenergic and dopaminergic system seen when atypicals are used alone or in conjunction with the SSRIs. The use of atypical antidepressant ziprasidone, for instance, has been shown to result in a release of dopamine in rat prefrontal cortex (Rollema et al., 2000), while the use of olanzapine was shown to result in increased firing rates of noradrenergic cells in the locus coeruleus (Dawe et al., 2001). In addition, the combination of fluoxetine and olanzapine has also been shown to produce marked increases in the levels of dopamine, serotonin, and norepinephrine in the prefrontal cortex of the rat (Zhang et al., 2000).

Retrospective chart reviews and open trials provide preliminary support for a potential role for augmentation of SSRIs with atypical antipsychotics among patients with inadequate response to SSRIs, including ziprasidone (Geodon; Dunner et al., 2003; Papakostas et al., 2004c), olanzapine (Zyprexa; Corya et al., 2003), risperidone (Risperdal; Ostroff and Nelson, 1999; Rapaport et al., 2003), and aripiprazole (Abilify; Worthington et al., 2003). In addition, risperidone augmentation of fluvoxamine was also shown to be effective as a first-line treatment for MDD (Hirose and Ashby, 2002). There is also a small case study of risperidone augmentation of milnacipran (Tani et al., 2004). Open trials also support a potential role for augmentation of SSRIs with olanzapine in the treatment of apathy in SSRI-remitters (Marangell et al., 2002). In addition, the acute antidepressant effects of olanzapine also appear to be sustained during the continuation and maintenance phases of treatment (Corya et al., 2003) while the addition of olanzapine to fluoxetine in depression also appears to reduce outpatient, and inpatient utilization and medical costs (Corey-Lisle et al., 2003). Open-label risperidone augmentation of SSRIs was also found to result in improvements in cognitive functioning in MDD (Bilder et al., 2003). The results of one (Shelton et al., 2001) but not a second (Dube et al., 2002) placebo-controlled trial supports the use of olanzapine as augmentation for SSRIs in SSRI-resistant MDD.

Despite the increase in prefrontal levels of dopamine in animals treated with olanzapine and fluoxetine, olanzapine augmentation of SSRIs was not found to be consistently more effective than placebo in ameliorating the sexual side-effects of SSRIs, having an advantage only in improving patient self-reports of global sexual function (Michelson et al., 2002). Clozapine (Clozaril) and quetiapine (Seroquel) have not yet been studied in MDD.

The main disadvantages of the use of atypical antipsychotics in MDD are the relative risk of sedation, hyperprolactinemia, extrapyramidal symptoms, weight gain, and QTc prolongation, the incidence of which appears to vary from agent to agent. Daily dose ranges of olanzapine, ziprasidone and aripiprazole used in clinical trials for depression were 5–20 mg, 20–80 mg bid, and 15–30 mg respectively. Due to the considerable metabolism of aripiprazole by the CYP system, patients on paroxetine or fluoxetine should be started on low doses (10 mg daily).

6.16

Conclusion

Over the last few decades, the monoamine theory of depression has guided the discovery and development of dozens of new treatment for depression. In recent years, the rapid emergence of monoamine-based antidepressants which differ in terms of their effects on the noradrenergic, dopaminergic and serotonergic system is beginning to redefine depressive subtypes in ways that highlight their differential effects on the treatment of select depressive symptoms, symptom clusters and syndromes, allowing us to make generalizations about the underlying neurophysiological process of depression and recovery. At present, however, our choice of treatment in depression continues to be largely based on considerations of the particular side-effect profile of each agent. Whether we will be able to match the treatment to the presenting features of depressed patients remains to be determined. And although the number of non-monoamine-based treatments is increasing, due to their established efficacy, tolerability, and long-term safety, psychiatrists will continue to rely largely on monoamine-based treatments for depression in the near future.

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References

- ABDELRAHMAN, N., KLEINMAN, Y., RUND, D., DA'AS, N., Hyponatremia associated with the initiation of reboxetine therapy. *Eur. J. Clin. Pharmacol.* **2003**, 59 (2), 177.
- ABSHER, J. R., BLACK, D. W., Tranylcypromine withdrawal delirium. *J. Clin. Psychopharmacol.* **1988**, 8 (5), 379–380.
- ACHONG, M. R., KEANE, P. M., Pheochromocytoma unmasked by desipramine therapy. *Ann. Intern. Med.* **1981**, 94 (3), 358–359.
- ADLAKHA, A., MANOCHA, A. P., BECHARD, D. L., Imipramine-induced syndrome of inappropriate antidiuretic hormone secretion. *South Med. J.* **1991**, 84 (12), 1507–1509.
- ADLER, L. A., ANGRIST, B. M., Paroxetine and akathisia. *Biol. Psychiatry* **1995**, 37 (5), 336–337.
- ADLI, M., BERGHOFER, A., LINDEN, M., HELMCHEN, H., MÜLLER-OERLINGHAUSEN, B., MACKERT, A., STAMM, T., BAUER, M., Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: results of a 2-year observational algorithm study. *J. Clin. Psychiatry* **2002**, 63 (9), 782–790.
- ADNITT, P. I., OLEESKY, S., SCHNEIDEN, H., Potentiation of insulin hypoglycemia. *Lancet* **1966**, 1 (7440), 770.

- ADNITT, P. I., Monoamineoxidase inhibition and insulin sensitivity. *J. Endocrinol.* **1968**, 42 (3), 417–423.
- AGUNDEZ, J. A., LEDESMA, M. C., LADERO, J. M., BENITEZ, J., Prevalence of CYP2D6 gene duplication and its repercussion on the oxidative phenotype in a white population. *Clin. Pharmacol. Ther.* **1995**, 57 (3), 265–269.
- AHMED, A., Neutropenia associated with mirtazapine use: is a drop in the neutrophil count in asymptomatic older adults a cause for concern? *J. Am. Geriatr. Soc.* **2002**, 50 (8), 1461–1463.
- AIZENBERG, D., ZEMISHLANY, Z., WEIZMAN, A., Cyproheptadine treatment of sexual dysfunction induced by serotonin reuptake inhibitors. *Clin. Neuropharmacol.* **1995**, 18 (4), 320–324.
- AKILLU, E., PERSSON, I., BERTILSSON, L., JOHANSSON, I., RODRIGUES, F., INGELMAN-SUNDBERG, M., Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. *J. Pharmacol. Exp. Ther.* **1996**, 278 (1), 441–446.
- ALDERMAN, C. P., SESHADRI, P., BEN-TOVIM, D. I., Effects of serotonin reuptake inhibitors on hemostasis. *Ann. Pharmacother.* **1996**, 30 (11), 1232–1234.
- ALEVIZOS, B., CHRISTODOULOU, G. N., IOANNIDIS, C., VOULGARI, A., MANTIDIS, A., SPILIADIS, C., The efficacy of amineptine in the treatment of depressive patients with irritable bowel syndrome. *Clin. Neuropharmacol.* **1989**, 12 (Suppl. 2), S66–S76.
- ALLAIN, H., POLIAK, P., NEUKIRCH, H. C., Symptomatic effect of selegiline in *de novo* Parkinsonian patients. The French Selegiline Multicenter Trial. *Mov. Disord.* **1993**, 8 (Suppl. 1), S36–S40.
- ALPERT, J. E., Drug–drug interactions in psychopharmacology. In: STERN, T. A., HERMAN, J. B., SLAVIN, P. (Eds.), *Massachusetts General Hospital Guide to Primary Care Psychiatry* (2nd ed.). New York: McGraw-Hill, **2003**.
- ALPERT, J. E., FAVA, M., KREMER, C., Gepirone extended release in patients with anxious depression. American Psychiatric Association 156th Annual Meeting. San Francisco, California, **2003**.
- ALPERT, J. E., MADDOCKS, A., NIERENBERG, A. A., O'SULLIVAN, R., PAVA, J. A., WORTHINGTON, J. J. 3RD, BIEDERMAN, J., ROSENBAUM, J. F., FAVA, M., Attention deficit hyperactivity disorder in childhood among adults with major depression. *Psychiatry Res.* **1996**, 62 (3), 213–219.
- ALPERT, M., SILVA, R. R., POUGET, E. R., Prediction of treatment response in geriatric depression from baseline folate level: interaction with an SSRI or a tricyclic antidepressant. *J. Clin. Psychopharmacol.* **2003**, 23 (3), 309–313.
- AITSHULER, L. L., PIERRE, J. M., WIRSHING, W. C., AMES, D., Sertraline and akathisia. *J. Clin. Psychopharmacol.* **1994**, 14 (4), 278–279.
- AMORE, M., JORI, M. C., AMISERT Investigators. Faster response on amisulpride 50 mg versus sertraline 50–100 mg in patients with dysthymia or double depression: a randomized, double-blind, parallel group study. *Int. Clin. Psychopharmacol.* **2001**, 16 (6), 317–324.
- AMSTERDAM, J., BRUNSWICK, D. J., GILBERTINI, M., Sustained efficacy of gepirone–IR in major depressive disorder: a double-blind placebo substitution trial. *J. Psychiatry Res.* **2004** (in press).
- AMSTERDAM, J. D., A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J. Clin. Psychiatry* **2003**, 64 (2), 208–214.
- AMSTERDAM, J. D., BERWISH, N. J., High dose tranylcypromine therapy for refractory depression. *Pharmacopsychiatry* **1989**, 22 (1), 21–25.
- AMSTERDAM, J. D., BRUNSWICK, D. J., HUNDERT, M., A single-site, double-blind, placebo-controlled, dose-ranging study of YKP10A – a putative, new antidepressant. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, 26 (7–8), 1333–1338.
- AMSTERDAM, J. D., GARCIA-ESPANA, F., GOODMAN, D., HOOPER, M., HORNIG-ROHAN, M., Breast enlargement during chronic antidepressant therapy. *J. Affect Disord.* **1997b**, 46 (2), 151–156.
- AMSTERDAM, J. D., GARCIA-ESPANA, F., ROSENZWEIG, M., Clomipramine augmentation in treatment-resistant depression. *Depress. Anxiety* **1997a**, 5 (2), 84–90.

- AMSTERDAM, J. D., HORNIG-ROHAN, M., MAISLIN, G., Efficacy of alprazolam in reducing fluoxetine-induced jitteriness in patients with major depression. *J. Clin. Psychiatry* **1994b**, 55 (9), 394–400.
- AMSTERDAM, J. D., MAISLIN, G., POTTER, L., Fluoxetine efficacy in treatment-resistant depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1994a**, 18 (2), 243–261.
- ANAND, V. S., Clomipramine-induced galactorrhoea and amenorrhoea. *Br. J. Psychiatry* **1985**, 147, 87–88.
- ANDERSON, I. M., TOMENSON, B. M., Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* **1995**, 310 (6992), 1433–1438.
- ANDERSON, I. M., Meta-analytical studies on new antidepressants. *Br. Med. Bull.* **2001**, 57, 161–178.
- ANDERSON, I. M., Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J. Affect Disord.* **2000**, 58 (1), 19–36.
- ANDERSON, J. W., GREENWAY, F. L., FUJIOKA, K., GADDE, K. M., MCKENNEY, J., O'NEIL, P. M., Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. *Obes. Res.* **2002**, 10 (7), 633–641.
- ANDREE, B., HEDMAN, A., THORBERG, S. O., NILSSON, D., HALLDIN, C., FARDE, L., Positron emission tomographic analysis of dose-dependent NAD-299 binding to 5-hydroxytryptamine-1A receptors in the human brain. *Psychopharmacology (Berl.)* **2003**, 167 (1), 37–45.
- ANDREE, B., THORBERG, S. O., HALLDIN, C., FARDE, L., Pindolol binding to 5-HT_{1A} receptors in the human brain confirmed with positron emission tomography. *Psychopharmacology (Berl.)* **1999**, 144 (3), 303–305.
- ANDREOLI, V., CAILLARD, V., DEO, R. S., RYBAKOWSKI, J. K., VERSIANI, M., Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. *J. Clin. Psychopharmacol.* **2002**, 22 (4), 393–399.
- ANGHELESCU, I., KLAWE, C., DAHMEN, N., Venlafaxine in a patient with idiopathic leukopenia and mirtazapine-induced severe neutropenia. *J. Clin. Psychiatry* **2002**, 63 (9), 838.
- ANISMAN, H., RAVINDRAN, A. V., GRIFFITHS, J., MERALI, Z., Interleukin-1 beta production in dysthymia before and after pharmacotherapy. *Biol. Psychiatry* **1999**, 46 (12), 1649–1655.
- ANSSEAU, M., PAPART, P., TROISFONTAINES, B., BARTHOLOME, F., BATAILLE, M., CHARLES, G., SCHITTECATTE, M., DARIMONT, P., DEVOITILLE, J. M., DE WILDE, J., et al. Controlled comparison of milnacipran and fluoxetine in major depression. *Psychopharmacology (Berl.)* **1994**, 114 (1), 131–137.
- ANSSEAU, M., VON FRENCKELL, R., MERTENS, C., DE WILDE, J., BOTTE, L., DEVOITILLE, J. M., EVRARD, J. L., DE NAYER, A., DARIMONT, P., DEJAFFE, G., et al. Controlled comparison of two doses of milnacipran (F 2207) and amitriptyline in major depressive inpatients. *Psychopharmacology (Berl.)* **1989**, 98 (2), 163–168.
- ANTTILA, S. A., LEINONEN, E. V., A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev.* **2001**, 7 (3), 249–264.
- APPELBERG, B. G., SYVALAHTI, E. K., KOSKINEN, T. E., MEHTONEN, O. P., MUHONEN, T. T., NAUKKARINEN, H. H., Buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J. Clin. Psychiatry* **2001**, 62 (6), 448–452.
- APPOLINARIO, J. C., GODOY-MATOS, A., FONTENELLE, L. F., CARRARO, L., CABRAL, M., VIEIRA, A., COUTINHO, W., An open-label trial of sibutramine in obese patients with binge-eating disorder. *J. Clin. Psychiatry* **2002**, 63 (1), 28–30.
- APSELOFF, G., WILNER, K. D., GERBER, N., TREMAINE, L. M., Effect of sertraline on protein binding of warfarin. *Clin. Pharmacokinet.* **1997**, 32 (Suppl. 1), 37–42.
- ARIAS, B., CATALAN, R., GASTO, C., GUTIERREZ, B., FANANAS, L., 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow-up study. *J. Clin. Psychopharmacol.* **2003**, 23 (6), 563–567.

- ARINZON, Z. H., LEHMAN, Y. A., FIDELMAN, Z. G., KRASNYSKY, I. I., ARINZON, Z. H., LEHMAN, Y. A., FIDELMAN, Z. G., KRASNYSKY, I. I., *Ann. Pharmacother.* **2002**, 36 (7–8), 1175–1177.
- ARMITAGE, R., The effects of antidepressants on sleep in patients with depression. *Can. J. Psychiatry* **2000**, 45 (9), 803–809.
- ARNOTT, S., NUTT, D., Successful treatment of fluvoxamine-induced anorgasmia by cyproheptadine. *Br. J. Psychiatry* **1994**, 164 (6), 838–839.
- ARONSON, M. D., HAFEZ, H., A case of trazodone-induced ventricular tachycardia. *J. Clin. Psychiatry* **1986**, 47 (7), 388–389.
- ARYA, D. K., TAYLOR, W. S., Lactation associated with fluoxetine treatment. *Aust. NZ J. Psychiatry* **1995**, 29 (4), 697.
- ASCHER, J. A., COLE, J. O., COLIN, J. N., FEIGHNER, J. P., FERRIS, R. M., FIBIGER, H. C., GOLDEN, R. N., MARTIN, P., POTTER, W. Z., RICHELSON, E., et al. Bupropion: a review of its mechanism of antidepressant activity. *J. Clin. Psychiatry* **1995**, 56 (9), 395–401.
- ASHTON, A. K., AHRENS, K., GUPTA, S., MASAND, P. S., Antidepressant-induced sexual dysfunction and Ginkgo Biloba. *Am. J. Psychiatry* **2000**, 157 (5), 836–837.
- ASHTON, A. K., ROSEN, R. C., Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. *J. Clin. Psychiatry* **1998**, 59 (3), 112–115.
- ASKINAZI, C., WEINTRAUB, R. J., KARAMOUC, N., Elderly depressed females as a possible subgroup of patients responsive to methylphenidate. *J. Clin. Psychiatry* **1986**, 47 (9), 467–469.
- ASNIS, G. M., CHAKRABURTY, A., DUBOFF, E. A., KRYSTAL, A., LONDBORG, P. D., ROSENBERG, R., ROTH-SCHECHTER, B., SCHARF, M. B., WALSH, J. K., Zolpidem for persistent insomnia in SSRI-treated depressed patients. *J. Clin. Psychiatry* **1999**, 60 (10), 668–676.
- ASTIER, B., LAMBAS SENAS, L., SOULIERE, F., SCHMITT, P., URBAIN, N., RENTERO, N., BERT, L., DENORAY, L., RENAUD, B., LESOURD, M., MUNOZ, C., CHOUVET, G., *In vivo* comparison of two 5-HT_{1A} receptors agonists alnespirone (S-20499) and buspirone on locus coeruleus neuronal activity. *Eur. J. Pharmacol.* **2003**, 459 (1), 17–26.
- ATKIN, D. H., FITZPATRICK, R. E., Laser treatment of imipramine-induced hyperpigmentation. *J. Am. Acad. Dermatol.* **2000**, 43 (1 Pt 1), 77–80.
- ATMACA, M., KULUGLU, M., TEZCAN, E., BUYUKBAYRAM, A., Switching to tianeptine in patients with antidepressant-induced sexual dysfunction. *Hum. Psychopharmacol.* **2003b**, 18 (4), 277–280.
- ATMACA, M., KULUGLU, M., TEZCAN, E., USTUNDAG, B., SEMERCIOZ, A., Serum leptin levels in patients with premature ejaculation before and after citalopram treatment. *BJU Int.* **2003a**, 91 (3), 252–254.
- AVILA, A., CARDONA, X., MARTIN-BARANERA, M., MAHO, P., SASTRE, F., BELLO, J., Does nefazodone improve both depression and Parkinson disease? A pilot randomized trial. *J. Clin. Psychopharmacol.* **2003**, 23 (5), 509–513.
- AYONRINDE, O. T., REUTENS, S. G., SANFILIPPO, F. M., Paroxetine-induced SIADH. *Med. J. Aust.* **1995**, 163 (7), 390.
- BAGHERI, H., SCHMITT, L., BERLAN, M., MONTASTRUC, J. L., Effect of 3 weeks treatment with yohimbine on salivary secretion in healthy volunteers and in depressed patients treated with tricyclic antidepressants. *Br. J. Clin. Pharmacol.* **1992**, 34 (6), 555–558.
- BAGSHAW, S. M., CLOAD, B., GILMOUR, J., LEUNG, S. T., BOWEN, T. J., Drug-induced rash with eosinophilia and systemic symptoms syndrome with bupropion administration. *Ann. Allergy Asthma Immunol.* **2003**, 90 (5), 572–575.
- BAILEY, D. L., LE MELLEDO, J. M., Effects of selective serotonin reuptake inhibitors on cholesterol levels in patients with panic disorder. *J. Clin. Psychopharmacol.* **2003**, 23 (3), 317–319.
- BAK, S., TSIROPOULOS, I., KJAERGAARD, J. O., ANDERSEN, M., MELLERUP, E., HALLAS, J., GARCIA RODRIGUEZ, L. A., CHRISTENSEN, K., GAIST, D., Selective serotonin reuptake inhibitors and the risk of stroke: a population-based case-control study. *Stroke* **2002**, 33 (6), 1465–1473.
- BAKER, G. B., PRIOR, T. I., Stereochemistry and drug efficacy and development: relevance of chirality to antidepressant and antipsychotic drugs. *Ann. Med.* **2002**, 34 (7–8), 537–543.

- BAKER, G. B., URICHUK, L. J., MCKENNA, K. F., KENNEDY, S. H., Metabolism of monoamine oxidase inhibitors. *Cell Mol. Neurobiol.* **1999**, 19 (3), 411–426.
- BAKISH, D., RAVINDRAN, A., HOOPER, C., LAPIERRE, Y., Psychopharmacological treatment response of patients with a DSM-III diagnosis of dysthymic disorder. *Psychopharmacol. Bull.* **1994**, 30 (1), 53–59.
- BALESTRIERI, G., CERUDELLI, B., CIACCIO, S., RIZZONI, D., Hyponatraemia and seizure due to overdose of trazodone. *BMJ* **1992**, 304 (6828), 686.
- BALESTROS, J., CALLADO, J. F., Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomized controlled trials. *J. Affect Disord.* **2004** (in press).
- BALIGA, R. R., MCHARDY, K. C., Syndrome of inappropriate antidiuretic hormone secretion due to fluvoxamine therapy. *Br. J. Clin. Pract.* **1993**, 47 (2), 62–63.
- BALL, C. J., Fluvoxamine and SIADH. *Br. J. Clin. Pract.* **1993**, 47 (4), 227.
- BALOGH, S., HENDRICKS, S. E., KANG, J., Treatment of fluoxetine-induced anorgasmia with amantadine. *J. Clin. Psychiatry* **1992**, 53 (6), 212–213.
- BALON, R., Fluoxetine-induced sexual dysfunction and yohimbine. *J. Clin. Psychiatry* **1993**, 54 (4), 161–162.
- BARCLAY, T. S., LEE, A. J., Citalopram-associated SIADH. *Ann. Pharmacother.* **2002**, 36 (10), 1558–1563.
- BARDIN, E. D., KRIEGER, J. N., Pharmacological priapism: comparison of trazodone- and papaverine-associated cases. *Int. Urol. Nephrol.* **1990**, 22 (2), 147–152.
- BARTLIK, B. D., KAPLAN, P., KAPLAN, H. S., Psychostimulants apparently reverse sexual dysfunction secondary to selective serotonin re-uptake inhibitors. *J. Sex Marital Ther.* **1995**, 21 (4), 264–271.
- BAUER, M., HELLWEG, R., BAUMGARTNER, A., Fluoxetine-induced akathisia does not reappear after switch to paroxetine. *J. Clin. Psychiatry* **1996**, 57 (12), 593–594.
- BEASLEY, C. M. JR., DORNSEIF, B. E., PULTZ, J. A., BOSOMWORTH, J. C., SAYLER, M. E., Fluoxetine versus trazodone: efficacy and activating-sedating effects. *J. Clin. Psychiatry* **1991**, 52 (7), 294–299.
- BEASLEY, C. M. JR., KOKE, S. C., NILSSON, M. E., GONZALES, J. S., Adverse events and treatment discontinuations in clinical trials of fluoxetine in major depressive disorder: an updated meta-analysis. *Clin. Ther.* **2000**, 22 (11), 1319–1330.
- BEASLEY, C. M. JR., MASICA, D. N., HEILIGENSTEIN, J. H., WHEADON, D. E., ZERBE, R. L., Possible monoamine oxidase inhibitor-serotonin uptake inhibitor interaction: fluoxetine clinical data and preclinical findings. *J. Clin. Psychopharmacol.* **1993**, 13 (5), 312–320.
- BEASLEY, C. M. JR., SAYLER, M. E., CUNNINGHAM, G. E., WEISS, A. M., MASICA, D. N., Fluoxetine in tricyclic refractory major depressive disorder. *J. Affect Disord.* **1990**, 20 (3), 193–200.
- BECH, P., Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. *Int. J. Neuropsychopharmacol.* **2001**, 4 (4), 337–345.
- BECKER, R. E., DUFRESNE, R. L., Perceptual changes with bupropion, a novel antidepressant. *Am. J. Psychiatry* **1982**, 139 (9), 1200–1201.
- BECKMANN, H., ATHEN, D., OLTEANU, M., ZIMMER, R., DL-phenylalanine versus imipramine: a double-blind controlled study. *Arch. Psychiatr. Nervenkr.* **1979**, 227, 49–58.
- BEHNKE, K., SOGAARD, J., MARTIN, S., BAUML, J., RAVINDRAN, A. V., AGREN, H., VESTERBLOKLAND, E. D., Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. *J. Clin. Psychopharmacol.* **2003**, 23 (4), 358–364.
- BELL, S., SHIPMAN, M., Reduced testosterone level in a venlafaxine treated patient. *Ann. Clin. Psychiatry* **2000**, 12 (3), 171–173.
- BEN-ARIE, O., GEORGE, G. C., A case of tranylcypromine ('Parnate') addiction. *Br. J. Psychiatry* **1979**, 135, 273–274.
- BENAZZI, F., Nefazodone withdrawal symptoms. *Can. J. Psychiatry* **1998a**, 43 (2), 194–195.
- BENAZZI, F., Serotonin syndrome with mirtazapine-fluoxetine combination. *Int. J. Geriatr. Psychiatry* **1998b**, 13 (7), 495–496.
- BENAZZI, F., Severe anticholinergic side effects with venlafaxine-fluoxetine

- combination. *Can. J. Psychiatry* **1997**, *42* (9), 980–981.
- BENKERT, O., GRUNDER, G., WETZEL, H., HACKETT, D., A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. *J. Psychiatr. Res.* **1996**, *30* (6), 441–451.
- BENKERT, O., SZEGEDI, A., KOHNEN, R., Mirtazapine compared with paroxetine in major depression. *J. Clin. Psychiatry* **2000**, *61* (9), 656–663.
- BENSON, E., Bupropion-induced hypersensitivity reactions. *Med. J. Aust.* **2001**, *174* (12), 650–651.
- BERGMANN, T. K., BATHUM, L., BROSEN, K., Duplication of CYP2D6 predicts high clearance of desipramine but high clearance does not predict duplication of CYP2D6. *Eur. J. Clin. Pharmacol.* **2001**, *57* (2), 123–127.
- BERK, M., JACOBSON, B. F., HURLY, E., Fluoxetine and hemostatic function: a pilot study. *J. Clin. Psychiatry* **1995**, *56* (1), 14–16.
- BERLANGA, C., ORTEGA-SOTO, H. A., A 3-year follow-up of a group of treatment-resistant depressed patients with a MAOI/tricyclic combination. *J. Affect Disord.* **1995**, *34* (3), 187–192.
- BERMAN, R. M., ANAND, A., CAPPIELLO, A., MILLER, H. L., HU, X. S., OREN, D. A., CHARNEY, D. S., The use of pindolol with fluoxetine in the treatment of major depression: final results from a double-blind, placebo-controlled trial. *Biol. Psychiatry* **1999**, *45* (9), 1170–1177.
- BERMAN, R. M., DARNELL, A. M., MILLER, H. L., ANAND, A., CHARNEY, D. S., Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: a double-blind, placebo-controlled trial. *Am. J. Psychiatry* **1997**, *154* (1), 37–43.
- BERRY, R. B., YAMAURA, E. M., GILL, K., REIST, C., Acute effects of paroxetine on genioglossus activity in obstructive sleep apnea. *Sleep* **1999**, *22* (8), 1087–1092.
- BERSANI, G., POZZI, F., MARINI, S., GRISPINI, A., PASINI, A., CIANI, N., 5-HT₂ receptor antagonism in dysthymic disorder: a double-blind placebo-controlled study with ritanserin. *Acta Psychiatr. Scand.* **1991**, *83* (4), 244–248.
- BERTILSSON, L., ABERG-WISTEDT, A., GUSTAFSSON, L. L., NORDIN, C., Extremely rapid hydroxylation of debrisoquine: a case report with implication for treatment with nortriptyline and other tricyclic antidepressants. *Ther. Drug Monit.* **1985**, *7* (4), 478–480 (no abstract available).
- BERTSCHY, G., VANDEL, S., Fluoxetine-related indifference and akathisia. A case report. *Therapie* **1993**, *48* (2), 158–159.
- BHATARA, V. S., MAGNUS, R. D., PAUL, K. L., PRESKORN, S. H., Serotonin syndrome induced by venlafaxine and fluoxetine: a case study in polypharmacy and potential pharmacodynamic and pharmacokinetic mechanisms. *Ann. Pharmacother.* **1998**, *32* (4), 432–436.
- BILDER, R., LIBERZON, I., CANUSO, C., PANDINA, G., BOSSIE, C., LOESCHER, A., GHARABAWI, G., Cognitive effects of risperidone augmentation of SSRI monotherapy in patients with unipolar treatment resistant depression. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- BILICI, M., EFE, H., KOROGU, M. A., UYDU, H. A., BEKAROGLU, M., DEGER, O., Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatment. *J. Affect Disord.* **2001**, *64* (1), 43–51.
- BIRDSALL, T. C., 5-Hydroxytryptophan: a clinically-effective serotonin precursor. *Altern. Med. Rev.* **1998**, *3* (4), 271–280.
- BIRKEBAEK, N. H., PERRILD, B. D., Pheochromocytoma diagnosed in an enuretic boy after imipramine-induced hypertension. *Pediatr. Hematol. Oncol.* **1986**, *3* (3), 283–285.
- BISWAS, P. N., WILTON, L. V., SHAKIR, S. A., The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13 554 patients in England. *J. Psychopharmacol.* **2003**, *17* (1), 121–126.
- BLACK, B., UHDE, T. W., Acute dystonia and fluoxetine. *J. Clin. Psychiatry* **1992**, *53* (9), 327.
- BLACKBURN, T. P., MINABE, Y., MIDDLEMISS, D. N., SHIRAYAMA, Y., HASHIMOTO, K., ASHBY, C. R. JR., Effect of acute and chronic administration of the selective 5-HT_{2C} receptor antagonist SB-243213 on midbrain dopamine neurons in the

- rat: An in vivo extracellular single cell study. *Synapse* **2002**, 46 (3), 129–139.
- BLANCH, J., DE PABLO, J., ROUSAUD, A., MINARRO, A., VILLARROYA, A., MASANA, G., GATELL, J. M., GASTRO, C., Open trial of the efficacy and tolerability of mirtazapine in the treatment of major depression in HIV-1 infected outpatients. *Eur. Neuropsychopharmacol.* **2001**, 11 (3), S228.
- BLIER, P., Pharmacology of rapid-onset antidepressant treatment strategies. *J. Clin. Psychiatry* **2001**, 62 (Suppl. 15), 12–17.
- BLIER, P., WARD, H. E., CHANTAL, H., O'HARA, S., PIGNOTT, T., Mirtazapine combinations from treatment initiation to augment the antidepressant response in unipolar depression. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- BLIER, P., WARD, N. M., Is there a role for 5-HT_{1A} agonists in the treatment of depression? *Biol. Psychiatry* **2003**, 53 (3), 193–203.
- BLOUIN, A. G., BLOUIN, J. H., PEREZ, E. L., BUSHNIK, T., ZURO, C., MULDER, E., Treatment of bulimia with fenfluramine and desipramine. *J. Clin. Psychopharmacol.* **1988**, 8 (4), 261–269.
- BLUMENFELD, M., LEVY, N. B., SPINOWITZ, B., CHARYTAN, C., BEASLEY, C. M. JR., DUBEY, A. K., SOLOMON, R. J., TODD, R., GOODMAN, A., BERGSTROM, R. F., Fluoxetine in depressed patients on dialysis. *Int. J. Psychiatry Med.* **1997**, 27 (1), 71–80.
- BODKIN, J. A., AMSTERDAM, J. D., Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. *Am. J. Psychiatry* **2002**, 159 (11), 1869–1875.
- BODKIN, J. A., LASSER, R. A., WINES, J. D. JR., GARDNER, D. M., BALDESSARINI, R. J., Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. *J. Clin. Psychiatry* **1997**, 58 (4), 137–145.
- BOFFA, E., LOFCHY, J., Paroxetine and tardive akathisia. *Can. J. Psychiatry* **2000**, 45 (4), 398.
- BOLDEN-WATSON, C., HAIGHT, B., AMES, M., ROCKETT, C., METZ, A., FAVA, M., Comparison of bupropion SR, fluoxetine, sertraline, and placebo using the Bech Melancholia Scale (HAM-D-6). 42nd Annual New Clinical Drug Evaluation Unit meeting, Boca Raton, Florida, **2002**.
- BOLDEN-WATSON, C., RICHELSON, E., Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci.* **1993**, 52 (12), 1023–1029.
- BOLO, N. R., HODE, Y., NEDELEC, J. F., LAINE, E., WAGNER, G., MACHER, J. P., Brain pharmacokinetics and tissue distribution *in vivo* of fluvoxamine and fluoxetine by fluorine magnetic resonance spectroscopy. *Neuropsychopharmacology* **2000**, 23 (4), 428–438.
- BONDAREV, M. L., BONDAREVA, T. S., YOUNG, R., GLENNON, R. A., Behavioral and biochemical investigations of bupropion metabolites. *Eur. J. Pharmacol.* **2003**, 474 (1), 85–93.
- BONDI, M., MENOZZI, M., BERTOLINI, M. G., VENNARI, M. G., DEL RIO, G., Metabolic effects of fluoxetine in obese menopausal women. *J. Endocrinol. Invest.* **2000**, 23, 280–286.
- BONIERBALE, M., LANCON, C., TIGNOL, J., The ELIXIR study: evaluation of sexual dysfunction in 4557 depressed patients in France. *Curr. Med. Res. Opin.* **2003**, 19 (2), 114–124.
- BONIN, B., VANDEL, P., KANTELEP, J. P., Mirtazapine and restless leg syndrome: a case report. *Therapie* **2000**, 55 (5), 655–656.
- BONIN, B., VANDEL, P., SECHTER, D., BIZOUARD, P., Paroxetine and galactorrhea. *Pharmacopsychiatry* **1997**, 30 (4), 133–134.
- BONIN, B., VANDEL, P., VANDEL, S., Fluvoxamine and galactorrhea. A case report. *Therapie* **1994**, 49 (2), 149–151.
- BONKOVSKY, H. L., BLANCHETTE, P. L., SCHNED, A. R., Severe liver injury due to phenelzine with unique hepatic deposition of extracellular material. *Am. J. Med.* **1986**, 80 (4), 689–692.
- BONNET, U., Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev.* **2003**, 9 (1), 97–140.
- BORAL, G. C., SHAH, L. P., The beneficial effects of amineptine (Survector 100) in the treatment of depression: preliminary results of an Indian multicenter trial.

- Clin. Neuropharmacol.* **1989**, 12 (Suppl. 2), S51–S57.
- BORDET, R., THOMAS, P., DUPUIS, B., Effect of pindolol on onset of action of paroxetine in the treatment of major depression: intermediate analysis of a double-blind, placebo-controlled trial. *Reseau de Recherche et d'Experimentation Psychopharmacologique. Am. J. Psychiatry* **1998**, 155 (10), 1346–1351.
- BORKOWSKA, A., BRUS, A., ARASZKIEWICZ, A., RYBAKOWSKI, J. K., The effect of mirtazapine on cognitive functions in patients with unipolar depression. *Eur. Neuropsychopharmacol.* **2001**, 11 (3), S190.
- BORNSTEIN, S., Cross-over trial comparing the antidepressant effects of amineptine and maprotiline. *Curr. Med. Res. Opin.* **1979**, 6 (2), 107–110.
- BORSINI, F., EVANS, K., JASON, K., ROHDE, F., ALEXANDER, B., POLLENTIER, S., Pharmacology of flibanserin. *CNS Drug Rev.* **2002**, 8 (2), 117–142.
- BORSON, S., McDONALD, G. J., GAYLE, T., DEFFEBACH, M., LAKSHMINARAYAN, S., VAN TUINEN, C., Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. *Psychosomatics* **1992**, 33 (2), 190–201.
- BOSCH, X., VERA, M., Aplastic anaemia during treatment with fluoxetine. *Lancet* **1998**, 351 (9108), 1031.
- BOSTWICK, J. M., JAFFEE, M. S., Buspirone as an antidote to SSRI-induced bruxism in 4 cases. *J. Clin. Psychiatry* **1999**, 60 (12), 857–860.
- BOUCKOMS, A., MANGINI, L., Pergolide: an antidepressant adjuvant for mood disorders? *Psychopharmacol. Bull.* **1993**, 29 (2), 207–211.
- BOUMAN, W. P., PINNER, G., JOHNSON, H., Incidence of selective serotonin reuptake inhibitor (SSRI) induced hyponatraemia due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion in the elderly. *Int. J. Geriatr. Psychiatry* **1998**, 13 (1), 12–15.
- BOURAS, N., BRIDGES, P., Bromocriptine in depression. *Curr. Med. Res. Opin.* **1982**, 8, 150–153.
- BOURGOIS, J. A., BABINE, S. E., BAHADUR, N., A case of SIADH and hyponatremia associated with citalopram. *Psychosomatics* **2002**, 43 (3), 241–242.
- BOUWER, C., STEIN, D. J., Buspirone is an effective augmenting agent of serotonin selective re-uptake inhibitors in severe treatment-refractory depression. *S. Afr. Med. J.* **1997**, 87 (4 Suppl.), 534–537, 540.
- BOYER, P., LECRUBIER, Y., STALLA-BOURDILLON, A., FLEUROT, O., Amisulpride versus amineptine and placebo for the treatment of dysthymia. *Neuropsychobiology* **1999**, 39 (1), 25–32.
- BOYER, P., TASSIN, J. P., FALISSART, B., TROY, S., Sequential improvement of anxiety, depression and anhedonia with sertraline treatment in patients with major depression. *J. Clin. Pharm. Ther.* **2000**, 25 (5), 363–371.
- BRADLEY, R. H., BARKIN, R. L., JEROME, J., DEYOUNG, K., DODGE, C. W., Efficacy of venlafaxine for the long-term treatment of chronic pain with associated major depressive disorder. *Am. J. Ther.* **2003**, 10 (5), 318–323.
- BRADY, K. T., LYDIARD, R. B., KELLNER, C., Tranylcypromine abuse. *Am. J. Psychiatry* **1991**, 148 (9), 1268–1269.
- BRAITBERG, G., CURRY, S. C., Seizure after isolated fluoxetine overdose. *Ann. Emerg. Med.* **1995**, 26 (2), 234–237.
- BRANNAN, S. K., MALLINCKRODT, C. H., TOLLEFSON, G. D., DETKE, M. J., WATKIN, J. G., Onset and maintenance of antidepressant efficacy for duloxetine 60 mg QD. 156th Annual Meeting of the American Psychiatric Association, San Francisco, California, **2003**.
- BREITBART, W., ROSENFELD, B., KAIM, M., FUNESTI-ESCH, J., A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. *Arch. Intern. Med.* **2001**, 161 (3), 411–420.
- BREMNER, J. D., ABRAHAMS, L. M., CRUPIE, J. E., MCCAWLEY, A., PROCTOR, R. C., SATHANANTHAN, G. L., Multicenter double-blind comparison of nomifensine and imipramine for efficacy and safety in depressed outpatients. *J. Clin. Psychiatry* **1984**, 45 (4 Pt 2), 56–59.
- BRENNAN, D., MACMANUS, M., HOWE, J., McLoughlin, J., 'Neuroleptic malignant

- syndrome' without neuroleptics. *Br. J. Psychiatry* **1988**, 152, 578–579.
- BRESSLER, R., VARGAS-CORD, M., LEOVITZ, H. E., Tranylcypromine: a potent insulin secretagogue and hypoglycemic agent. *Diabetes* **1968**, 17 (10), 617–624.
- BRODIE-MEIJER, C. C., DIEMONT, W. L., BUIJS, P. J., Nefazodone-induced clitoral priapism. *Int. Clin. Psychopharmacol.* **1999**, 14 (4), 257–258.
- BRONZO, M. R., STAHL, S. M., Galactorrhea induced by sertraline. *Am. J. Psychiatry* **1993**, 150 (8), 1269–1270.
- BROSEN, K., KLYSNER, R., GRAM, L. F., OTTON, S. V., BECH, P., BERTILSSON, L., Steady-state concentrations of imipramine and its metabolites in relation to the sparteine/debrisoquine polymorphism. *Eur. J. Clin. Pharmacol.* **1986a**, 30 (6), 679–684.
- BROSEN, K., OTTON, S. V., GRAM, L. F., Imipramine demethylation and hydroxylation: impact of the sparteine oxidation phenotype. *Clin. Pharmacol. Ther.* **1986**, 40 (5), 543–549.
- BROSS, R., HOFFER, L. J., Fluoxetine increases resting energy expenditure and basal body temperature in humans. *Am. J. Clin. Nutr.* **1995**, 61 (5), 1020–1025.
- BROWN, E. S., HONG, S. C., Antidepressant-induced bruxism successfully treated with gabapentin. *J. Am. Dent. Assoc.* **1999**, 130 (10), 1467–1469.
- BROWN, K., RATNER, M., STOLL, M., Pheochromocytoma unmasked by imipramine in an 8-year-old girl. *Pediatr. Emerg. Care* **2003**, 19 (3), 174–177.
- BROWN, W. A., HARRISON, W., Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J. Clin. Psychiatry* **1995**, 56 (1), 30–34.
- BRUBACHER, J. R., HOFFMAN, R. S., LURIN, M. J., Serotonin syndrome from venlafaxine-tranylcypromine interaction. *Vet. Hum. Toxicol.* **1996**, 38 (5), 358–361.
- BRUBAKER, R. V., Fluoxetine-induced sexual dysfunction reversed by loratadine. *J. Clin. Psychiatry* **2002**, 63 (6), 534.
- BRUNSWICK, D. J., AMSTERDAM, J. D., FAWCETT, J., QUITKIN, F. M., REIMHERR, F. W., ROSENBAUM, J. F., BEASLEY, C. M., Fluoxetine and norfluoxetine plasma concentrations during relapse prevention treatment. 3rd annual New Clinical Drug Evaluation Unit meeting, Boca Raton, Florida, **2000**.
- BRZEZINSKI, A. A., WURTMAN, J. J., WURTMAN, R. J., GLEASON, R., GREENFIELD, J., NADER, T., d-Fenfluramine suppresses the increased calorie and carbohydrate intakes and improves the mood of women with premenstrual depression. *Obstet. Gynecol.* **1990**, 76 (2), 296–301.
- BULL, S. A., HUNKELER, E. M., LEE, J. Y., ROWLAND, C. R., WILLIAMSON, T. E., SCHWAB, J. R., HURT, S. W., Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann. Pharmacother.* **2002**, 36 (4), 578–584.
- BUNNEY, W. E., DAVIS, J. M., Norepinephrine in depressive reactions. *Arch. Gen. Psychiatry* **1965**, 13, 483–494.
- BURKE, D., FANKER, S., Fluoxetine and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *Aust. NZ J. Psychiatry* **1996**, 30 (2), 295–298.
- BURKE, D., FRANKER, S., Fluoxetine-induced SIADH: most likely in the elderly? *Aust. NZ J. Psychiatry* **1996**, 30 (2), 299–301.
- BURKE, W. J., BOSE, A., WANG, J., STAHL, S., Switching depressed patients from citalopram to escitalopram is well tolerated and effective. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- BYMASTER, F. P., DRESHFIELD-AHMAD, L. J., THRELKELD, P. G., SHAW, J. L., THOMPSON, L., NELSON, D. L., HEMRICK-LUECKE, S. K., WONG, D. T., Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters *in vitro* and *in vivo*, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* **2001**, 25 (6), 871–880.
- CALABRESE, J. R., LONDBORG, P. D., SHELTON, M. D., THASE, M. E., Citalopram treatment of fluoxetine-intolerant depressed patients. *J. Clin. Psychiatry* **2003**, 64 (5), 562–567.
- CALHOUN, J. W., CALHOUN, D. D., Prolonged bleeding time in a patient treated with sertraline. *Am. J. Psychiatry* **1996**, 153 (3), 443.
- CANTILLON, M., THASE, M., WAMSLEY, J., Melancholic depression: Venlafaxine vs fluoxetine. *Eur. Neuropsychopharmacol.* **2001**, 11 (3), S196.

- CAPURON, L., GUMNICK, J. F., MUSSELMAN, D. L., LAWSON, D. H., REEMSNYDER, A., NEMEROFF, C. B., MILLER, A. H., Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* **2002**, 26 (5), 643–652.
- CAPURON, L., NEURAUTER, G., MUSSELMAN, D. L., LAWSON, D. H., NEMEROFF, C. B., FUCHS, D., MILLER, A. H., Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. *Biol. Psychiatry* **2003**, 54 (9), 906–914.
- CARACCI, G., DECINA, P., Fluoxetine and prolonged seizure. *Convuls. Ther.* **1991**, 7 (2), 145–147.
- CARDENAS, L., HOULE, S., KAPUR, S., BUSTO, U. E., Oral D-amphetamine causes prolonged displacement of [¹¹C]raclopride as measured by PET. *Synapse* **2004**, 51 (1), 27–31.
- CARPENTER, L. L., JOCIC, Z., HALL, J. M., RASMUSSEN, S. A., PRICE, L. H., Mirtazapine augmentation in the treatment of refractory depression. *J. Clin. Psychiatry* **1999**, 60 (1), 45–49.
- CARPENTER, L. L., YASMIN, S., PRICE, L. H., A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol. Psychiatry* **2002**, 51 (2), 183–188.
- CARVAJAL, G. P., GARCIA, D., SANCHEZ, S. A., VELASCO, M. A., RUEDA, D., LUCENA, M. I., Hepatotoxicity associated with the new antidepressants. *J. Clin. Psychiatry* **2002**, 63 (2), 135–137.
- CARVALHAL, A. S., DE ABREU, P. B., SPODE, A., CORREA, J., KAPCZINSKI, F., An open trial of reboxetine in HIV-seropositive outpatients with major depressive disorder. *J. Clin. Psychiatry* **2003**, 64 (4), 421–424.
- CASIS, O., SANCHEZ-CHAPULA, J. A., Mechanism of block of cardiac transient outward K⁺ current (I_{to}) by antidepressant drugs. *J. Cardiovasc. Pharmacol.* **1998**, 32 (4), 527–534.
- CASSANO, G. B., JORI, M. C., AMIMAJOR Group. Efficacy and safety of amisulpride 50 mg versus paroxetine 20 mg in major depression: a randomized, double-blind, parallel group study. *Int. Clin. Psychopharmacol.* **2002**, 17 (1), 27–32.
- CASSEM, E. H., PAPAPOSTAS, G. I., FAVA, M., STERN, T. A., Mood-Disordered Patients. In: STERN, T. A., HERMAN, J. B. (Eds.), *The MGH Handbook of General Hospital Psychiatry* (5th ed.). Inc St. Louis, MO: Mosby – Year Book, **2003**.
- CATALANO, G., CATALANO, M. C., EPSTEIN, M. A., TSAMBIRAS, P. E., QTc interval prolongation associated with citalopram overdose: a case report and literature review. *Clin. Neuropharmacol.* **2001**, 24 (3), 158–162.
- CAZZULLO, C. L., BESSONE, E., BERTRANDO, P., PEDRAZZOLI, L., CUSINI, M., Treatment of depression in HIV-infected patients. *J. Psychiatry Neurosci.* **1998**, 23 (5), 293–297.
- CERAVOLO, R., NUTI, A., PICCINNI, A., DELL'AGNELLO, G., BELLINI, G., GAMBACCINI, G., DELL'OSSO, L., MURRI, L., BONUCCELLI, U., Paroxetine in Parkinson's disease: effects on motor and depressive symptoms. *Neurology* **2000**, 55 (8), 1216–1218.
- CERAVOLO, R., PICCINI, P., BAILEY, D. L., JORGA, K. M., BRYSON, H., BROOKS, D. J., 18F-dopa PET evidence that tolcapone acts as a central COMT inhibitor in Parkinson's disease. *Synapse* **2002**, 43 (3), 201–207.
- CHAMBOST, M., LIRON, L., PEILLON, D., COMBE, C. (Serotonin syndrome during fluoxetine poisoning in a patient taking moclobemide). *Can. J. Anaesth.* **2000**, 47 (3), 246–250.
- CHARBONNIER, J. F., REBOUL, P., ROUGIER, M., AUBIN, B., CHASSAING, J. L., PHILIPPE, P., PLANCHE, R., HOEPFNER PETERSEN, H. E. (Citalopram. An open study of a highly selective serotonin-uptake inhibitor administered by infusion to depressive patients), *Encephale* **1987**, 13 (4), 249–254.
- CHARLIER, C., BROLY, F., LHERMITTE, M., PINTO, E., ANSSEAU, M., PLOMTEUX, G., Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. *Ther. Drug Monit.* **2003**, 25 (6), 738–742.
- CHARNEY, D. S., PRICE, L. H., HENINGER, G. R., Desipramine-yohimbine combination treatment of refractory depression. Implications for the beta-adrenergic receptor hypothesis of antidepressant

- action. *Arch. Gen. Psychiatry* **1986**, 43 (12), 1155–1161.
- CHATTERJEE, A., TOSYALI, M. C., Thrombocytopenia and delirium associated with tranlycypromine overdose. *J. Clin. Psychopharmacol.* **1995**, 15 (2), 143–144.
- CHELSEN, J., STROUS, R. D., LUSTIG, M., BARUCH, Y., Remission of SSRI-induced akathisia after switch to nefazodone. *J. Clin. Psychiatry* **2001**, 62 (7), 570–571.
- CHENGAPPA, K. N., KAMBHAMPATI, R. K., PERKINS, K., NIGAM, R., ANDERSON, T., BRAR, J. S., VEMULAPALLI, H. K., ATZERT, R., KEY, P., KANG, J. S., LEVINE, J., Bupropion sustained release as a smoking cessation treatment in remitted depressed patients maintained on treatment with selective serotonin reuptake inhibitor antidepressants. *J. Clin. Psychiatry* **2001**, 62 (7), 503–508.
- CHIASSON, L., LAW DCW, LEITER, L. A., TILDESLEY, H. D., BIRMINGHAM, C. L., EKOE, J. M., Hamet P et al. Fluoxetine has potential in obese NIDDM-multiple-centre Canadian trial. *Diabetes* **1989**, 38, 154A.
- CHIAVERINI, C., BALDIN, B., CHICHMANIAN, R. M., ORTONNE, J. P., LACOUR, J. P., (Bupropion (Zyban) induced urticaria: 2 cases). *Ann. Dermatol. Venerol.* **2003**, 130 (2 Pt 1), 208–209.
- CHILDS, P. A., RODIN, I., MARTIN, N. J., ALLEN, N. H., PLASKETT, L., SMYTHE, P. J., THOMPSON, C., Effect of fluoxetine on melatonin in patients with seasonal affective disorder and matched controls. *Br. J. Psychiatry* **1995**, 166 (2), 196–198.
- CHIN, C. K., ROE, C. J., THOMAS, G. W., Fluoxetine: a treatment option for severe symptomatic postural hypotension in a diabetic haemodialysis patient. *Aust. NZ J. Med.* **1996**, 26 (5), 714.
- CHOI, S., Nefazodone (Serzone) withdrawn because of hepatotoxicity. *CAMJ.* **2003**, 169 (11), 1187.
- CHOI, B. H., CHOI, J. S., YOON, S. H., RHIE, D. J., MIN, D. S., JO, Y. H., KIM, M. S., HAHN, S. J., Effects of norfluoxetine, the major metabolite of fluoxetine, on the cloned neuronal potassium channel Kv3.1. *Neuropharmacology* **2001**, 41 (4), 443–453.
- CHOI, J. S., HAHN, S. J., RHIE, D. J., YOON, S. H., JO, Y. H., KIM, M. S., Mechanism of fluoxetine block of cloned voltage-activated potassium channel Kv1.3. *J. Pharmacol. Exp. Ther.* **1999**, 291 (1), 1–6.
- CHONG, S. A., Fluvoxamine and mandibular dystonia. *Can. J. Psychiatry* **1995**, 40 (7), 430–431.
- CHONG, S. A., TAN, C. H., Fluvoxamine and akathisia. *J. Clin. Psychopharmacol.* **1996**, 16 (4), 334–335.
- CHOUINARD, G., ANNABLE, L., BRADWEJN, J., An early phase II clinical trial of tomooxetine (LY139603) in the treatment of newly admitted depressed patients. *Psychopharmacology (Berl.)* **1984**, 83 (1), 126–128.
- CLAIRE, R. J., SERVIS, M. E., CRAM, D. L JR., Potential interaction between warfarin sodium and fluoxetine. *Am. J. Psychiatry* **1991**, 148 (11), 1604.
- CLAYTON, A. H., MCGARVEY, E. L., ABOUESH, A. I., PINKERTON, R. C., Substitution of an SSRI with bupropion sustained release following SSRI-induced sexual dysfunction. *J. Clin. Psychiatry* **2001a**, 62 (3), 185–190.
- CLAYTON, A., MCGARVEY, E., WARNOCK, J., KORNSTEIN, S., Bupropion sustained release as an antidote to SSRI-induced sexual dysfunction. 41st Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, **2001b**.
- CLAYTON, A. H., PRADKO, J. F., CROFT, H. A., MONTANO, C. B., LEADBETTER, R. A., BOLDEN-WATSON, C., BASS, K. I., DONAHUE, R. M., JAMERSON, B. D., METZ, A., Prevalence of sexual dysfunction among newer antidepressants. *J. Clin. Psychiatry* **2002**, 63 (4), 357–366.
- CLAYTON, A. H., ZAJECKA, J., FERGUSON, J. M., FILIPIAK-REISNER, J. K., BROWN, M. T., SCHWARTZ, G. E., Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder. *Int. Clin. Psychopharmacol.* **2003**, 18 (3), 151–156.
- CLERC, G., Milnacipran/Fluvoxamine Study Group. Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine. *Int. Clin. Psychopharmacol.* **2001**, 16 (3), 145–151.

- CLONKOWSKA, A., ZIENOWICZ, M., BIDZINSKI, A., MACIEJAK, P., LEHNER, M., TARACHA, E., WISLOWSKA, A., PLAŹNIK, A., The role of neurosteroids in the anxiolytic, antidepressive- and anticonvulsive effects of selective serotonin reuptake inhibitors. *Med. Sci. Monit.* **2003**, *9* (11), RA270–RA275.
- COHEN, A. J., Fluoxetine-induced yawning and anorgasmia reversed by cyproheptadine treatment. *J. Clin. Psychiatry* **1992**, *53* (5), 174.
- COHEN, A. J., BARTLIK, B., Ginkgo biloba for antidepressant-induced sexual dysfunction. *J. Sex Marital Ther.* **1998**, *24* (2), 139–143.
- COHN, J. B., VARGA, L., LYFORD, A., A two-center double-blind study of nomifensine, imipramine, and placebo in depressed geriatric outpatients. *J. Clin. Psychiatry* **1984**, *45* (4 Pt 2), 68–72.
- COLEMAN, C. C., CUNNINGHAM, L. A., FOSTER, V. J., BATEY, S. R., DONAHUE, R. M., HOUSER, T. L., ASCHER, J. A., Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann. Clin. Psychiatry* **1999**, *11* (4), 205–215.
- COLEMAN, C. C., KING, B. R., BOLDEN-WATSON, C., BOOK, M. J., SEGRAVES, R. T., RICHARD, N., ASCHER, J., BATEY, S., JAMERSON, B., METZ, A., A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. *Clin. Ther.* **2001**, *23* (7), 1040–1058.
- COMBES, A., PEYTAVIN, G., THERON, D., Conduction disturbances associated with venlafaxine. *Ann. Intern. Med.* **2001**, *134* (2), 166–167.
- CONNERS, C. K., CASAT, C. D., GUALTIERI, C. T., WELLER, E., READER, M., REISS, A., WELLER, R. A., KHAYRALLAH, M., ASCHER, J., Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J. Am. Acad. Child Adolesc. Psychiatry* **1996**, *35* (10), 1314–1321.
- CONNOR, D. F., FLETCHER, K. E., SWANSON, J. M., A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **1999**, *38* (12), 1551–1559.
- COOPER, A. J., ASHCROFT, G., Potentiation of insulin hypoglycaemia by M. A. O. I. antidepressant drugs. *Lancet* **1966**, *1* (7434), 407–409.
- COOPER, T. B., SUCKOW, R. F., GLASSMAN, A., Determination of bupropion and its major basic metabolites in plasma by liquid chromatography with dual-wavelength ultraviolet detection. *J. Pharm. Sci.* **1984**, *73* (8), 1104–1107.
- COREY-LISLE, P. K., BIRNBAUM, H., GREENBERG, P., MARYNCHENKO, M., DUBE, S., Economic impact of olanzapine plus fluoxetine combination therapy among patients treated for depression: a pilot study. *Psychopharmacol. Bull.* **2003**, *37* (3), 90–98.
- CORRIGAN, M. H., DENAHAN, A. Q., WRIGHT, C. E., RAGUAL, R. J., EVANS, D. L., Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. *Depress. Anxiety* **2000**, *11* (2), 58–65.
- CORYA, S. A., ANDERSEN, S. W., DETKE, H. C., KELLY, L. S., VAN CAMPEN, L. E., SANGER, T. M., WILLIAMSON, D. J., DUBE, S., Long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination: a 76-week open-label study. *J. Clin. Psychiatry* **2003**, *64* (11), 1349–1356.
- COSTA E SILVA, J. A., RUSCHEL, S. I., CAETANO, D., ROCHA, F. L., DA SILVA LIPPI, J. R., ARRUDA, S., OZUN, M., Placebo-controlled study of tianeptine in major depressive episodes. *Neuropsychobiology* **1997**, *35* (1), 24–29.
- COULTER, D. M., PILLANS, P. I., Hypertension with moclobemide. *Lancet* **1995**, *346* (8981), 1032.
- COWEN, P. J., SARGENT, P. A., Changes in plasma prolactin during SSRI treatment: evidence for a delayed increase in 5-HT neurotransmission. *J. Psychopharmacol.* **1997**, *11* (4), 345–348.
- CRANE, G. E., The psychiatric side-effects of iproniazid. *Am. J. Psychiatry* **1956**, *112*, 494–501.
- CREMERS, T. I., WIERSMA, L. J., BOSKER, F. J., DEN BOER, J. A., WESTERINK, B. H., WIKSTROM, H. V., Is the beneficial antidepressant effect of coadministration of pindolol really due to somatodendritic autoreceptor antagonism? *Biol. Psychiatry* **2001**, *50* (1), 13–21.

- CROFT, H., HOUSER, T. L., JAMERSON, B. D., LEADBETTER, R., BOLDEN-WATSON, C., DONAHUE, R., METZ, A., Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. *Clin. Ther.* **2002**, 24 (4), 662–672.
- CROFT, H., SETTLE, E. JR., HOUSER, T., BATEY, S. R., DONAHUE, R. M., ASCHER, J. A., A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin. Ther.* **1999**, 21 (4), 643–658.
- CUNNINGHAM, L. A., BORISON, R. L., CARMAN, J. S., CHOUINARD, G., CROWDER, J. E., DIAMOND, B. I., FISCHER, D. E., HEARST, E., A comparison of venlafaxine, trazodone, and placebo in major depression. *J. Clin. Psychopharmacol.* **1994**, 14 (2), 99–106.
- CURRIER, M. B., MOLINA, G., KATO, M., A prospective trial of sustained-release bupropion for depression in HIV-seropositive and AIDS patients. *Psychosomatics* **2003**, 44 (2), 120–125.
- CURTIN, F., BERNEY, P., KAUFMANN, C., Moclobemide discontinuation syndrome predominantly presenting with influenza-like symptoms. *J. Psychopharmacol.* **2002**, 16 (3), 271–272.
- CUSIN, C., SERRETTI, A., ZANARDI, R., LATTUADA, E., ROSSINI, D., LILLI, R., LORENZI, C., SMERALDI, E., Influence of monoamine oxidase A and serotonin receptor 2A polymorphisms in SSRI antidepressant activity. *Int. J. Neuropsychopharmacol.* **2002**, 5 (1), 27–35.
- CYR, M., BROWN, C. S., Nefazodone: its place among antidepressants. *Ann. Pharmacother.* **1996**, 30 (9), 1006–1012.
- DALERY, J., DAGENS-LAFONT, V., DE BODINAT, C., Efficacy of tianeptine vs placebo in the long-term treatment (16.5 months) of unipolar major recurrent depression. *Hum. Psychopharmacol.* **2001** Jan., 16 (S1), S39–S47.
- DALERY, J., ROCHAT, C., PEYRON, E., BERNARD G., The efficacy and acceptability of amineptine versus fluoxetine in major-depression. *Int. Clin. Psychopharmacol.* **1997**, 12 (Suppl. 3), S35–S38.
- DALTON, E. J., ROTONDI, D., LEVITAN, R. D., KENNEDY, S. H., BROWN, G. M., Use of slow-release melatonin in treatment-resistant depression. *J. Psychiatry Neurosci.* **2000**, 25 (1), 48–52.
- DALTON, S. O., JOHANSEN, C., MELLEMEKJAER, L., NORGARD, B., SORENSEN, H. T., OLSEN, J. H., Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch. Intern. Med.* **2003**, 163 (1), 59–64.
- DAM, J., RYDE, L., SVEJSO, J., LAUGE, N., LAURITSEN, B., BECH, P., Morning fluoxetine plus evening mianserin versus morning fluoxetine plus evening placebo in the acute treatment of major depression. *Pharmacopsychiatry* **1998**, 31 (2), 48–54.
- DAMS, R., BENIJTS, T. H., LAMBERT, W. E., VAN BOCKLAER, J. F., VAN VARENBERGH, D., VAN PETEGHEM, C., DE LEENHEER, A. P., A fatal case of serotonin syndrome after combined moclobemide–citalopram intoxication. *J. Anal. Toxicol.* **2001**, 25 (2), 147–151.
- DANISH UNIVERSITY ANTIDEPRESSANT GROUP. Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. *Psychopharmacology (Berl.)* **1986**, 90 (1), 131–138.
- DANISH UNIVERSITY ANTIDEPRESSANT GROUP. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J. Affect Disord.* **1990**, 18 (4), 289–299.
- DARDENNES, R. M., EVEN, C., BALLON, N., BANGE, F., Serotonin syndrome caused by a clomipramine–moclobemide interaction. *J. Clin. Psychiatry* **1998**, 59 (7), 382–383.
- DAVE, M., Fluoxetine-associated dystonia. *Am. J. Psychiatry* **1994**, 151 (1), 149.
- DAVENPORT, E., VELAMOO, R., A case of paroxetine-induced galactorrhea. *Can. J. Psychiatry* **2002**, 47 (9), 890–891.
- DAVIDSON, E., ROSCHKE, J., KLAWE, C., GRUNDER, G., SCHMOLDT, A., Tranylcypromine abuse associated with delirium and thrombocytopenia. *J. Clin. Psychopharmacol.* **2000**, 20 (2), 270–271.
- DAVIDSON, J., Seizures and bupropion: a review. *J. Clin. Psychiatry* **1989**, 50 (7), 256–261.

- DAVIDSON, J., PELTON, S., Forms of atypical depression and their response to anti-depressant drugs. *Psychiatry Res.* **1986**, *17* (2), 87–95.
- DAVIDSON, J. R., MEONI, P., HAUDIQUE, V., CANTILLON, M., HACKETT, D., Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. *Depress. Anxiety* **2002**, *16* (1), 4–13.
- DAVIS, J. S., BOYLE, M. J., HANNAFORD, R., WATSON, A., Bupropion and serum sickness-like reaction. *Med. J. Aust.* **2001**, *174* (9), 479–480.
- DAWE, G. S., HUFF, K., VANDERGRIF, J., O'NEILL, M. J., SHARP, T., RASMUSSEN, K., Activation of the locus coeruleus by olanzapine: firing patterns and immediate early gene expression. *Biol. Psychiatry* **2001**, *50*, 510–520.
- DE ABAJO, F. J., JICK, H., DERBY, L., JICK, S., SCHMITZ, S., Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br. J. Clin. Pharmacol.* **2000**, *50* (1), 43–47.
- DE BELLIS, M. D., GOLD, P. W., GERACIOTI, T. D. JR., LISTWAK, S. J., KLING, M. A., Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *Am. J. Psychiatry* **1993**, *150* (4), 656–657.
- DE BOER, T. H., MAURA, G., RAITERI, M., DE VOS, C. J., WIERINGA, J., PINDER, R. M., Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, Org 3770 and its enantiomers. *Neuropharmacology* **1988**, *27* (4), 399–408.
- DE BOER, T. H., The pharmacologic profile of mirtazapine. *J. Clin. Psychiatry* **1996**, *57* (Suppl. 4), 19–25.
- DE JONG, J. C., VAN DEN BERG, P. B., TOBI, H., DE JONG-VAN DEN BERG, L. T., Combined use of SSRIs and NSAIDs increases the risk of gastrointestinal adverse effects. *Br. J. Clin. Pharmacol.* **2003**, *55* (6), 591–595.
- DE JONGHE, F., RAVINELLI, D. P., TUYNMAN-QUA, H., A randomized, double-blind study of Fluoxetine and maprotiline in the treatment of major depression. *Pharmacopsychiatry* **1991**, *24*, 62–67.
- DE MAISTRE, E., ALLART, C., LECOMPTE, T., BOLLAERT, P. E., Severe bleeding associated with use of low molecular weight heparin and selective serotonin reuptake inhibitors. *Am. J. Med.* **2002**, *113* (6), 530–532.
- DE MEESTER, A., CARBUTTI, G., GABRIEL, L., JACQUES, J. M., Fatal overdose with trazodone: case report and literature review. *Acta Clin. Belg.* **2001**, *56* (4), 258–261.
- DE MONTIGNY, C., SILVERSTONE, P. H., DEBONNEL, G., BLIER, P., BAKISH, D., Venlafaxine in treatment-resistant major depression: a Canadian multicenter, open-label trial. *J. Clin. Psychopharmacol.* **1999**, *19* (5), 401–406.
- DE NAYER, A., DE CLERCQ, M., MIGNON, A., Symptom relief obtained with Venlafaxine versus fluoxetine in depressed patients with concomitant anxiety. *Eur. Neuropsychopharmacol.* **2000**, *10* (3), S242.
- DE SANTIAGO HERNANDO, M. L., ROLDAN SAN JUAN, J., GUTIERREZ AGRAMUNT, A., Munoz Gomez B. (Serum sickness-like reaction induced by bupropion). *Med. Clin. (Barc.)* **2002**, *119* (2), 76.
- DE SIMONI, M. G., DE LUIGI, A., CLAVENNA, A., MANFRIDI, A., *In vivo* studies on the enhancement of serotonin reuptake by tianeptine. *Brain Res.* **1992**, *574* (1–2), 93–97.
- DE WIT, S., CREMERS, L., HIRSCH, D., ZULIAN, C., CLUMECK, N., KORMOSS, N., Efficacy and safety of trazodone versus clorazepate in the treatment of HIV-positive subjects with adjustment disorders: a pilot study. *J. Int. Med. Res.* **1999**, *27* (5), 223–232.
- DEBATTISTA, C., DIGHRAMJI, K., MENZA, M., ROSENTHAL, M. H., FIEVE, R. R., the modafinil in depression study group. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. *J. Clin. Psychiatry* **2003a**, *64* (9), 1057–1064.
- DEBATTISTA, C., LEMBKE, A., SOLVASON, H. B., GHEBREMICHAEL, R., POIRIER, J., A prospective trial of modafinil as an adjunctive treatment of major depression. *J. Clin. Psychopharmacol.* **2004**, *24* (1), 87–90.

- DEBATTISTA, C., SOLVASON, H. B., POIRIER, J., KENDRICK, E., SCHATZBERG, A. F., A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. *J. Clin. Psychopharmacol.* **2003b**, 23 (1), 27–30.
- DEBONNEL, G., GOBBI, G., TURCOTTE, J., BOUCHER, N., HEBERT, C., DE MONTIGNY, C., BLIER, P., Effects of mirtazapine, paroxetine and their combination: a double-blind study in major depression. *Eur. Neuropsychopharmacol.* **2000**, 10 (3), S252.
- DEEG, M. A., LIPKIN, E. W., Hypoglycemia associated with the use of fluoxetine. *West J. Med.* **1996**, 164 (3), 262.
- DEGKEWITZ, R., FROWSTEIN, R., KULENKAMPFF, C., et al., The influence of reserpine, chlorpromazine, iproniazid and vitamin B6 on the effects of L-DOPA in man. *Klin. Wochenschr.* **1960**, 38, 120–123.
- DELALLEAU, B., DULCIRE, C., LE MOINE, P., KAMOUN, A., Analysis of the side effects of tianeptine. *Clin. Neuropharmacol.* **1988**, 11 (Suppl. 2), S83–9.
- DELINI-STULA, A., BAIER, D., KOHNEN, R., LAUX, G., PHILIPP, M., SCHOLZ, H. J., Undesirable blood pressure changes under naturalistic treatment with moclobemide, a reversible MAO-A inhibitor – results of the drug utilization observation studies. *Pharmacopsychiatry* **1999**, 32 (2), 61–67.
- DELL'AGNELLO, G., CERAVOLO, R., NUTI, A., BELLINI, G., PICCINNI, A., D'AVINO, C., DELL'OSSO, L., BONUCCELLI, U., SSRIs do not worsen Parkinson's disease: evidence from an open-label, prospective study. *Clin. Neuropharmacol.* **2001**, 24 (4), 221–227.
- DELVA, N. J., HORGAN, S. A., HAWKEN, E. R., Valproate prophylaxis for migraine induced by selective serotonin reuptake inhibitors. *Headache* **2000**, 40 (3), 248–251.
- DEMERS, J. C., MALONE, M., Serotonin syndrome induced by fluvoxamine and mirtazapine. *Ann. Pharmacother.* **2001**, 35 (10), 1217–1220.
- DEMOPULOS, C., FAVA, M., MCLEAN, N. E., ALPERT, J. E., NIERENBERG, A. A., ROSENBAUM, J. F., Hypochondriacal concerns in depressed outpatients. *Psychosom. Med.* **1996**, 58 (4), 314–320.
- DEMYTTENAERE, K., HUYGENS, R., VAN BUGGENHOUT, R., Tamsulosin as an effective treatment for reboxetine-associated urinary hesitancy. *Int. Clin. Psychopharmacol.* **2001**, 16 (6), 353–355.
- DEMYTTENAERE, K., HUYGENS, R., Painful ejaculation and urinary hesitancy in association with antidepressant therapy: relief with tamsulosin. *Eur. Neuropsychopharmacol.* **2002**, 12 (4), 337–341.
- DEN BOER, J. A., WESTENBERG, H. G., Serotonin function in panic disorder: a double blind placebo controlled study with fluvoxamine and ritanserin. *Psychopharmacology (Berl.)* **1990**, 102 (1), 85–94.
- DEN BRABER, E., SCHUTTE, A. J., VAN DER FLIER, S., Tolerability of mirtazapine versus SSRIs in patients with major depression. *Eur. Neuropsychopharmacol.* **2003**, 13 (4), S252.
- DENT, L. A., ORROCK, M. W., Warfarin–fluoxetine and diazepam–fluoxetine interaction. *Pharmacotherapy* **1997**, 17 (1), 170–172.
- DESILVA, K. E., LE FLORE, D. B., MARSTON, B. J., RIMLAND, D., Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* **2001**, 15 (10), 1281–1285.
- DETKE, M., GILABERTE, I., PERAHIA, D. G., WANG, F., LEE, T. C., TRAN, P., MINER, C., IYENGAR, S., MONTGOMERY, S., Duloxetine versus placebo in the prevention of relapse of major depressive disorder. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- DETKE, M. J., LU, Y., GOLDSTEIN, D. J., HAYES, J. R., DEMITRACK, M. A., Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J. Clin. Psychiatry* **2002b**, 63 (4), 308–315.
- DETKE, M. J., LU, Y., GOLDSTEIN, D. J., McNAMARA, R. K., DEMITRACK, M. A., Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J. Psychiatr. Res.* **2002a**, 36 (6), 383–390.
- DETWEILER, M. B., HARPOLD, G. J., Bupropion-induced acute dystonia. *Ann. Pharmacother.* **2002**, 36 (2), 251–254.

- DEVANE, C. L., DONOVAN, J. L., LISTON, H. L., MARKOWITZ, J. S., CHENG, K. T., RISCH, S. C., WILLARD, L., Comparative CYP3A4 inhibitory effects of venlafaxine, fluoxetine, sertraline, and nefazodone in healthy volunteers. *J. Clin. Psychopharmacol.* **2004**, *24* (1), 4–10.
- DEVANE, C. L., NEMEROFF, C. B., **2002** guide to psychotropic drug interactions. *Primary Psychiatry* **2002**, *9*, 28–57.
- DEVARAJAN, S., DURSUN, S. M., Reboxetine plus citalopram in treatment-resistant depression. *Eur. Neuropsychopharmacol.* **2000**, *10* (3), S280.
- DHEENAN, S., VENKATESAN, J., GRUBB, B. P., HENRICH, W. L., Effect of sertraline hydrochloride on dialysis hypotension. *Am. J. Kid Dis.* **1998**, *31* (4), 624–630.
- DIAMOND, S., PEPPER, B. J., DIAMOND, M. L., FREITAG, F. G., URBAN, G. J., ERDEMOGLU, A. K., Serotonin syndrome induced by transitioning from phenelzine to venlafaxine: four patient reports. *Neurology* **1998**, *51* (1), 274–276.
- DIETRICH, D. E., BODE, L., SPANNHUTH, C. W., LAU, T., HUBER, T. J., BRODHUN, B., LUDWIG, H., EMRICH, H. M., Amantadine in depressive patients with Borna disease virus (BDV) infection: an open trial. *Bipolar Disord.* **2000**, *2* (1), 65–70.
- DILER, R. S., YOLGA, A. Y., AVCI, A., Fluoxetine-induced extrapyramidal symptoms in an adolescent: a case report. *Swiss Med. Wkly.* **2002**, *132* (9–10), 125–126.
- DIMELLIS, D., Serotonin syndrome produced by a combination of venlafaxine and mirtazapine. *World. J. Biol. Psychiatry* **2002**, *3* (3), 167.
- DIMITRIOU, E. C., DIMITRIOU, C. E., Buspirone augmentation of antidepressant therapy. *J. Clin. Psychopharmacol.* **1998**, *18* (6), 465–469.
- DINGEMANSE, J., WALLNOFER, A., GIESCHKE, R., GUENTERT, T., AMREIN, R., Pharmacokinetic and pharmacodynamic interactions between fluoxetine and moclobemide in the investigation of development of the “serotonin syndrome”. *Clin. Pharmacol. Ther.* **1998**, *63* (4), 403–413.
- DOLBERG, O. T., HIRSCHMANN, S., GRUNHAUS, L., Melatonin for the treatment of sleep disturbances in major depressive disorder. *Am. J. Psychiatry* **1998**, *155* (8), 1119–1121.
- DOLBERG, O. T., KLAG, E., GROSS, Y., SCHREIBER, S., Relief of serotonin selective reuptake inhibitor induced sexual dysfunction with low-dose mianserin in patients with traumatic brain injury. *Psychopharmacology (Berl.)* **2002**, *161* (4), 404–407.
- DOMINGUEZ-MORAN, J. A., CALLEJO, J. M., FERNANDEZ-RUIZ, L. C., MARTINEZ-CASTRILLO, J. C., Acute paroxysmal dystonia induced by fluoxetine. *Mov. Disord.* **2001**, *16* (4), 767–769.
- DONG, J., BLIER, P., Modification of norepinephrine and serotonin, but not dopamine, neuron firing by sustained bupropion treatment. *Psychopharmacology (Berl.)* **2001**, *155* (1), 52–57.
- DORDING, C. M., MISCHOULON, D., PETERSEN, T. J., KORNBLUH, R., GORDON, J., NIERENBERG, A. A., ROSENBAUM, J. F., FAVA, M., The pharmacologic management of SSRI-induced side effects: a survey of psychiatrists. *Ann. Clin. Psychiatry* **2002**, *14* (3), 143–147.
- DOUGHERTY, J. A., YOUNG, H., SHAFI, T., Serotonin syndrome induced by amitriptyline, meperidine, and venlafaxine. *Ann. Pharmacother.* **2002**, *36* (10), 1647–1648.
- DREIXLER, J. C., BIAN, J., CAO, Y., ROBERTS, M. T., ROIZEN, J. D., HOUAMED, K. M., Block of rat brain recombinant SK channels by tricyclic antidepressants and related compounds. *Eur. J. Pharmacol.* **2000**, *401* (1), 1–7.
- DRUCKENBROD, R., MULSANT, B. H., Fluoxetine-induced syndrome of inappropriate antidiuretic hormone secretion: a geriatric case report and a review of the literature. *J. Geriatr. Psychiatry Neurol.* **1994**, *7* (4), 254–256.
- DUBE, S., CORYA, S., ANDERSON, S. W., DETKE, H. C., BLANSETTE, S., TOLLEFSON, G. D., Efficacy of olanzapine/fluoxetine combination in treatment-resistant depression. 41st Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2002**.
- DUBINI, A., BOSCH, M., POLIN, V., Noradrenaline-selective versus serotonin-selective antidepressant therapy:

- differential effects on social functioning. *J. Psychopharmacol.* **1997**, 11 (4 Suppl.), S17–S23.
- DUNCAN, D., SAYAL, K., MCCONNELL, H., TAYLOR, D., Antidepressant interactions with warfarin. *Int. Clin. Psychopharmacol.* **1998**, 13 (2), 87–94.
- DUNNER, D. L., AMSTERDAM, J. D., SHELTON, R. C., HASSMAN, H. A., ROSENTHAL, M., ROMANO, S. J., Adjunctive ziprasidone in treatment-resistant depression: a pilot study. American Psychiatric Association Annual Meeting, San Francisco, **2003**.
- DUNNER, D. L., ZISOOK, S., BILLOW, A. A., BATEY, S. R., JOHNSTON, J. A., ASCHER, J. A., A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J. Clin. Psychiatry* **1998**, 59 (7), 366–373.
- DURHAM, L. K., WEBB, S. M., MILOS, P. M., CLARY, C. M., SEYMOUR, A. B., The serotonin transporter polymorphism, 5HTTLPR, is associated with a faster response time to sertraline in an elderly population with major depressive disorder. *Psychopharmacology (Berl.)* **2004**, 174 (4), 525–529.
- EBERT, D., ALBERT, R., MAY, A., STOSIEK, I., KASCHKA, W., Combined SSRI–RIMA treatment in refractory depression. Safety data and efficacy. *Psychopharmacology (Berl.)* **1995**, 119 (3), 342–344.
- EDWARDS, J. G., GOLDIE, A., PAPAYANNI-PAPASTHATIS, S., Effect of paroxetine on the electrocardiogram. *Psychopharmacology (Berl.)* **1989**, 97 (1), 96–98.
- EHRENTAUF, S., ROTHENHAUSLER, H. B., GERBES, A. L., RAU, H. G., THIEL, M., SCHIRREN, C. A., KAPFHAMMER, H. P., Acute liver failure in nefazodone therapy? A case report. *Nervenarzt* **2002**, 73 (7), 686–689.
- EISEN, A., Fluoxetine and desipramine: a strategy for augmenting antidepressant response. *Pharmacopsychiatry* **1989**, 22, 272–273.
- ELIZUR, A., WINTNER, I., DAVIDSON, S., The clinical and psychological effects of pemoline in depressed patients – a controlled study. *Int. Pharmacopsychiatry* **1979**, 14 (3), 127–134.
- ELLIOTT, A. J., RUSSO, J., BERGAM, K., CLAYPOOLE, K., ULDALL, K. K., ROY-BYRNE, P. P., Antidepressant efficacy in HIV-seropositive outpatients with major depressive disorder: an open trial of nefazodone. *J. Clin. Psychiatry* **1999**, 60 (4), 226–231.
- ELLIOTT, A. J., ULDALL, K. K., BERGAM, K., RUSSO, J., CLAYPOOLE, K., ROY-BYRNE, P. P., Randomized, placebo-controlled trial of paroxetine versus imipramine in depressed HIV-positive outpatients. *Am. J. Psychiatry* **1998**, 155 (3), 367–372.
- ELLISON, J. M., STANZIANI, P., SSRI-associated nocturnal bruxism in four patients. *J. Clin. Psychiatry* **1993**, 54 (11), 432–434.
- EL-MALLAKH, R. S., An open study of methylphenidate in bipolar depression. *Bipolar Disord.* **2000**, 2 (1), 56–59.
- ENGBRETSSEN, K. M., HARRIS, C. R., WOOD, J. E., Cardiotoxicity and late onset seizures with citalopram overdose. *J. Emerg. Med.* **2003**, 25 (2), 163–166.
- ENTSUAH, A. R., HUANG, H., THASE, M. E., Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J. Clin. Psychiatry* **2001**, 62 (11), 869–877.
- ENTSUAH, R., CHITRA, R., A benefit–risk analysis of once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. *Psychopharmacol. Bull.* **1997**, 33 (4), 671–676.
- ENTSUAH, R., Venlafaxine vs SSRIs: comparison of somatic symptom resolution. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- ERALP BELLIBAS, S., Ritonavir–fluoxetine interaction. *Antimicrob. Agents Chemother.* **1999**, 43 (7), 1815.
- EVERETT, H. C., The use of bethanechol chloride with tricyclic antidepressants. *Am. J. Psychiatry* **1975**, 132 (11), 1202–1204.
- FABIAN, T. J., AMICO, J. A., KROBOTH, P. D., MULSANT, B. H., COREY, S. E., BEGLEY, A. E., BENSASI, S. G., WEBER, E., DEW, M. A., REYNOLDS, C. F. 3RD, POLLOCK, B. G., Paroxetine-induced hyponatremia in older adults: a 12-week prospective study. *Arch. Intern. Med.* **2004**, 164 (3), 327–332.
- FABRE, L. F., Buspirone in the management of major depression: a placebo-controlled

- comparison. *J. Clin. Psychiatry* **1990**, 51 (Suppl.), 55–61.
- FABRE, L. F., BRODIE, H. K., GARVER, D., ZUNG, W. W., A multicenter evaluation of bupropion versus placebo in hospitalized depressed patients. *J. Clin. Psychiatry* **1983**, 44 (5 Pt 2), 88–94.
- FANN, W. E., LYLE, F. A., HIGGINBOTHAM, W., Nomifensine vs. imipramine in depressed inpatients. *J. Clin. Psychiatry* **1984**, 45 (4 Pt 2), 60–62.
- FARAH, A., Interferon-induced depression treated with citalopram. *J. Clin. Psychiatry* **2002**, 63 (2), 166–167.
- FAULL, C. M., ROOKE, P., BAYLIS, P. H., The effect of a highly specific serotonin agonist on osmoregulated vasopressin secretion in healthy men. *Clin. Endocrinol. (Oxf.)* **1991**, 35 (5), 423–430.
- FAVA, M., Weight gain and antidepressants. *J. Clin. Psychiatry* **2000**, 61 (Suppl. 11), 37–41.
- FAVA, M., ALPERT, J., NIERENBERG, A., LAGOMASINO, I., SONAWALLA, S., TEDLOW, J., WORTHINGTON, J., BAER, L., ROSENBAUM, J. F., Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. *J. Clin. Psychopharmacol.* **2002a**, 22 (4), 379–387.
- FAVA, M., ALPERT, J., NIERENBERG, A. A., GHAEI, N., O'SULLIVAN, R., TEDLOW, J., WORTHINGTON, J., ROSENBAUM, J. F., Fluoxetine treatment of anger attacks: a replication study. *Ann. Clin. Psychiatry* **1996a**, 8 (1), 7–10.
- FAVA, M., AMSTERDAM, J. D., DELTITO, J. A., SALZMAN, C., SCHWALLER, M., DUNNER, D. L., A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. *Ann. Clin. Psychiatry* **1998a**, 10 (4), 145–150.
- FAVA, M., BLESS, E., OTTO, M. W., PAVA, J. A., ROSENBAUM, J. F., Dysfunctional attitudes in major depression. Changes with pharmacotherapy. *J. Nerv. Ment. Dis.* **1994c**, 182 (1), 45–49.
- FAVA, M., BORUS, J. S., ALPERT, J. E., NIERENBERG, A. A., ROSENBAUM, J. F., BOTTIGLIERI, T., Folate, vitamin B12, and homocysteine in major depressive disorder. *Am. J. Psychiatry* **1997b**, 154 (3), 426–428.
- FAVA, M., BOUFFIDES, E., PAVA, J. A., MCCARTHY, M. K., STEINGARD, R. J., ROSENBAUM, J. F., Personality disorder comorbidity with major depression and response to fluoxetine treatment. *Psychother. Psychosom.* **1994b**, 62 (3–4), 160–167.
- FAVA, M., DAVIDSON, K., ALPERT, J. E., NIERENBERG, A. A., WORTHINGTON, J., O'SULLIVAN, R., ROSENBAUM, J. F., Hostility changes following antidepressant treatment: relationship to stress and negative thinking. *J. Psychiatr. Res.* **1996b**, 30 (6), 459–467.
- FAVA, M., DEBATTISTA, C., THASE, M. E., HUGHES, R. J., Modafinil as adjunctive therapy for excessive sleepiness in adults with major depressive disorder, sleepiness, and fatigue. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003c**.
- FAVA, M., DUNNER, D. L., GREIST, J. H., PRESKORN, S. H., TRIVEDI, M. H., ZAJECKA, J., COHEN, M., Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. *J. Clin. Psychiatry* **2001**, 62 (6), 413–420.
- FAVA, M., FARABAUGH, A. H., SICKINGER, A. H., WRIGHT, E., ALPERT, J. E., SONAWALLA, S., NIERENBERG, A. A., WORTHINGTON, J. J. 3RD, Personality disorders and depression. *Psychol. Med.* **2002c**, 32 (6), 1049–1057.
- FAVA, M., HOOG, S. L., JUDGE, R. A., KOPP, J. B., NILSSON, M. E., GONZALES, J. S., Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. *J. Clin. Psychopharmacol.* **2002b**, 22 (2), 137–147.
- FAVA, M., JUDGE, R., HOOG, S. L., NILSSON, M. E., KOKE, S. C., Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J. Clin. Psychiatry* **2000b**, 61 (11), 863–867.
- FAVA, M., LABBATE, L. A., ABRAHAM, M. E., ROSENBAUM, J. F., Hypothyroidism and hyperthyroidism in major depression revisited. *J. Clin. Psychiatry* **1995**, 56 (5), 186–192.
- FAVA, M., MCGRATH, P. J., SHEU, W. P., Reboxetine Study Group. Switching to

- reboxetine: an efficacy and safety study in patients with major depressive disorder unresponsive to fluoxetine. *J. Clin. Psychopharmacol.* **2003a**, 23 (4), 365–369.
- FAVA, M., MULROY, R., ALPERT, J., NIERENBERG, A. A., ROSENBAUM, J. F., Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. *Am. J. Psychiatry* **1997c**, 154 (12), 1760–1762.
- FAVA, M., PAPAOSTAS, G. I., PETERSEN, T., MAHAL, Y., QUITKIN, F., STEWART, J., McGRATH, P., Switching to bupropion in fluoxetine-resistant major depressive disorder. *Ann. Clin. Psychiatry* **2003b**, 15 (1), 17–22.
- FAVA, M., RANKIN, M., Sexual functioning and SSRIs. *J. Clin. Psychiatry* **2002**, 63 (Suppl. 5), 13–16, discussion 23–25.
- FAVA, M., RANKIN, M. A., ALPERT, J. E., NIERENBERG, A. A., WORTHINGTON, J. J., An open trial of oral sildenafil anti-depressant-induced sexual dysfunction. *Psychother. Psychosom.* **1998b**, 67 (6), 328–331.
- FAVA, M., ROSENBAUM, J. F., COHEN, L., REITER, S., MCCARTHY, M., STEINGARD, R., CLANCY, K., High-dose fluoxetine in the treatment of depressed patients not responsive to a standard dose of fluoxetine. *J. Affect Disord.* **1992**, 25 (4), 229–234.
- FAVA, M., ROSENBAUM, J. F., HOOG, S. L., TEPNER, R. G., KOPP, J. B., NILSSON, M. E., Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. *J. Affect Disord.* **2000a**, 59 (2), 119–126.
- FAVA, M., ROSENBAUM, J. F., KOLSKY, A. R., ALPERT, J. E., NIERENBERG, A. A., SPILLMANN, M., MOORE, C., RENSHAW, P., BOTTIGLIERI, T., MOROZ, G., MAGNI, G., Open study of the catechol-O-methyltransferase inhibitor tolcapone in major depressive disorder. *J. Clin. Psychopharmacol.* **1999**, 19 (4), 329–335.
- FAVA, M., ROSENBAUM, J. F., McGRATH, P. J., STEWART, J. W., AMSTERDAM, J. D., QUITKIN, F. M., Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *Am. J. Psychiatry* **1994a**, 151 (9), 1372–1374.
- FAVA, M., ROSENBAUM, J. F., PAVA, J. A., MCCARTHY, M. K., STEINGARD, R. J., BOUFFIDES, E., Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *Am. J. Psychiatry* **1993**, 150 (8), 1158–1163.
- FAVA, M., ROSENBAUM, J. F., Pharmacotherapy and somatic therapies. In: BECKHAM, E. E., LEBER, W. R. (Eds.), *Handbook of Depression*. New York: Guilford Publications, **1995a**, 280–301.
- FAVA, M., TOALSON, P., WOHLREICH, M. M., MALLINCKRODT, C. H., WATKIN, J. G., DETKE, M. J., Does the alleviation of painful somatic symptoms of depression lead to higher remission rates? 55th Institute on Psychiatric Services, Boston, MA, **2003d**.
- FAVA, M., UEBELACKER, L. A., ALPERT, J. E., NIERENBERG, A. A., PAVA, J. A., ROSENBAUM, J. F., Major depressive subtypes and treatment response. *Biol. Psychiatry* **1997a**, 42 (7), 568–576.
- FAVALE, E., AUDENINO, D., COCITO, L., ALBANO, C., The anticonvulsant effect of citalopram as indirect evidence of serotonergic impairment in human epileptogenesis. *Seizure* **2003**, 12 (5), 316–318.
- FAVALE, E., RUBINO, V., MAINARDI, P., LUNARDI, G., ALBANO, C., Anticonvulsant effect of fluoxetine in humans. *Neurology* **1995**, 45 (10), 1926–1927.
- FAWCETT, J., KRAVITZ, H. M., ZAJECKA, J. M., SCHAFF, M. R., CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. *J. Clin. Psychopharmacol.* **1991**, 11 (2), 127–132.
- FAYS, S., TRECHOT, P., SCHMUTZ, J. L., CUNY, J. F., TRUCHETET, F., BARBAUD, A., Bupropion and generalized acute urticaria: eight cases. *Br. J. Dermatol.* **2003**, 148 (1), 177–178.
- FEIGER, A. D., HEISER, J. F., SHRIVASTAVA, R. K., WEISS, K. J., SMITH, W. T., SITSSEN, J. M., GIBERTINI, M., Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder. *J. Clin. Psychiatry* **2003**, 64 (3), 243–249.
- FEIGER, A. D., A double-blind comparison of gepirone extended release, imipramine, and placebo in the treatment of out-patient major depression. *Psychopharmacol. Bull.* **1996**, 32 (4), 659–665.

- FEIGHNER, J. P., Cardiovascular safety in depressed patients: focus on venlafaxine. *J. Clin. Psychiatry* **1995**, *56* (12), 574–579.
- FEIGHNER, J. P., BOYER, W. F., TYLER, D. L., NEBORSKY, R. J., Adverse consequences of fluoxetine–MAOI combination therapy. *J. Clin. Psychiatry* **1990**, *51* (6), 222–225.
- FEIGHNER, J. P., GARDNER, E. A., JOHNSTON, J. A., BATEY, S. R., KHAYRALLAH, M. A., ASCHER, J. A., LINEBERRY, C. G., Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J. Clin. Psychiatry* **1991**, *52* (8), 329–335.
- FEIGHNER, J. P., HERBSTEIN, J., DAMLOUJI, N., Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. *J. Clin. Psychiatry* **1985**, *46* (6), 206–209.
- FERGUSON, J., CUNNINGHAM, L., MERIDETH, C., APTER, J., FEIGHNER, J., IONESCU-PIOGGIA, M., SAMARA, B., JOHNSTON, J. A., ASCHER, J., Bupropion in tricyclic antidepressant nonresponders with unipolar major depressive disorder. *Ann. Clin. Psychiatry* **1994**, *6* (3), 153–160.
- FERGUSON, J. M., MENDELS, J., SCHWART, G. E., Effects of reboxetine on Hamilton Depression Rating Scale factors from randomized, placebo-controlled trials in major depression. *Int. Clin. Psychopharmacol.* **2002**, *17* (2), 45–51.
- FERGUSON, J. M., SHRIVASTAVA, R. K., STAHL, S. M., HARTFORD, J. T., BORIAN, F., IENI, J., McQUADE, R. D., JODY, D., Reemergence of sexual dysfunction in patients with major depressive disorder: double-blind comparison of nefazodone and sertraline. *J. Clin. Psychiatry* **2001**, *62* (1), 24–29.
- FERGUSON, J. M., WESNES, K. A., SCHWARTZ, G. E., Reboxetine versus paroxetine versus placebo: effects on cognitive functioning in depressed patients. *Int. Clin. Psychopharmacol.* **2003**, *18* (1), 9–14.
- FERGUSON, K. L., Imipramine-provoked paradoxical pheochromocytoma crisis: a case of cardiogenic shock. *Am J. Emerg. Med.* **1994**, *12* (2), 190–192.
- FERNANDES, N. F., MARTIN, R. R., SCHENKER, S., Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. *Am. J. Gastroenterol.* **2000**, *95* (2), 532–535.
- FERNANDEZ, F., LEVY, J. K., SAMLEY, H. R., PIROZZOLO, F. J., LACHAR, D., CROWLEY, J., ADAMS, S., ROSS, B., RUIZ, P., Effects of methylphenidate in HIV-related depression: a comparative trial with desipramine. *Int. J. Psychiatry Med.* **1995**, *25* (1), 53–67.
- FERRANDO, S. J., GOLDMAN, J. D., CHARNES, W. E., Selective serotonin reuptake inhibitor treatment of depression in symptomatic HIV infection and AIDS. Improvements in affective and somatic symptoms. *Gen. Hosp. Psychiatry* **1997**, *19* (2), 89–97.
- FERRANDO, S. J., RABKIN, J. G., DE MOORE, G. M., RABKIN, R., Antidepressant treatment of depression in HIV-seropositive women. *J. Clin. Psychiatry* **1999**, *60* (11), 741–746.
- FERRARI, M. D., GOADSBY, P. J., ROON, K. I., LIPTON, R. B., Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* **2002**, *22* (8), 633–658.
- FERRERI, M., COLONNA, L., LEGER, J. M., Efficacy of amineptine in the prevention of relapse in unipolar depression. Efficacy of amineptine in the prevention of relapse in unipolar depression. *Int. Clin. Psychopharmacol.* **1997**, *12* (Suppl. 3), S39–S45.
- FERRERI, M., LAVERGNE, F., BERLIN, I., PAYAN, C., PUECH, A. J., Benefits from mianserin augmentation of fluoxetine in patients with major depression: non-responders to fluoxetine alone. *Acta Psychiatr. Scand.* **2001**, *103* (1), 66–72.
- FERSZT, R., KUHLE, K. P., BODE, L., SEVERUS, E. W., WINZER, B., BERGHOFFER, A., BEELITZ, G., BRODHUN, B., MULLER-OERLINGHAUSEN, B., LUDWIG, H., Amantadine revisited: an open trial of amantadinesulfate treatment in chronically depressed patients with Borna disease virus infection. *Pharmacopsychiatry* **1999**, *32* (4), 142–147.
- FINDLING, R. L., Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents, and adults: a case series. *J. Child Adolesc. Psychopharmacol.* **1996**, *6* (3), 165–175.

- FINGE, T., MALAVIALLE, C., Lambert J. (Fatal form of serotonin syndrome). *Ann. Fr. Anesth. Reanim.* **1997**, 16 (1), 80–81.
- FINKEL, M. S., LAGHRISSE-THODE, F., POLLOCK, B. G., RONG, J., Paroxetine is a novel nitric oxide synthase inhibitor. *Psychopharmacol. Bull.* **1996**, 32 (4), 653–658.
- FINKEL, S. I., RICHTER, E. M., CLARY, C. M., Comparative efficacy and safety of sertraline versus nortriptyline in major depression in patients 70 and older. *Int. Psychogeriatr.* **1999**, 11 (1), 85–99.
- FISCH, M. J., LOEHRER, P. J., KRISTELLER, J., PASSIK, S., JUNG, S. H., SHEN, J., ARQUETTE, M. A., BRAMES, M. J., EINHORN, L. H., Hoosier Oncology Group. Fluoxetine versus placebo in advanced cancer outpatients: a double-blinded trial of the Hoosier Oncology Group. *J. Clin. Oncol.* **2003**, 21 (10), 1937–1943.
- FISCHER, P., TAUSCHER, J., KUFFERLE, B., KASPER, S., Weak antidepressant response after buspirone augmentation of serotonin reuptake inhibitors in refractory severe depression. *Int. Clin. Psychopharmacol.* **1998**, 13 (2), 83.
- FISHER, A., DAVIS, M., CROFT-BAKER, J., PURCELL, P., MCLEAN, A., Citalopram-induced severe hyponatraemia with coma and seizure. Case report with literature and spontaneous reports review. *Adverse Drug React. Toxicol. Rev.* **2002**, 21 (4), 179–187.
- FLEISCHHACKER, W. W., Propanolol for fluoxetine-induced akathisia. *Biol. Psychiatry* **1991**, 30 (5), 531–532.
- FLEISHAKER, J. C., FRANCOM, S. F., HERMAN, B. D., KNUTH, D. W., AZIE, N. E., Lack of effect of reboxetine on cardiac repolarization. *Clin. Pharmacol. Ther.* **2001**, 70 (3), 261–269.
- FLEMENBAUM, A., PAVOR nocturnus: a complication of single daily tricyclic or neuroleptic dosage. *Am. J. Psychiatry* **1976**, 133 (5), 570–572.
- FLINT, A. J., RIFAT, S. L., The effect of sequential antidepressant treatment on geriatric depression. *J. Affect Disord.* **1996**, 36 (3–4), 95–105.
- FLORES, G., PEREZ-PATRIGEON, S., COBOS-AYALA, C., VERGARA, J., Severe symptomatic hyponatremia during citalopram therapy. *BMC Nephrol.* **2004**, 5 (1), 2.
- FOLEY, K. F., COZZI, N. V., Inhibition of transport function and desipramine binding at the human noradrenaline transporter by N-ethylmaleimide and protection by substrate analogs. *Naunyn Schmiedebergs Arch. Pharmacol.* **2002**, 365 (6), 457–461.
- FORD, M. A., ANDERSON, M. L., RINDONE, J. P., JASKAR, D. W., Lack of effect of fluoxetine on the hypoprothrombinemic response of warfarin. *J. Clin. Psychopharmacol.* **1997**, 17 (2), 110–112.
- FOWLER, J. S., VOLKOW, N. D., LOGAN, J., FRANCESCHI, D., WANG, G. J., MACGREGOR, R., SHEA, C., GARZA, V., PAPPAS, N., CARTER, P., NETUSIL, N., BRIDGE, P., LIEDERMAN, D., ELKASHEF, A., ROTROSEN, J., HITZEMANN, R., Evidence that L-deprenyl treatment for one week does not inhibit MAO A or the dopamine transporter in the human brain. *Life Sci.* **2001**, 68 (24), 2759–2768.
- FOWLER, J. S., VOLKOW, N. D., LOGAN, J., WANG, G. J., MACGREGOR, R. R., SCHYLER, D., WOLF, A. P., PAPPAS, N., ALEXOFF, D., SHEA, C., et al. Slow recovery of human brain MAO B after L-deprenyl (Selegiline) withdrawal. *Synapse* **1994**, 18 (2), 86–93.
- FOWLIE, S., BURTON, J., Hyperprolactinaemia and nonpuerperal lactation associated with clomipramine. *Scott. Med. J.* **1987**, 32 (2), 52.
- FREEMAN, A. M. 3RD, WESTPHAL, J. R., NORRIS, G. T., ROGGERO, B. A., WEBB, P. B., FREEMAN, K. L., RUSH, J. A., HEARNE, E. M. 3RD, EVONIUK, G., Efficacy of ondansetron in the treatment of generalized anxiety disorder. *Depress. Anxiety* **1997**, 5 (3), 140–141.
- FREY, J., DARBONNE, C., Fluoxetine suppresses human cataplexy: a pilot study. *Neurology* **1994**, 44 (4), 707–709.
- FRIEDMAN, E. H., Fluoxetine-induced akathisia in male OCD patients. *J. Clin. Psychiatry* **1990**, 51 (5), 212.
- FRYER, J. D., LUKAS, R. J., Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine. *J. Pharmacol. Exp. Ther.* **1999**, 288 (1), 88–92.

- FUGH-BERMAN, A., COTT, J. M., Dietary supplements and natural products as psychotherapeutic agents. *Psychosom. Med.* **1999**, *61* (5), 712–728.
- FUKUDA, T., NISHIDA, Y., IMAOKA, S., HIROI, T., NAOHARA, M., FUNAE, Y., AZUMA, J., The decreased *in vivo* clearance of CYP2D6 substrates by CYP2D6*10 might be caused not only by the low-expression but also by low affinity of CYP2D6. *Arch. Biochem. Biophys.* **2000b**, *380* (2), 303–308.
- FUKUDA, T., NISHIDA, Y., ZHOU, Q., YAMAMOTO, I., KONDO, S., AZUMA, J., The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. *Eur. J. Clin. Pharmacol.* **2000a**, *56* (2), 175–180.
- GADDE, K. M., PARKER, C. B., MANER, L. G., WAGNER HR 2ND, LOGUE, E. J., DREZNER, M. K., KRISHNAN, K. R., Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. *Obes. Res.* **2001**, *9* (9), 544–551.
- GALEOTTI, N., GHELARDINI, C., BARTOLINI, A., Involvement of potassium channels in amitriptyline and clomipramine analgesia. *Neuropharmacology* **2001**, *40* (1), 75–84.
- GALEOTTI, N., GHELARDINI, C., CAPACCIOLI, S., QUATTRONE, A., NICOLIN, A., BARTOLINI, A., Blockade of clomipramine and amitriptyline analgesia by an antisense oligonucleotide to mKv1.1, a mouse Shaker-like K⁺ channel. *Eur. J. Pharmacol.* **1997**, *330* (1), 15–25.
- GALLETLY, C., CLARK, A., TOMLINSON, L., Evaluation of dexfenfluramine in a weight loss program for obese infertile women. *Int. J. Eat Disord.* **1996**, *19* (2), 209–212.
- GARATTINI, S., MENNINI, T., Pharmacology of amineptine: synthesis and updating. *Clin. Neuropharmacol.* **1989**, *12* (Suppl. 2), S13–S18.
- GARATTINI, S., Pharmacology of amineptine, an antidepressant agent acting on the dopaminergic system: a review. *Int. Clin. Psychopharmacol.* **1997**, *12* (Suppl. 3), S15–S19.
- GARBER, A., GREGORY, R. J., Benzotropine in the treatment of venlafaxine-induced sweating. *J. Clin. Psychiatry* **1997**, *58* (4), 176–177.
- GARLAND, E. J., BAERG, E. A., Amotivational syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. *J. Child Adolesc. Psychopharmacol.* **2001**, *11* (2), 181–186.
- GARNER, E. M., KELLY, M. W., THOMPSON, D. F., Tricyclic antidepressant withdrawal syndrome. *Ann. Pharmacother.* **1993**, *27* (9), 1068–1072.
- GEHLERT, D. R., SCHÖBER, D. A., HEMRICK-LUECKE, S. K., KRUSHINSKI, J., HOWBERT, J. J., ROBERTSON, D. W., FULLER, R. W., WONG, D. T., Novel halogenated analogs of tomoxetine that are potent and selective inhibitors of norepinephrine uptake in brain. *Neurochem. Int.* **1995**, *26* (1), 47–52.
- GELENBERG, A. J., MCGAHUEY, C., LAUKES, C., OKAYLI, G., MORENO, F., ZENTNER, L., DELGADO, P., Mirtazapine substitution in SSRI-induced sexual dysfunction. *J. Clin. Psychiatry* **2000**, *61* (5), 356–360.
- GELENBERG, A. J., WOJCIK, J. D., FALK, W. E., BALDESSARINI, R. J., ZEISEL, S. H., SCHOENFELD, D., MOK, G. S., Tyrosine for depression: a double-blind trial. *J. Affect Disord.* **1990**, *19* (2), 125–132.
- GELENBERG, A. J., WOJCIK, J. D., GROWDON, J. H., et al. Tyrosine for the treatment of depression. *Am. J. Psychiatry* **1980**, *137*, 622–623.
- GEORGE, M. S., TRIMBLE, M. R., Dystonic reaction associated with fluvoxamine. *J. Clin. Psychopharmacol.* **1993**, *13* (3), 220–221.
- GEORGE, T. P., GODLESKI, L. S., Possible serotonin syndrome with trazodone addition to fluoxetine. *Biol. Psychiatry* **1996**, *39* (5), 384–385.
- GEORGOTAS, A., FRIEDMAN, E., MCCARTHY, M., MANN, J., KRAKOWSKI, M., SIEGEL, R., FERRIS, S., Resistant geriatric depressions and therapeutic response to monoamine oxidase inhibitors. *Biol. Psychiatry* **1983**, *18* (2), 195–205.
- GEORGOTAS, A., MCCUE, R. E., FRIEDMAN, E., COOPER, T. B., Electrocardiographic effects of nortriptyline, phenelzine, and placebo under optimal treatment conditions. *Am. J. Psychiatry* **1987**, *144* (6), 798–801.
- GERBER, P. E., LYND, L. D., Selective serotonin-reuptake inhibitor-induced movement disorders. *Ann. Pharmacother.* **1998**, *32* (6), 692–698.

- GERETSEGGER, C., BONDY, B., AICHHORN, W., KEGLEVIC, M., STUPPAECK, C., Pindolol augmentation of paroxetine: a double-blind, placebo controlled trial. *Eur. Neuropsychopharmacol.* **2002**, *12* (3), S196.
- GERLACH, M., DOUBLE, K., ARZBERGER, T., LEBLHUBER, F., TATSCHNER, T., RIEDERER, P., Dopamine receptor agonists in current clinical use: comparative dopamine receptor binding profiles defined in the human striatum. *J. Neural Transm.* **2003**, *110* (10), 1119–1127.
- GERSHON, S., HOMBERG, G., MATTSON, E., et al. Imipramine hydrochloride: its effects on clinical, autonomic, and psychological functions. *Arch. Gen. Psychiatry* **1962**, *6*, 96–101.
- GERSTENBERG, G., AOSHIMA, T., FUKASAWA, T., YOSHIDA, K., TAKAHASHI, H., HIGUCHI, H., MURATA, Y., SHIMOYAMA, R., OHKUBO, T., SHIMIZU, T., OTANI, K., Relationship between clinical effects of fluvoxamine and the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. *Psychopharmacology (Berl.)* **2003a**, *167* (4), 443–448.
- GERSTENBERG, G., AOSHIMA, T., FUKASAWA, T., YOSHIDA, K., TAKAHASHI, H., HIGUCHI, H., MURATA, Y., SHIMOYAMA, R., OHKUBO, T., SHIMIZU, T., OTANI, K., Effects of the CYP 2D6 genotype and cigarette smoking on the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. *Ther. Drug Monit.* **2003b**, *25* (4), 463–468.
- GEX-FABRY, M., BALANT-GORGIA, A. E., BALANT, L. P., RUDAZ, S., VEUTHEY, J., VERTSCHY, G., Time course of clinical response to venlafaxine: relevance to plasma level and chirality. *Pharmacokinet. Dispos.* **2004** (in press).
- GIERS, G., SALAMA, A., MUELLER-ECKHARDT, C., Follow-up study on 24 patients with nomifensine-induced immune haemolytic anaemia. *Transfus. Med.* **1991**, *1* (2), 115–119.
- GILL, H. S., DEVANE, C. L., RISCH, S. C., Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. *J. Clin. Psychopharmacol.* **1997**, *17* (5), 377–389.
- GIRAULT, C., RICHARD, J. C., CHEVRON, V., GOULLE, J. P., DROY, J. M., BONMARCHAND, G., LEROY, J., Syndrome of inappropriate secretion of antidiuretic hormone in two elderly women with elevated serum fluoxetine. *J. Toxicol. Clin. Toxicol.* **1997**, *35* (1), 93–95.
- GIRISHCHANDRA, B. G., JOHNSON, L., CRESP, R. M., ORR, K. G., Mirtazapine-induced akathisia. *Med. J. Aust.* **2002**, *176* (5), 242.
- GITLIN, M. J., Treatment of sexual side effects with dopaminergic agents. *J. Clin. Psychiatry* **1995**, *56* (3), 124.
- GITLIN, M. J., Venlafaxine, monoamine oxidase inhibitors, and the serotonin syndrome. *J. Clin. Psychopharmacol.* **1997**, *17* (1), 66–67.
- GITLIN, M. J., SURI, R., ALTSCHULER, L., ZUCKERBROW-MILLER, J., FAIRBANKS, L., Bupropion-sustained release as a treatment for SSRI-induced sexual side effects. *J. Sex Marital Ther.* **2002**, *28* (2), 131–138.
- GLASSMAN, A. H., O'CONNOR, C. M., CALIFF, R. M., SWEDBERG, K., SCHWARTZ, P., BIGGER, J. T. JR., KRISHNAN, K. R., VAN ZYL, L. T., SWENSON, J. R., FINKEL, M. S., LANDAU, C., SHAPIRO, P. A., PEPINE, C. J., MARDEKIAN, J., HARRISON, W. M., BARTON, D., MCLIVOR, M., Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* **2002**, *288* (6), 701–709.
- GLEASON, O. C., YATES, W. R., ISBELL, M. D., PHILIPSEN, M. A., An open-label trial of citalopram for major depression in patients with hepatitis C. *J. Clin. Psychiatry* **2002**, *63* (3), 194–198.
- GLICK, S. D., HASKEW, R. E., MAISONNEUVE, I. M., CARLSON, J. N., JERUSSI, T. P., Enantioselective behavioral effects of sibutramine metabolites. *Eur. J. Pharmacol.* **2000**, *397* (1), 93–102.
- GLOD, C. A., LYNCH, A., FLYNN, E., BERKOWITZ, C., BALDESSARINI, R. J., Open trial of bupropion SR in adolescent major depression. *J. Child Adolesc. Psychiatr. Nurs.* **2003**, *16* (3), 123–130.
- GLOWINSKI, J., AXELROD, J., Inhibition of uptake of tritiated-noradrenaline in the

- intact rat brain by imipramine and structurally related compounds. *Nature* **1964**, *204*, 1318–1319.
- GOBERT, A., CUSSAC, D., LEJEUNE, F., NEWMAN-TANCREDI, A., AUDINOT, V., BOUTIN, J. A., CARR, C., MILLIGAN, G., RIVET, J. M., BROCCO, M., DEKEYNE, A., LACOSTE, J. M., CORDI, A., MILLAN, M. J., The novel antidepressant, S35966, is a mixed serotonin and noradrenaline reuptake inhibitor and an antagonist at α_2 -adrenoceptors. *Eur. Neuropsychopharmacol.* **2002**, *12* (3), S248.
- GOBERT, A., MILLAN, M. J., Modulation of dialysate levels of dopamine, noradrenaline, and serotonin (5-HT) in the frontal cortex of freely-moving rats by (–)-pindolol alone and in association with 5-HT reuptake inhibitors: comparative roles of beta-adrenergic, 5-HT_{1A}, and 5-HT_{1B} receptors. *Neuropsychopharmacology* **1999**, *21* (2), 268–284.
- GOBERT, A., RIVET, J. M., CISTARELLI, L., MELON, C., MILLAN, M. J., Buspirone modulates basal and fluoxetine-stimulated dialysate levels of dopamine, noradrenaline and serotonin in the frontal cortex of freely moving rats: activation of serotonin_{1A} receptors and blockade of α_2 -adrenergic receptors underlie its actions. *Neuroscience* **1999**, *93* (4), 1251–1262.
- GOBERT, A., RIVET, J. M., CISTARELLI, J. M., MILLAN, M. J., Buspirone enhances duloxetine- and fluoxetine-induced increases in dialysate levels of dopamine and noradrenaline, but not serotonin, in the frontal cortex of freely moving rats. *J. Neurochem.* **1997**, *68* (3), 1326–1329.
- GOETZ, C. G., TANNER, C. M., KLAUANS, H. L., Bupropion in Parkinson's disease. *Neurology* **1984**, *34* (8), 1092–1094.
- GOKCEL, A., GUMURDULU, Y., KARAKOSE, H., KARADEMIR, B. M., ANARAT, R., Effects of sibutramine in non-dieting obese women. *J. Endocrinol. Invest.* **2002**, *25* (2), 101–105.
- GOLDBERG, I. K., L-tyrosine in depression. *Lancet* **1980**, *ii*, 364–365.
- GOLDBERG, R. J., HUK, M., Serotonin syndrome from trazodone and buspirone. *Psychosomatics* **1992**, *33* (2), 235–236.
- GOLDEN, R. N., DE VANE, C. L., LAIZURE, S. C., RUDORFER, M. V., SHERER, M. A., POTTER, W. Z., Bupropion in depression II, The role of metabolites in clinical outcome. *Arch. Gen. Psychiatry* **1988**, *45* (2), 145–149.
- GOLDEN, R. N., NEMEROFF, C. B., MCSORLEY, P., PITTS, C. D., DUBE, E. M., Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J. Clin. Psychiatry* **2002**, *63* (7), 577–584.
- GOLDSTEIN, B. J., BRAUZER, B., KENTSMITH, D., ROSENTHAL, S., CHARALAMPOUS, K. D., Double-blind placebo-controlled multicenter evaluation of the efficacy and safety of nomifensine in depressed outpatients. *J. Clin. Psychiatry* **1984**, *45* (4 Pt 2), 52–55.
- GOLDSTEIN, D. J., LU, Y., DETKE, M. J., HUDSON, J., IYENGAR, S., DEMITRACK, M. A., Effects of duloxetine on painful physical symptoms associated with depression. *Psychosomatics* **2004**, *45* (1), 17–28.
- GOLDSTEIN, D. J., MALLINCKRODT, C., LU, Y., DEMITRACK, M. A., Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J. Clin. Psychiatry* **2002**, *63* (3), 225–231.
- GOLDSTEIN, L., BARKER, M., SEGALL, F., ASIHENE, R., BALSER, S., LAUTENBACH, D., MCCOY, M., Seizure and transient SIADH associated with sertraline. *Am. J. Psychiatry* **1996**, *153* (5), 732.
- GOLDSTEIN, S. E., BIRNBOM, F., LALIBERTE, R., Nomifensine in the treatment of depressed geriatric patients. *J. Clin. Psychiatry* **1982**, *43* (7), 287–289.
- GOMEZ GOMEZ, J. M., TEIXIDO PERRAMON, C., Combined treatment with venlafaxine and tricyclic antidepressants in depressed patients who had partial response to clomipramine or imipramine: initial findings. *J. Clin. Psychiatry* **2000**, *61* (4), 285–289.
- GOMEZ-GIL, E., SALMERON, J. M., MAS, A., Phenelzine-induced fulminant hepatic failure. *Ann. Intern. Med.* **1996**, *124* (7), 692–693.
- GONUL, A. S., AKDENIZ, F., DONAT, O., VAHIP, S., Selective serotonin reuptake inhibitors combined with venlafaxine in depressed patients who had partial response to venlafaxine: four cases. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2003**, *27* (5), 889–891.

- GONZALEZ, E., MINGUEZ, L., SANGUINO, R. M., Galactorrhea after paroxetine treatment. *Pharmacopsychiatry* **2000**, 33 (3), 118.
- GONZALEZ-PINTO, A., GUTIERREZ, M., GONZALEZ, N., ELIZAGARATE, E., PEREZ DE HEREDIA, J. L., MICO, J. A., Efficacy and safety of venlafaxine-ECT combination in treatment-resistant depression. *J. Neuro-psychiatry Clin. Neurosci.* **2002**, 14 (2), 206–209.
- GOODNICK, P. J., SANDOVAL, R., BRICKMAN, A., KLIMAS, N. G., Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. *Biol. Psychiatry* **1992**, 32 (9), 834–838.
- GOODNICK, P. J., Use of antidepressants in treatment of comorbid diabetes mellitus and depression as well as in diabetic neuropathy. *Ann. Clin. Psychiatry* **2001**, 13 (1), 31–41.
- GORDON, C., WHALE, R., COWEN, P. J., Sertraline treatment does not increase plasma prolactin levels in healthy subjects. *Psychopharmacology (Berl.)* **1998**, 137 (2), 201–202.
- GORDON, G. H., MICHIELS, T. M., MAHUTTE, C. K., LIGHT, R. W., Effect of desipramine on control of ventilation and depression scores in patients with severe chronic obstructive pulmonary disease. *Psychiatry Res.* **1985**, 15 (1), 25–32.
- GRANIER, F., GIRARD, M., SCHMITT, L., BOSCREDON, J., OULES, J., ESCANDE, M., Depression and anxiety: mianserin and nomifensine compared in a double-blind multicentre trial. *Acta Psychiatr. Scand. (Suppl.)* **1985**, 320, 67–74.
- GRASSI, B., GAMBINI, O., GARGHENTINI, G., LAZZARIN, A., SCARONE, S., Efficacy of paroxetine for the treatment of depression in the context of HIV infection. *Pharmacopsychiatry* **1997**, 30 (2), 70–71.
- GRAUDINS, A., STEARMAN, A., CHAN, B., Treatment of the serotonin syndrome with cyproheptadine. *J. Emerg. Med.* **1998**, 16 (4), 615–619.
- GRAUDINS, A., VOSSLER, C., WANG, R., Fluoxetine-induced cardiotoxicity with response to bicarbonate therapy. *Am J. Emerg. Med.* **1997**, 15 (5), 501–503.
- GRAY, D. S., FUJIYOKA, K., DEWINE, W., BRAY, G. A., Fluoxetine treatment of the obese diabetic. *Int. J. Obes.* **1992**, 16, 193–198.
- GREEN, T. R., Bupropion for SSRI-induced fatigue. *J. Clin. Psychiatry* **1997**, 58 (4), 174.
- GREENBERG, H. E., SCHARF, S. M., GREEN, H., Nortriptyline-induced depression of ventilatory control in a patient with chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* **1993**, 147 (5), 1303–1305.
- GREENBLATT, D. J., VON MOLTKE, L. L., HARMATZ, J. S., SHADER, R. I., Human cytochromes and some newer antidepressants: kinetics, metabolism, and drug interactions. *J. Clin. Psychopharmacol.* **1999**, 19 (5 Suppl. 1), 23S–35S.
- GREENO, C. G., WING, R. R., A double-blind placebo controlled trial of the effect of fluoxetine on daily intake in overweight women with and without binge-eating disorders. *Am. J. Clin. Nutr.* **1996**, 64, 267–273.
- GRIFFIN, N., DRAPER, R. J., WEBB, M. G., Addiction to tranlycypromine. *BMJ (Clin. Res. Ed.)* **1981**, 283 (6287), 346.
- GRIFFITH, J. D., CARRANZA, J., GRIFFITH, C., MILLER, L. L., Bupropion: clinical assay for amphetamine-like abuse potential. *J. Clin. Psychiatry* **1983**, 44 (5 Pt 2), 206–208.
- GROF, P., JOFFE, R., KENNEDY, S., PERSAD, E., SYROTIUK, J., BRADFORD, D., An open study of oral flesinoxan, a 5-HT_{1A} receptor agonist, in treatment-resistant depression. *Int. Clin. Psychopharmacol.* **1993**, 8 (3), 167–172.
- GROSS, R., DANNON, P. N., LEPKIFKER, E., ZOHAR, J., KOTLER, M., Generalized seizures caused by fluoxetine overdose. *Am J. Emerg. Med.* **1998**, 16 (3), 328–329.
- GRUBB, B. P., SAMOIL, D., KOSINSKI, D., TEMESY-ARMOS, P., AKPUNONU, B., The use of serotonin reuptake inhibitors for the treatment of recurrent syncope due to carotid sinus hypersensitivity unresponsive to dual chamber cardiac pacing. *Pacing Clin. Electrophysiol.* **1994**, 17 (8), 1434–1436.
- GRUNNET, M., JESPERSEN, T., ANGELO, K., FROKJAER-JENSEN, C., KLAERKE, D. A., OLESEN, S. P., JENSEN, B. S., Pharmacological modulation of SK3 channels. *Neuropharmacology* **2001**, 40 (7), 879–887.
- GUELF, J. D., ANSSEAU, M., CORRUBLE, E., SAMUELIAN, J. C., TONELLI, I., TOURNOUX,

- A., PLETAN, Y., A double-blind comparison of the efficacy and safety of milnacipran and fluoxetine in depressed inpatients. *Int. Clin. Psychopharmacol.* **1998**, *13* (3), 121–128.
- GUELF, J. D., ANSSEAU, M., TIMMERMAN, L., KORSGAARD, S., Mirtazapine–Venlafaxine Study Group. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. *J. Clin. Psychopharmacol.* **2001**, *21* (4), 425–431.
- GUPTA, A. K., SARAVAY, S. M., Venlafaxine-induced hyponatremia. *J. Clin. Psychopharmacol.* **1997**, *17* (3), 223–225.
- GUPTA, S., MASAND, P., ASHTON, A. K., BERRY, S. L., Phenelzine-induced sexual dysfunction treated with sildenafil. *J. Sex Marital Ther.* **1999**, *25* (2), 131–135.
- GWIRTSMAN, H. E., SZUBA, M. P., TOREN, L., FEIST, M., The antidepressant response to tricyclics in major depressives is accelerated with adjunctive use of methylphenidate. *Psychopharmacol. Bull.* **1994**, *30* (2), 157–164.
- HADDJERI, N., BLIER, P., DE MONTIGNY, C., Noradrenergic modulation of central serotonergic neurotransmission: acute and long-term actions of mirtazapine. *Int. Clin. Psychopharmacol.* **1995**, *10* (Suppl. 4), 11–17.
- HAFFMANS, P. M., VOS, M. S., The effects of trazodone on sleep disturbances induced by brofaromine. *Eur. Psychiatry* **1999**, *14* (3), 167–171.
- HAJDU, P., ULENS, C., PANYI, G., TYTGAT, J., Drug- and mutagenesis-induced changes in the selectivity filter of a cardiac two-pore background K⁺ channel. *Cardiovasc. Res.* **2003**, *58* (1), 46–54.
- HALL, M. J., Breast tenderness and enlargement induced by sertraline. *Am. J. Psychiatry* **1994**, *151* (9), 1395–1396.
- HALLE, M. T., DILSAVER, S. C., Tranylcypromine withdrawal phenomena. *J. Psychiatry Neurosci.* **1993**, *18* (1), 49–50.
- HANNA, G. L., MCCracken, J. T., CANTWELL, D. P., Prolactin in childhood obsessive-compulsive disorder: clinical correlates and response to clomipramine. *J. Am. Acad. Child Adolesc. Psychiatry* **1991**, *30* (2), 173–178.
- HANSEN, L., Fluoxetine dose-increment related akathisia in depression: implications for clinical care, recognition and management of selective serotonin reuptake inhibitor-induced akathisia. *J. Psychopharmacol.* **2003**, *17* (4), 451–452.
- HANZEL, D. A., PROIA, N. G., HUDGEL, D. W., Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest* **1991**, *100* (2), 416–421.
- HAREL, Z., BIRO, F. M., TEDFORD, W. L., Effects of long term treatment with sertraline (Zoloft) simulating hypothyroidism in an adolescent. *J. Adolesc. Health* **1995**, *16* (3), 232–234.
- HARGRAVE, R., MARTINEZ, D., BERNSTEIN, A. J., Fluoxetine-induced seizures. *Psychosomatics* **1992**, *33* (2), 236–239.
- HARIA, M., FITTON, A., MCTAVISH, D., Trazodone. A review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. *Drugs Aging* **1994**, *4* (4), 331–355.
- HARRIGAN, R. A., BRADY, W. J., ECG abnormalities in tricyclic antidepressant ingestion. *Am J. Emerg. Med.* **1999**, *17* (4), 387–393.
- HARRISON, W., STEWART, J., LOVELACE, R., QUITKIN, F., Case report of carpal tunnel syndrome associated with tranylcypromine. *Am. J. Psychiatry* **1983**, *140* (9), 1229–1230.
- HARTTER, S., WANG, X., WEIGMANN, H., FRIEDBERG, T., ARAND, M., OESCH, F., HIEMKE, C., Differential effects of fluvoxamine and other antidepressants on the biotransformation of melatonin. *J. Clin. Psychopharmacol.* **2001**, *21* (2), 167–174.
- HARVEY, A. T., RUDOLPH, R. L., PRESKORN, S. H., Evidence of the dual mechanisms of action of venlafaxine. *Arch. Gen. Psychiatry* **2000**, *57* (5), 503–509.
- HASAN, F., MCCRODden, J. M., KENNEDY, N. P., TIPTON, K. F., The involvement of intestinal monoamine oxidase in the transport and metabolism of tyramine. *J. Neural Transm. Suppl.* **1988**, *26*, 1–9.
- HAUSER, P., KHOSLA, J., AURORA, H., LAURIN, J., KLING, M. A., HILL, J., GULATI, M., THORNTON, A. J., SCHULTZ, R. L., VALENTINE, A. D., MEYERS, C. A., HOWELL, C. D., A prospective study of the incidence and open-label treatment of interferon-induced major depressive

- disorder in patients with hepatitis C. *Mol. Psychiatry* **2002**, *7* (9), 942–947.
- HAUSER, P., SOLER, R., REED, S., KANE, R., GULATI, M., KHOSLA, J., KLING, M. A., VALENTINE, A. D., MEYERS, C. A., Prophylactic treatment of depression induced by interferon-alpha. *Psychosomatics* **2000**, *41* (5), 439–441.
- HAUSER, R. A., ZESIEWICZ, T. A., Sertraline for the treatment of depression in Parkinson's disease. *Mov. Disord.* **1997**, *12* (5), 756–759.
- HAWLEY, C. J., SIVAKUMARAN, T., OCHOKI, M., BEVAN, J., Coadministration therapy with reboxetine and serotonin specific re-uptake inhibitors in twenty-four patients with major depression. *Eur. Neuropsychopharmacol.* **2000**, *10* (3), S231.
- HAYASHI, Y., OHYAGI, Y., INOUE, I., ARAKAWA, K., TANIWAKI, T., NAKAGAWA, M., KUWABARA, Y., YAMADA, T., Kira J. (A case of amoxapine-induced tardive dystonia successfully treated with a low dose anticholinergic agent). *Rinsho Shinkeigaku* **2000**, *40* (4), 367–371.
- HEAL, D. J., ASPLEY, S., PROW, M. R., JACKSON, H. C., MARTIN, K. F., CHEETHAM, S. C., Sibutramine: a novel anti-obesity drug. A review of the pharmacological evidence to differentiate it from d-amphetamine and d-fenfluramine. *Int. J. Obes. Relat. Metab. Disord.* **1998**, *22* (Suppl. 1), S18–S28, discussion S29.
- HEISLER, M. A., GUIDRY, J. R., ARNECKE, B., Serotonin syndrome induced by administration of venlafaxine and phenelzine. *Ann. Pharmacother.* **1996**, *30* (1), 84.
- HEMERYCK, A., BELPAIRE, F. M., Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug–drug interactions: an update. *Curr. Drug Metab.* **2002**, *3* (1), 13–37.
- HEMMETER, U., ANNEN, B., BISCHOF, R., BRUDERLIN, U., HATZINGER, M., ROSE, U., HOLTSBOER-TRACHSLER, E., Polysomnographic effects of adjuvant ginkgo biloba therapy in patients with major depression medicated with trimipramine. *Pharmacopsychiatry* **2001**, *34* (2), 50–59.
- HEMRICK-LUECKE, S. K., SNODDY, H. D., FULLER, R. W., Evaluation of nefazodone as a serotonin uptake inhibitor and a serotonin antagonist *in vivo*. *Life Sci.* **1994**, *55* (7), 479–483.
- HENRY, J. A., ALEXANDER, C. A., SENER, E. K., Relative mortality from overdose of antidepressants. *BMJ* **1995**, *310* (6974), 221–224.
- HENRY, M. E., MOORE, C. M., KAUFMAN, M. J., MICHELSON, D., SCHMIDT, M. E., STODDARD, E., VUCKEVIC, A. J., BERREIRA, P. J., COHEN, B. M., RENSHAW, P. F., Brain kinetics of paroxetine and fluoxetine on the third day of placebo substitution: a fluorine MRS study. *Am. J. Psychiatry* **2000**, *157* (9), 1506–1508.
- HERGOVICH, N., AIGNER, M., EICHLER, H. G., ENTLICHER, J., DRUCKER, C., JILMA, B., Paroxetine decreases platelet serotonin storage and platelet function in human beings. *Clin. Pharmacol. Ther.* **2000**, *68* (4), 435–442.
- HERNANDEZ, J. L., RAMOS, F. J., INFANTE, J., REBOLLO, M., GONZALEZ-MACIAS, J., Severe serotonin syndrome induced by mirtazapine monotherapy. *Ann. Pharmacother.* **2002**, *36* (4), 641–643.
- HERTZMAN, P. A., BLEVINS, W. L., MAYER, J., GREENFIELD, B., TING, M., GLEICH, G. J., Association of the eosinophilia–myalgia syndrome with the ingestion of tryptophan. *N. Engl. J. Med.* **1990**, *322* (13), 869–873.
- HESSE, L. M., VENKATAKRISHNAN, K., COURT, M. H., VON MOLTKE, L. L., DUAN, S. X., SHADER, R. I., GREENBLATT, D. J., CYP2B6 mediates the *in vitro* hydroxylation of bupropion: potential drug interactions with other antidepressants. *Drug Metab. Dispos.* **2000**, *28* (10), 1176–1183.
- HEWER, W., ROST, W., GATTAZ, W. F., Cardiovascular effects of fluvoxamine and maprotiline in depressed patients. *Eur. Arch. Psychiatry Clin. Neurosci.* **1995**, *246* (1), 1–6.
- HEWLETT, W. A., SCHMID, S. P., SALOMON, R. M., Pilot trial of ondansetron in the treatment of 8 patients with obsessive–compulsive disorder. *J. Clin. Psychiatry* **2003**, *64* (9), 1025–1030.
- HICKIE, I. B., WILSON, A. J., WRIGHT, J. M., BENNETT, B. K., WAKEFIELD, D., LLOYD, A. R., A randomized, double-blind placebo-controlled trial of moclobemide in patients with chronic fatigue syndrome. *J. Clin. Psychiatry* **2000**, *61* (9), 643–648.

- HILTON, S. E., MARADIT, H., MOLLER, H. J., Serotonin syndrome and drug combinations: focus on MAOI and RIMA. *Eur. Arch. Psychiatry Clin. Neurosci.* **1997**, *247* (3), 113–119.
- HIMMELHOCH, J. M., SCHECHTMAN, K., AUCHENBACH, R., The role of trazodone in the treatment of depressed cardiac patients. *Psychopathology* **1984**, *17* (Suppl. 2), 51–63.
- HINZE-SELCH, D., SCHULD, A., KRAUS, T., KUHN, M., UHR, M., HAACK, M., POLLMACHER, T., Effects of antidepressants on weight and on the plasma levels of leptin, TNF- α and soluble TNF receptors: A longitudinal study in patients treated with amitriptyline or paroxetine. *Neuropsychopharmacology* **2000**, *23* (1), 13–19.
- HIROSE, S., ASHBY, C. R. JR., An open pilot study combining risperidone and a selective serotonin reuptake inhibitor as initial antidepressant therapy. *J. Clin. Psychiatry* **2002**, *63* (8), 733–736.
- HIRSCHFELD, R. M., RUSSELL, J. M., DELGADO, P. L., FAWCETT, J., FRIEDMAN, R. A., HARRISON, W. M., KORAN, L. M., MILLER, I. W., THASE, M. E., HOWLAND, R. H., CONNOLLY, M. A., MICELI, R. J., Predictors of response to acute treatment of chronic and double depression with sertraline or imipramine. *J. Clin. Psychiatry* **1998**, *59* (12), 669–675.
- HODGMAN, M. J., MARTIN, T. G., KRENZELOK, E. P., Serotonin syndrome due to venlafaxine and maintenance tranylcypromine therapy. *Hum. Exp. Toxicol.* **1997**, *16* (1), 14–17.
- HOEHN-SARIC, R., HARRIS, G. J., PEARLSON, G. D., COX, C. S., MACHLIN, S. R., CAMARGO, E. E., A fluoxetine-induced frontal lobe syndrome in an obsessive compulsive patient. *J. Clin. Psychiatry* **1991**, *52* (3), 131–133.
- HOEHN-SARIC, R., LIPSEY, J. R., MCLEOD, D. R., Apathy and indifference in patients on fluvoxamine and fluoxetine. *J. Clin. Psychopharmacol.* **1990**, *10* (5), 343–345.
- HOENCAMP, E., HAFFMANS, P. M., DIJKEN, W. A., HOOGDUIN, C. A., NOLEN, W. A., VAN DYCK, R., Brofaromine versus lithium addition to maprotiline. A double-blind study in maprotiline refractory depressed outpatients. *J. Affect Disord.* **1994**, *30* (3), 219–227.
- HOJER, J., PERSONNE, M., SKAGIUS, A. S., Hansson O. (Serotonin syndrome – several cases of this often overlooked diagnosis). *Tidsskr. Nor. Lægeforen* **2002**, *122* (17), 1660–1663.
- HOLLAND, J. C., ROMANO, S. J., HEILIGENSTEIN, J. H., TEPNER, R. G., WILSON, M. G., A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer. *Psychooncology* **1998**, *7* (4), 291–300.
- HOLLANDER, E., MCCARLEY, A., Yohimbine treatment of sexual side effects induced by serotonin reuptake blockers. *J. Clin. Psychiatry* **1992**, *53* (6), 207–209.
- HONG, C. J., HU, W. H., CHEN, C. C., HSIAO, C. C., TSAI, S. J., RUWE, F. J., A double-blind, randomized, group-comparative study of the tolerability and efficacy of 6 weeks' treatment with mirtazapine or fluoxetine in depressed Chinese patients. *J. Clin. Psychiatry* **2003**, *64* (8), 921–926.
- HORNIG-ROHAN, M., AMSTERDAM, J. D., Venlafaxine versus stimulant therapy in patients with dual diagnosis ADD and depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, *26* (3), 585–589.
- HOVORKA, J., HERMAN, E., NEMCOVA, I. I., Treatment of interictal depression with citalopram in patients with epilepsy. *Epilepsy Behav.* **2000**, *1* (6), 444–447.
- HUANG, C. C., Persistent tardive dyskinesia associated with amoxapine therapy. *Am. J. Psychiatry* **1986**, *143* (8), 1069–1070.
- HUGHES, J. R., STEAD, L. F., LANCASTER, T., Antidepressants for smoking cessation. *Cochrane Database Syst. Rev.* **2003**, (2), CD000031.
- HULL, M., KOTTLORS, M., BRAUNE, S., Prolonged coma caused by low sodium and hypo-osmolality during treatment with citalopram. *J. Clin. Psychopharmacol.* **2002**, *22* (3), 337–338.
- HUMPHRIES, J. E., WHEBY, M. S., VANDENBERG, S. R., Fluoxetine and the bleeding time. *Arch. Pathol. Lab. Med.* **1990**, *114* (7), 727–728.
- HUTCHISON, L. C., Mirtazapine and bone marrow suppression: a case report. *J. Am. Geriatr. Soc.* **2001**, *49* (8), 1129–1130.
- HYATT, M., MESSER, M., Yohimbine and imipramine-induced orthostasia. *Am. J. Psychiatry* **1986**, *143* (3), 389–390.

- INDER, W. J., PRICKETT, T. C., MULDER, R. T., DONALD, R. A., JOYCE, P. R., Reduction in basal afternoon plasma ACTH during early treatment of depression with fluoxetine. *Psychopharmacology (Berl.)* **2001**, *156* (1), 73–78.
- INOUE, T., TSUCHIYA, K., MIURA, J., SAKAKIBARA, S., DENDA, K., KASAHARA, T., KOYAMA, T., Bromocriptine treatment of tricyclic and heterocyclic antidepressant-resistant depression. *Biol. Psychiatry* **1996**, *40* (2), 151–153.
- INVERNIZZI, G., AGUGLIA, E., BERTOLINO, A., CASACCHIA, M., CIANI, N., MARCHESI, G. F., NARDINI, M., RAPISARDA, V., The efficacy and safety of tianeptine in the treatment of depressive disorder: results of a controlled double-blind multicentre study vs. amitriptyline. *Neuropsychobiology* **1994**, *30* (2–3), 85–93.
- IOSIFESCU, D. V., CLEMENTI-CRAVEN, N., RYAN, J. L., NIERENBERG, A. A., PAPAKOSTAS, G., ALPERT, J. E., FAVA, M., Cardiovascular risk factors predict treatment outcome in Major Depressive Disorder. American Psychiatric Association 156th Annual Meeting, San Francisco, California, **2003**.
- IOSIFESCU, D. V., HOWARTH, S., ALPERT, J. E., NIERENBERG, A. A., WORTHINGTON, J. J., FAVA, M., T3 blood levels and treatment outcome in depression. *Int. J. Psychiatry Med.* **2001**, *31* (4), 367–373.
- IOSIFESCU, D. V., NIERENBERG, A. A., ALPERT, J. E., SMITH, M., BITRAN, S., DORDING, C., FAVA, M., The impact of medical comorbidity on acute treatment in major depressive disorder. *Am. J. Psychiatry* **2004** (in press).
- IRAQI, A., BAICKLE, E., A case report of hyponatremia with citalopram use. *J. Am. Med. Dir. Assoc.* **2004**, *5* (1), 64–65.
- IRWIN, M., SPAR, J. E., Reversible cardiac conduction abnormality associated with trazodone administration. *Am. J. Psychiatry* **1983**, *140* (7), 945–946.
- ISAAC, M. T., ISAAC, M. B., GALLO, F., TOURNOUX, A., Milnacipran and pindolol: a randomized trial of reduction of antidepressant latency. *Hum. Psychopharmacol.* **2003**, *18* (8), 595–601.
- ISBISTER, G. K., BALIT, C. R., Bupropion overdose: QTc prolongation and its clinical significance. *Ann. Pharmacother.* **2003**, *37* (7–8), 999–1002.
- ISBISTER, G. K., McGETTIGAN, P., DAWSON, A., A fatal case of moclobemide–citalopram intoxication. *J. Anal. Toxicol.* **2001a**, *25* (8), 716–717.
- ISBISTER, G. K., PRIOR, F. H., FOY, A., Citalopram-induced bradycardia and presyncope. *Ann. Pharmacother.* **2001b**, *35* (12), 1552–1555.
- ITO, K., YOSHIDA, K., SATO, K., TAKAHASHI, H., KAMATA, M., HIGUCHI, H., SHIMIZU, T., ITOH, K., INOUE, K., TEZUKA, T., SUZUKI, T., OHKUBO, T., SUGAWARA, K., OTANI, K., A variable number of tandem repeats in the serotonin transporter gene does not affect the antidepressant response to fluvoxamine. *Psychiatry Res.* **2002**, *111* (2–3), 235–239.
- IVKOVIC, M., JASOVIC-GASIC, M., MARIC, N., PAUNOVIC, V. R., Fluoxetine and amitriptyline: differential cognitive effects in depressed patients. *Eur. Neuropsychopharmacol.* **2000**, *10* (3), S264.
- IWASHITA, T., SHIMIZU, T., Imipramine inhibits intrathecal substance P-induced behavior and blocks spinal cord substance P receptors in mice. *Brain Res.* **1992**, *581* (1), 59–66.
- IYENGAR, S., LU, Y., DETKE, M., LEE, T. C., SIMMONS, R. M., GOLDSTEIN, D., Efficacy of duloxetine in the treatment of the pain associated with diabetic neuropathy. Presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- IZUMI, T., INOUE, T., KITAGAWA, N., NISHI, N., SHIMANAKA, S., TAKAHASHI, Y., KUSUMI, I., ODAGAKI, Y., DENDA, K., OHMORI, T., KOYAMA, T., Open pergolide treatment of tricyclic and heterocyclic antidepressant-resistant depression. *J. Affect Disord.* **2000**, *61* (1–2), 127–132.
- JACOBSEN, F. M., Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. *J. Clin. Psychiatry* **1992**, *53* (4), 119–122.
- JACOBSEN, F. M., Low-dose trazodone as a hypnotic in patients treated with MAOIs and other psychotropics: a pilot study. *J. Clin. Psychiatry* **1990**, *51* (7), 298–302.
- JACOBSEN, F. M., Possible augmentation of antidepressant response by buspirone. *J. Clin. Psychiatry* **1991**, *52* (5), 217–220.

- JAFFEE, M. S., BOSTWICK, J. M., Buspirone as an antidote to venlafaxine-induced bruxism. *Psychosomatics* **2000**, 41 (6), 535–536.
- JAIN, A. K., KAPLAN, R. A., GADDE, K. M., WADDEN, T. A., ALLISON, D. B., BREWER, E. R., LEADBETTER, R. A., RICHARD, N., HAIGHT, B., JAMERSON, B. D., BUARON, K. S., METZ, A., Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obes. Res.* **2002**, 10 (10), 1049–1056.
- JAIN, M. W., ZUMBRUNNEN, T. L., KAZMI, Y. R., VANDENBERG, C. M., DESAI, H. D., WEIDLER, D. J., FLOCKHART, D. A., Pharmacokinetics of fluvoxamine in relation to CYP2C19 phenotype and genotype. *Drug Metab. Drug Interact.* **2002**, 19 (1), 1–11.
- JANOWSKY, D., CURTIS, G., ZISOOK, S., KUHN, K., RESOVSKY, K., LE WINTER, M., Ventricular arrhythmias possibly aggravated by trazodone. *Am. J. Psychiatry* **1983a**, 140 (6), 796–797.
- JANOWSKY, D., CURTIS, G., ZISOOK, S., KUHN, K., RESOVSKY, K., LE WINTER, M., Trazodone-aggravated ventricular arrhythmias. *J. Clin. Psychopharmacol.* **1983b**, 3 (6), 372–376.
- JENKINS, S. W., ROBINSON, D. S., FABRE, L. F. JR., ANDARY, J. J., MESSINA, M. E., REICH, L. A., Gepirone in the treatment of major depression. *J. Clin. Psychopharmacol.* **1990**, 10 (3 Suppl.), 77S–85S.
- JEZOVA, D., DUNCKO, R., Enhancement of stress-induced pituitary hormone release and cardiovascular activation by antidepressant treatment in healthy men. *J. Psychopharmacol.* **2002**, 16 (3), 235–240.
- JO, S. H., YOUM, J. B., LEE, C. O., EARM, Y. E., HO, W. K., Blockade of the HERG human cardiac K (+) channel by the antidepressant drug amitriptyline. *Br. J. Pharmacol.* **2000**, 129 (7), 1474–1480.
- JOFFE, H., GRONINGER, H., SOARES, C. N., NONACS, R., COHEN, L. S., An open trial of mirtazapine in menopausal women with depression unresponsive to estrogen replacement therapy. *J. Womens Health Gend. Based Med.* **2001**, 10 (10), 999–1004.
- JOFFE, R. T., BAKISH, D., Combined SSRI-moclobemide treatment of psychiatric illness. *J. Clin. Psychiatry* **1994**, 55 (1), 24–25.
- JOFFE, R. T., LEVITT, A. J., SOKOLOV, S. T., YOUNG, L. T., Response to an open trial of a second SSRI in major depression. *J. Clin. Psychiatry* **1996**, 57 (3), 114–115.
- JOFFE, R. T., SCHULLER, D. R., An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. *J. Clin. Psychiatry* **1993**, 54 (7), 269–271.
- JOFFE, R. T., SINGER, W., Effect of phenelzine on thyroid function in depressed patients. *Biol. Psychiatry* **1987**, 22 (8), 1033–1035.
- JOHANSSON, L., SOHN, D., THORBERG, S. O., JACKSON, D. M., KELDER, D., LARSSON, L. G., RENYI, L., ROSS, S. B., WALLSTEN, C., ERIKSSON, H., HU, P. S., JERNING, E., MOHELL, N., WESTLIND-DANIELSSON, A., The pharmacological characterization of a novel selective 5-hydroxytryptamine_{1A} receptor antagonist, NAD-299. *J. Pharmacol. Exp. Ther.* **1997**, 283 (1), 216–225.
- JOHN, L., PERREAULT, M. M., TAO, T., BLEW, P. G., Serotonin syndrome associated with nefazodone and paroxetine. *Ann. Emerg. Med.* **1997**, 29 (2), 287–289.
- JOHNSON, E. R., JONES, M. D., STEWART, J. N., Occurrence of a pheochromocytoma after ingestion of imipramine. *J. Am. Osteopath. Assoc.* **1979**, 78 (5), 332–335.
- JOHNSTON, J. A., LINEBERRY, C. G., ASCHER, J. A., DAVIDSON, J., KHAYRALLAH, M. A., FEIGHNER, J. P., STARK, P., A 102-center prospective study of seizure in association with bupropion. *J. Clin. Psychiatry* **1991**, 52 (11), 450–456.
- JOO, J. H., LENZE, E. J., MULSANT, B. H., BEGLEY, A. E., WEBER, E. M., STACK, J. A., MAZUMDAR, S., REYNOLDS, C. F. 3RD, POLLOCK, B. G., Risk factors for falls during treatment of late-life depression. *J. Clin. Psychiatry* **2002**, 63 (10), 936–941.
- JORGE, R. E., ROBINSON, R. G., ARNDT, S., STARKSTEIN, S., Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am. J. Psychiatry* **2003**, 160 (10), 1823–1829.
- JOUVENT, R., ABENSOUR, P., BONNET, A. M., WIDLOCHER, D., AGID, Y., LHERMITTE, F., Antiparkinsonian and antidepressant effects of high doses of bromocriptine. An independent comparison. *J. Affect Disord.* **1983**, 5 (2), 141–145.
- JOYCE, P. R., MULDER, R. T., LUTY, S. E., MCKENZIE, J. M., MILLER, A. L., ROGERS,

- G. R., KENNEDY, M. A., Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta3 subunit as predictors of response to fluoxetine and nortriptyline. *Int. J. Neuropsychopharmacol.* **2003b**, 6 (4), 339–346.
- JOYCE, P. R., MULDER, R. T., LUTY, S. E., MCKENZIE, J. M., RAE, A. M., A differential response to nortriptyline and fluoxetine in melancholic depression: the importance of age and gender. *Acta Psychiatr. Scand.* **2003a**, 108 (1), 20–23.
- JOYCE, P. R., WALSH, J., Nightmares during phenelzine withdrawal. *J. Clin. Psychopharmacol.* **1983**, 3 (2), 121.
- JUDD, F. K., MIJCH, A. M., COCKRAM, A., Fluoxetine treatment of depressed patients with HIV infection. *Aust. NZ J. Psychiatry* **1995**, 29 (3), 433–436.
- KANG, B. J., LEE, S. J., KIM, M. D., CHO, M. J., A placebo-controlled, double-blind trial of Ginkgo biloba for antidepressant-induced sexual dysfunction. *Hum. Psychopharmacol.* **2002**, 17 (6), 279–284.
- KANNER, A. M., KOZAK, A. M., FREY, M., The use of sertraline in patients with epilepsy: is it safe? *Epilepsy Behav.* **2000**, 1 (2), 100–105.
- KAPLAN, E. M., Efficacy of venlafaxine in patients with major depressive disorder who have unsustained or no response to selective serotonin reuptake inhibitors: an open-label, uncontrolled study. *Clin. Ther.* **2002**, 24 (7), 1194–2000.
- KAPUR, S., CHO, R., JONES, C., MCKAY, G., ZIPURSKY, R. B., Is amoxapine an atypical antipsychotic? Positron-emission tomography investigation of its dopamine2 and serotonin2 occupancy. *Biol. Psychiatry* **1999**, 45 (9), 1217–1220.
- KARSON, C. N., NEWTON, J. E., LIVINGSTON, R., JOLLY, J. B., COOPER, T. B., SPRIGG, J., KOMOROSKI, R. A., Human brain fluoxetine concentrations. *J. Neuropsychiatry Clin. Neurosci.* **1993**, 5 (3), 322–329.
- KASPER, S., PRASCHAK-RIEDER, N., TAUSCHER, J., WOLF, R., A risk-benefit assessment of mirtazapine in the treatment of depression. *Drug Saf.* **1997**, 17 (4), 251–264.
- KASPER, S., Managing reboxetine-associated urinary hesitancy in a patient with major depressive disorder: a case study. *Psychopharmacology (Berl.)* **2002**, 159 (4), 445–446.
- KASPER, S., WOLF, R., Successful treatment of reboxetine-induced urinary hesitancy with tamsulosin. *Eur. Neuropsychopharmacol.* **2002**, 12 (2), 119–122.
- KAUFMANN, M. W., CASSEM, N. H., MURRAY, G. B., JENIKE, M., Use of psychostimulants in medically ill patients with neurological disease and major depression. *Can. J. Psychiatry* **1984**, 29 (1), 46–49.
- KAVOUSSI, R. J., SEGRAVES, R. T., HUGHES, A. R., ASCHER, J. A., JOHNSTON, J. A., Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J. Clin. Psychiatry* **1997**, 58 (12), 532–537.
- KAYNAK, H., KAYNAK, D., GOZUKIRMIZI, E., GUILLEMINAULT, C., The effects of trazodone on sleep in patients treated with stimulant antidepressants. *Sleep Med.* **2004**, 5 (1), 15–20.
- KAZAL, L. A. JR., HALL, D. L., MILLER, L. G., NOEL, M. L., Fluoxetine-induced SIADH: a geriatric occurrence? *J. Fam. Pract.* **1993**, 36 (3), 341–343.
- KEEGAN, D., BOWEN, R. C., BLACKSHAW, S., SALEH, S., DAYAL, N., REMILLARD, F., SHRIKHANDE, S., CEBRIAN PEREZ, S., BOULTON, A., A comparison of fluoxetine and amitriptyline in the treatment of major depression. *Int. Clin. Psychopharmacol.* **1991**, 6 (2), 117–124.
- KELLER ASHTON, A., HAMER, R., ROSEN, R. C., Serotonin reuptake inhibitor-induced sexual dysfunction and its treatment: a large-scale retrospective study of 596 psychiatric outpatients. *J. Sex Marital Ther.* **1997**, 23 (3), 165–175.
- KENNEDY, S. H., MCCANN, S. M., MASELLIS, M., MCINTYRE, R. S., RASKIN, J., MCKAY, G., BAKER, G. B., Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J. Clin. Psychiatry* **2002**, 63 (3), 181–186.
- KENT, J. M., COPLAN, J. D., LOMBARDO, I., HWANG, D. R., HUANG, Y., MAWLAWI, O., VAN HEERTUM, R. L., SLIFSTEIN, M., ABDARGHAM, A., GORMAN, J. M., LARUELLE, M., Occupancy of brain serotonin

- transporters during treatment with paroxetine in patients with social phobia: a positron emission tomography study with ^{11}C McN 5652. *Psychopharmacology (Berl.)* **2002**, 164 (4), 341–348.
- KHALIFA, M., DALEAU, P., TURGEON, J., Mechanism of sodium channel block by venlafaxine in guinea pig ventricular myocytes. *J. Pharmacol. Exp. Ther.* **1999**, 291 (1), 280–284.
- KHAZAAL, Y., KRENZ, S., ZULLINO, D. F., Bupropion-induced somnambulism. *Addict. Biol.* **2003**, 8 (3), 359–362.
- KHOUZAM, H. R., MONTEIRO, A. J., GERKEN, M. E., Remission of cancer chemotherapy-induced emesis during antidepressant therapy with nefazodone. *Psychosom. Med.* **1998**, 60 (1), 89–91.
- KIEV, A., MASCO, H. L., WENGER, T. L., JOHNSTON, J. A., BATEY, S. R., HOLLOMAN, L. C., The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. *Ann. Clin. Psychiatry* **1994**, 6 (2), 107–115.
- KIM, D. K., LIM, S. W., LEE, S., SOHN, S. E., KIM, S., HAHN, C. G., CARROLL, B. J., Serotonin transporter gene polymorphism and antidepressant response. *Neuroreport* **2000a**, 11 (1), 215–219.
- KIM, K. Y., CRAIG, J. M., HAWLEY, J. M., Seizure possibly associated with fluvoxamine. *Ann. Pharmacother.* **2000b**, 34 (11), 1276–1278.
- KINNEY, J. L., Nomifensine maleate: a new second-generation antidepressant. *Clin. Pharm.* **1985**, 4 (6), 625–636.
- KINZIE, J. D., LEUNG, P., Clonidine in Cambodian patients with posttraumatic stress disorder. *J. Nerv. Ment. Dis.* **1989**, 177 (9), 546–550.
- KIRBY, D., HARRIGAN, S., AMES, D., Hyponatraemia in elderly psychiatric patients treated with Selective Serotonin Reuptake Inhibitors and venlafaxine: a retrospective controlled study in an inpatient unit. *Int. J. Geriatr. Psychiatry* **2002**, 17 (3), 231–237.
- KIRCHHEINER, J., KLEIN, C., MEINEKE, I., SASSE, J., ZANGER, U. M., MURDTER, T. E., ROOTS, I., BROCKMOLLER, J., Bupropion and 4-OH-bupropion pharmacokinetics in relation to genetic polymorphisms in CYP2B6. *Pharmacogenetics* **2003**, 13 (10), 619–626.
- KLEE, B., KRONIG, M. H., Case report of probable sertraline-induced akathisia. *Am. J. Psychiatry* **1993**, 150 (6), 986–987.
- KLEIN, J. J., SEGAL, R. L., WARNER, R. R., Galactorrhea due to imipramine. Report of a case. *N. Engl. J. Med.* **1964**, 271, 510–512.
- KNOWLES, S. R., SHAPIRO, L. E., SHEAR, N. H., Reactive metabolites and adverse drug reactions: Clinical considerations. *Clin. Rev. Allergy Immunol.* **2003**, 24 (3), 229.
- KO, D. T., HEBERT, P. R., COFFEY, C. S., SEDRAKYAN, A., CURTIS, J. P., KRUMHOLZ, H. M., Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* **2002**, 288 (3), 351–357.
- KOCH, S., PERRY, K. W., NELSON, D. L., CONWAY, R. G., THRELKELD, P. G., BYMASTER, F. P., R-fluoxetine increases extracellular DA, NE, as well as 5-HT in rat prefrontal cortex and hypothalamus: an in vivo microdialysis and receptor binding study. *Neuropsychopharmacology* **2002**, 27 (6), 949–959.
- KOHN, S., LABBATE, L. A., Venlafaxine and ecchymosis. *Can. J. Psychiatry* **1997**, 42 (1), 91.
- KOLE, M. H., SWAN, L., FUCHS, E., The antidepressant tianeptine persistently modulates glutamate receptor currents of the hippocampal CA3 commissural associational synapse in chronically stressed rats. *Eur. J. Neurosci.* **2002**, 16 (5), 807–816.
- KOLECKI, P., Isolated venlafaxine-induced serotonin syndrome. *J. Emerg. Med.* **1997a**, 15 (4), 491–493.
- KOLECKI, P., Venlafaxine induced serotonin syndrome occurring after abstinence from phenelzine for more than two weeks. *J. Toxicol. Clin. Toxicol.* **1997b**, 35 (2), 211–212.
- KONIG, F., HAUGER, B., VON HIPPEL, C., WOLFERSDORF, M., KASCHKA, W. P., Effect of paroxetine on thyroid hormone levels in severely depressed patients. *Neuropsychobiology* **2000**, 42 (3), 135–138.
- KONIG, F., WOLFERSDORF, M., Combination therapy using moclobemide with tricyclic and tetracyclic antidepressants to treat therapy-resistant depression. *Pharmacopsychiatry* **1997**, 30 (3), 93–96.
- KOPELMAN, P. G., ELLIOTT, M. W., SIMONDS, A., CRAMER, D., WARD, S., WEDZICHA,

- J. A., Short-term use of fluoxetine in asymptomatic obese subjects with sleep-related hypoventilation. *Int. J. Obes. Relat. Metab. Disord.* **1992**, 16 (10), 825–830.
- KORAN, L. M., CHUONG, H. W., BULLOCK, K. D., SMITH, S. C., Citalopram for compulsive shopping disorder: an open-label study followed by double-blind discontinuation. *J. Clin. Psychiatry* **2003**, 64 (7), 793–798.
- KORNBLUH, R., PAPAOKOSTAS, G. I., PETERSEN, T., NEAULT, N. B., NIERENBERG, A. A., ROSENBAUM, J. F., FAVA, M., A survey of prescribing preferences in the treatment of refractory depression: recent trends. *Psychopharmacol. Bull.* **2001**, 35 (3), 150–156.
- KORZETS, A., FLORO, S., ORI, Y., WEIZER, N., GRUZMAN, C., Clomipramine-induced pheochromocytoma crisis: a near fatal complication of a tricyclic antidepressant. *J. Clin. Psychopharmacol.* **1997**, 17 (5), 428–430.
- KOTLYAR, M., GOLDING, M., BREWER, E. R., CARSON, S. W., Possible nefazodone withdrawal syndrome. *Am. J. Psychiatry* **1999**, 156 (7), 1117.
- KOUTOUVIDIS, N., PRATIKAKIS, M., FOTIADOU, A., The use of mirtazapine in a group of 11 patients following poor compliance to selective serotonin reuptake inhibitor treatment due to sexual dysfunction. *Int. Clin. Psychopharmacol.* **1999**, 14 (4), 253–255.
- KRAHN, L. E., HANSON, C. A., PILEGGI, T. S., RUMMANS, T. A., Electroconvulsive therapy and cardiovascular complications in patients taking trazodone for insomnia. *J. Clin. Psychiatry* **2001**, 62 (2), 108–110.
- KRAICZI, H., HEDNER, J., DAHLOF, P., EJNELL, H., CARLSON, J., Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. *Sleep* **1999**, 22 (1), 61–67.
- KRAUS, M. R., SCHAFER, A., FALLER, H., CSEF, H., SCHEURLIN, M., Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. *Aliment. Pharmacol. Ther.* **2002a**, 16 (6), 1091–1099.
- KRAUS, T., HAACK, M., SCHULD, A., HINZSELCH, D., KOETHE, D., POLLMACHER, T., Body weight, the tumor necrosis factor system, and leptin production during treatment with mirtazapine or venlafaxine. *Pharmacopsychiatry* **2002b**, 35 (6), 220–225.
- KRONFOL, Z., GREDEN, J. F., ZIS, A. P., Imipramine-induced tremor: effects of a beta-adrenergic blocking agent. *J. Clin. Psychiatry* **1983**, 44 (6), 225–226.
- KUBERA, M., LIN, A. H., KENIS, G., BOSMANS, E., VAN BOCKSTAELE, D., MAES, M., Anti-Inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J. Clin. Psychopharmacol.* **2001**, 21 (2), 199–206.
- KUHN, K. U., QUEDNOW, B. B., THIEL, M., FALKAI, P., MAIER, W., ELGER, C. E., Antidepressive treatment in patients with temporal lobe epilepsy and major depression: a prospective study with three different antidepressants. *Epilepsy Behav.* **2003**, 4 (6), 674–679.
- KUHN, R., The treatment of depressive states with G22355 (imipramine hydrochloride). *Am. J. Psychiatry* **1958**, 115, 459–464.
- KUHS, H. (Unmasking pheochromocytoma by amitriptyline). *Nervenarzt* **1998**, 69 (1), 76–77.
- KUSALIC, M., ENGELSMANN, F., BRADWEJN, J., Thyroid functioning during treatment for depression. *J. Psychiatry Neurosci.* **1993**, 18 (5), 260–263.
- KUTNOWSKI, M., DAUBRESSE, J. C., FRIEDMAN, H., KOLANOWSKI, J., KRZENTOWSKI, G., SCHEEN, A., et al. Fluoxetine therapy in obese diabetic and glucose intolerant patients. *Int. J. Obes.* **1992**, 16 (Suppl. 4), S63–S66.
- LABBATE, L. A., POLLACK, M. H., Treatment of fluoxetine – induced sexual dysfunction with bupropion: a case report. *Ann. Clin. Psychiatry* **1994**, 6 (1), 13.
- LABBATE, L. A., GRIMES, J. B., HINES, A., POLLACK, M. H., Bupropion treatment of serotonin reuptake antidepressant-associated sexual dysfunction. *Ann. Clin. Psychiatry* **1997**, 9 (4), 241–245.
- LACOMBLEZ, L., BENSIMON, G., ISNARD, F., DIQUET, B., LECRUBIER, Y., PUECH, A. J., Effect of yohimbine on blood pressure in patients with depression and orthostatic hypotension induced by clomipramine. *Clin. Pharmacol. Ther.* **1989**, 45 (3), 241–251.

- LAINÉ, K., ANTTILA, M., HEINONEN, E., HELMINEN, A., HUUPPONEN, R., MAKI-IKOLA, O., REINIKAINEN, K., SCHEININ, M., Lack of adverse interactions between concomitantly administered selegiline and citalopram. *Clin. Neuropharmacol.* **1997**, *20* (5), 419–433.
- LAKE, M. B., BIRMAHER, B., WASSICK, S., MATHOS, K., YELOVICH, A. K., Bleeding and selective serotonin reuptake inhibitors in childhood and adolescence. *J. Child Adolesc. Psychopharmacol.* **2000**, *10* (1), 35–38.
- LAM, Y. W., ALFARO, C. L., ERESHEFSKY, L., MILLER, M., Pharmacokinetic and pharmacodynamic interactions of oral midazolam with ketoconazole, fluoxetine, fluvoxamine, and nefazodone. *J. Clin. Pharmacol.* **2003**, *43* (11), 1274–1282.
- LAMBERT, M. T., TRUTIA, C., PETTY, F., Extrapyramidal adverse effects associated with sertraline. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1998**, *22* (5), 741–748.
- LANDEN, M., BJÖRLING, G., AGREN, H., FAHLEN, T., A randomized, double-blind, placebo-controlled trial of bupropion in combination with an SSRI in patients with treatment-refractory depression. *J. Clin. Psychiatry* **1998**, *59* (12), 664–668.
- LANDEN, M., ERIKSSON, E., AGREN, H., FAHLEN, T., Effect of bupropion on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J. Clin. Psychopharmacol.* **1999**, *19* (3), 268–271.
- LANDOLT, H. P., RAIMO, E. B., SCHNIEROW, B. J., KESOE, J. R., RAPAPORT, M. H., GILLIN, J. C., Sleep and sleep electroencephalogram in depressed patients treated with phenelzine. *Arch. Gen. Psychiatry* **2001**, *58* (3), 268–276.
- LANE, R., BALDWIN, D., Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. *J. Clin. Psychopharmacol.* **1997**, *17* (3), 208–221.
- LAPIERRE, Y. D., SILVERSTONE, P., REESAL, R. T., SAXENA, B., TURNER, P., BAKISH, D., PLAMONDON, J., VINCENT, P. M., REMICK, R. A., KROFT, C., PAYEUR, R., ROSALES, D., LAM, R., BOLOGA, M., A Canadian multicenter study of three fixed doses of controlled-release ipasapirone in outpatients with moderate to severe major depression. *J. Clin. Psychopharmacol.* **1998**, *18* (4), 268–273.
- LARA, D. R., BUSNELLO, E. D., SOUZA, D. O., Ondansetron rather than metoclopramide for bupropion-induced nausea. *Can. J. Psychiatry* **2001**, *46* (4), 371.
- LARA, N., ARCHER, S. L., BAKER, G. B., LE MELLED, J. M., Paroxetine-induced increase in metabolic end products of nitric oxide. *J. Clin. Psychopharmacol.* **2003a**, *23* (4), 408–412.
- LARA, N., BAKER, G., ARCHER, S. L., LE MELLED, J. M., Increased cholesterol levels during paroxetine administration in healthy men. *J. Clin. Psychiatry* **2003b**, *64* (12), 1455–1459.
- LARSEN, J. K., GJERRIS, A., HOLM, P., ANDERSON, J., BILLE, A., CHRISTENSEN, E. M., HOYER, E., JENSEN, H., MEJLHEDE, A., LANGAGERGAARD, A., Moclobemide in depression: a randomized, multicentre trial against isocarboxazide and clomipramine emphasizing atypical depression. *Acta Psychiatr. Scand.* **1991**, *84* (6), 564–570.
- LATTANZI, L., DELL'OSSE, L., CASSANO, P., PINI, S., RUCCI, P., HOUCK, P. R., GEMIGNANI, A., BATTISTINI, G., BASSI, A., ABELLI, M., CASSANO, G. B., Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disord.* **2002**, *4* (5), 307–314.
- LAUBER, C., Nefazodone withdrawal syndrome. *Can. J. Psychiatry* **1999**, *44* (3), 285–286.
- LAUERMA, H., Successful treatment of citalopram-induced anorgasmia by cyproheptadine. *Acta Psychiatr. Scand.* **1996**, *93* (1), 69–70.
- LAURITZEN, L., BENDSEN, B. B., VILMAR, T., BENDSEN, E. B., LUNDE, M., BECH, P., Post-stroke depression: combined treatment with imipramine or desipramine and mianserin. A controlled clinical study. *Psychopharmacology (Berl.)* **1994**, *114* (1), 119–122.
- LAURITZEN, L., CLEMMESSEN, L., KLYSNER, R., LOLDRUP, D., LUNDE, M., SCHAUMBURG, E., WAARST, S., BECH, P., Combined treatment with imipramine and mianserin. A controlled pilot study. *Pharmacopsychiatry* **1992**, *25* (4), 182–186.
- LAVIN, M. R., MENDELOWITZ, A., KRONIG, M. H., Spontaneous hypertensive reactions with monoamine oxidase inhibitors. *Biol. Psychiatry* **1993**, *34* (3), 146–151.
- LAVRETSKY, H., KUMAR, A., Methylphenidate augmentation of citalopram in elderly

- depressed patients. *Am. J. Geriatr. Psychiatry* **2001**, 9 (3), 298–303.
- LAVRETSKY, H., MOON-DOO, K., KUMAR, A., Reynolds CF IIIrd. Combined treatment with methylphenidate and citalopram for accelerated response in the elderly: an open trial. *J. Clin. Psychiatry* **2003**, 64 (12), 1410–1414.
- LAYTON, D., CLARK, D. W., PEARCE, G. L., SHAKIR, S. A., Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? Results from a cohort study based on prescription event monitoring in England. *Eur. J. Clin. Pharmacol.* **2001**, 57 (2), 167–176.
- LAZARUS, L. W., MOBERG, P. J., LANGSLEY, P. R., LINGAM, V. R., Methylphenidate and nortriptyline in the treatment of poststroke depression: a retrospective comparison. *Arch. Phys. Med. Rehabil.* **1994**, 75 (4), 403–406.
- LAZARUS, L. W., WINEMILLER, D. R., LINGAM, V. R., NEYMAN, I., HARTMAN, C., ABASSIAN, M., KARTAN, U., GROVES, L., FAWCETT, J., Efficacy and side effects of methylphenidate for poststroke depression. *J. Clin. Psychiatry* **1992**, 53 (12), 447–449.
- LEANDER, J. D., Fluoxetine, a selective serotonin-uptake inhibitor, enhances the anticonvulsant effects of phenytoin, carbamazepine, and ameltolide (LY201116). *Epilepsia* **1992**, 33 (3), 573–576.
- LEARNED-COUGHLIN, S. M., BERGSTROM, M., SAVITCHEVA, I., ASCHER, J., SCHMITH, V. D., LANGSTROM, B., *In vivo* activity of bupropion at the human dopamine transporter as measured by positron emission tomography. *Biol. Psychiatry* **2003**, 54 (8), 800–805.
- LECHIN, F., VAN DER DIJS, B., JARA, H., OROZCO, B., BAEZ, S., BENAÏM, M., LECHIN, M., LECHIN, A., Effects of buspirone on plasma neurotransmitters in healthy subjects. *J. Neural Transm.* **1998**, 105 (6–7), 561–573.
- LECRUBIER, Y., BOYER, P., TURJANSKI, S., REIN, W., Amisulpride versus imipramine and placebo in dysthymia and major depression. Amisulpride Study Group. *J. Affect Disord.* **1997**, 43 (2), 95–103.
- LECRUBIER, Y., PLETAN, Y., SOLLES, A., TOURNOUX, A., MAGNE, V., Clinical efficacy of milnacipran: placebo-controlled trials. *Int. Clin. Psychopharmacol.* **1996**, 11 (Suppl. 4), 29–33.
- LECRUBIER, Y., PUECH, A. J., AUBIN, F., BOYER, P., DEYRIEUX, B., Improvement by amisulpride of the negative syndrome in non-psychotic subjects: a preliminary study. *Psychiatry Psychobiol.* **1988**, 3, 329–333.
- LECRUBIER, Y., PUECH, A. J., DES LAURIERS, A., Favourable effects of yohimbine on clomipramine-induced orthostatic hypotension: a double-blind study. *Br. J. Clin. Pharmacol.* **1981**, 12 (1), 90–93.
- LEE, M. S., NAM, J. W., A case of paroxetine-induced dyskinetic movements. *J. Clin. Psychopharmacol.* **2000**, 20 (6), 712–713.
- LEINONEN, E., SKARSTEIN, J., BEHNKE, K., AGREN, H., HELSDINGEN, J. T., Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. Nordic Antidepressant Study Group. *Int. Clin. Psychopharmacol.* **1999**, 14 (6), 329–337.
- LEIPZIG, R. M., CUMMING, R. G., TINETTI, M. E., Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J. Am. Geriatr. Soc.* **1999**, 47 (1), 30–39.
- LEMKE, M. R., Effect of reboxetine on depression in Parkinson's disease patients. *J. Clin. Psychiatry* **2002**, 63 (4), 300–304.
- LEMKE, M. R., BRECHT, M., KOESTER, J., KRAUS, P. H., REICHMANN, H., Depression and anhedonia in Parkinson's disease. *Eur. Neuropsychopharmacol.* **2002**, 12 (3), S109.
- LEMKE, M. R., WENDORFF, T., Differential effects of tricyclic antidepressants and paroxetine on gait performance in depression. *Eur. Neuropsychopharmacol.* **2000**, 10 (3), S254.
- LEMOINE, P., ACHARENTRE, A., BALVAY, G., BONNET, H., BURGAT, R., CARRIER, C., PERRIN, J., Double-blind trial of amineptine and clomipramine in the treatment of depression. *Curr. Med. Res. Opin.* **1981**, 7 (4), 234–240.
- LEO, R. J., Movement disorders associated with the serotonin selective reuptake inhibitors. *J. Clin. Psychiatry* **1996**, 57 (10), 449–454.

- LEO, R. J., LICHTER, D. G., HERSHEY, L. A., Parkinsonism associated with fluoxetine and cimetidine: a case report. *J. Geriatr. Psychiatry Neurol.* **1995**, *8* (4), 231–233.
- LEPINE, J. P., ALTAMURA, C., ANSSEAU, M., GUTIERREZ, J. L., BITTER, I., LADER, M., WAINTRAUB, L., Tianeptine and paroxetine in major depressive disorder, with a special focus on the anxious component in depression: an international, 6-week double-blind study dagger. *Hum. Psychopharmacol.* **2001**, *16* (3), 219–227.
- LESACA, T. G., Sertraline and galactorrhea. *J. Clin. Psychopharmacol.* **1996**, *16* (4), 333–334.
- LESPERANCE, F., FRASURE-SMITH, N., LALIBERTE, M. A., WHITE, M., LAFONTAINE, S., CALDERONE, A., TALAJIC, M., ROULEAU, J. L., An open-label study of nefazodone treatment of major depression in patients with congestive heart failure. *Can. J. Psychiatry* **2003**, *48* (10), 695–701.
- LEVANT, B., BANCROFT, G. N., Inhibition of [³H]-quinpirole binding by a monoamine oxidase inhibitor in subcellular fractions of rat striatum. *Life Sci.* **1998**, *63* (18), 1643–1651.
- LEVANT, B., MOEHLKAMP, J. D., MORGAN, K. A., LEONARD, N. L., CHENG, C. C., Modulation of [³H]-quinpirole binding in brain by monoamine oxidase inhibitors: evidence for a potential novel binding site. *J. Pharmacol. Exp. Ther.* **1996**, *278* (1), 145–153.
- LEVENSON, J. L., Prolonged QT interval after trazodone overdose. *Am. J. Psychiatry* **1999**, *156* (6), 969–970.
- LEVENSON, J. L., FALLON, H. J., Fluoxetine treatment of depression caused by interferon-alpha. *Am. J. Gastroenterol.* **1993**, *88* (5), 760–761.
- LEVIN, A., Nomifensine and maprotiline in endogenous depression: comparative efficacy and side effects. *Int. Pharmacopsychiatry* **1982**, *17* (Suppl. 1), 89–96.
- LEVINE, L. R., ENAS, G. G., THOMPSON, W. L., BYNNY, R. L., DAVER, A. D., KIRBY, R. W., KREINDLER, T. G., LEVY, B., LUCAS, C. P., Use of fluoxetine: a selective serotonin reuptake inhibitor, fluoxetine, in the treatment of obesity. *Int. J. Obes.* **1989**, *13*, 635–645.
- LEVINE, L. R., ROSENBLATT, S., BOSOMWORTH, J., Use of a serotonin re-uptake inhibitor, fluoxetine, in the treatment of obesity. *Int. J. Obes.* **1987**, *11* (Suppl. 3), 163–170.
- LEVITT, A. J., JOFFE, R. T., KAMIL, R., et al. Do depressed subjects who have failed both fluoxetine and a tricyclic antidepressant respond to the combination? *J. Clin. Psychiatry* **1999**, *60*, 613–616.
- LEVKOVITZ, Y., CAFTORI, R., AVITAL, A., RICHTER-LEVIN, G., The SSRIs drug fluoxetine, but not the noradrenergic tricyclic drug desipramine, improves memory performance during acute major depression. *Brain Res. Bull.* **2002**, *58* (4), 345–350.
- LEVSKY, M. E., SCHWARTZ, J. B., Sertraline-induced hyponatremia in an older patient. *J. Am. Geriatr. Soc.* **1998**, *46* (12), 1582–1583.
- LEVY, N. B., BLUMENFELD, M., BEASLEY, C. M. JR., DUBEY, A. K., SOLOMON, R. J., TODD, R., GOODMAN, A., BERGSTROM, R. R., Fluoxetine in depressed patients with renal failure and in depressed patients with normal kidney function. *Gen. Hosp. Psychiatry* **1996**, *18* (1), 8–13.
- LI, S. X., PERRY, K. W., WONG, D. T., Influence of fluoxetine on the ability of bupropion to modulate extracellular dopamine and norepinephrine concentrations in three mesocorticolimbic areas of rats. *Neuropharmacology* **2002**, *42* (2), 181–190.
- LICHT, R. W., QVITZAU, S., Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. *Psychopharmacology (Berl.)* **2002**, *161* (2), 143–151.
- LIEBOWITZ, M. R., QUITKIN, F. M., STEWART, J. W., MCGRATH, P. J., HARRISON, W., RABKIN, J., TRICAMO, E., MARKOWITZ, J. S., KLEIN, D. F., Phenelzine v imipramine in atypical depression. A preliminary report. *Arch. Gen. Psychiatry* **1984**, *41* (7), 669–677.
- LIEBOWITZ, M. R., QUITKIN, F. M., STEWART, J. W., MCGRATH, P. J., HARRISON, W. M., MARKOWITZ, J. S., RABKIN, J. G., TRICAMO, E., GOETZ, D. M., KLEIN, D. F., Antidepressant specificity in atypical depression. *Arch. Gen. Psychiatry* **1988**, *45* (2), 129–137.

- LIMKE, K. K., SHELTON, A. R., ELLIOTT, E. S., Fluvoxamine interaction with warfarin. *Ann. Pharmacother.* **2002**, 36 (12), 1890–1892.
- LINEBERRY, T. W., PETERS, G. E. JR., BOSTWICK, J. M., Bupropion-induced erythema multiforme. *Mayo Clin. Proc.* **2001**, 76 (6), 664–666.
- LINGAM, V. R., LAZARUS, L. W., GROVES, L., OH, S. H., Methylphenidate in treating poststroke depression. *J. Clin. Psychiatry* **1988**, 49 (4), 151–153.
- LINNEBUR, S. A., SASEEN, J. J., PACE, W. D., Venlafaxine-associated vaginal bleeding. *Pharmacotherapy* **2002**, 22 (5), 652–655.
- LINNOILA, M., GOLD, P., POTTER, W. Z., WEHR, T. A., Tricyclic antidepressants do not alter thyroid hormone levels in patients suffering from a major affective disorder. *Psychiatry Res.* **1981**, 4 (3), 357–360.
- LIPINSKI, J. F. JR., MALLIA, G., ZIMMERMAN, P., POPE, H. G. JR., Fluoxetine-induced akathisia: clinical and theoretical implications. *J. Clin. Psychiatry* **1989**, 50 (9), 339–342.
- LIPPMANN, S., BEDFORD, P., MANSHADI, M., MATHER, S., Trazodone cardiotoxicity. *Am. J. Psychiatry* **1983**, 140 (10), 1383.
- LISKIN, B., WALSH, B. T., ROOSE, S. P., JACKSON, W., Imipramine-induced inappropriate ADH secretion. *J. Clin. Psychopharmacol.* **1984**, 4 (3), 146–147.
- LITTLE, K. Y., d-Amphetamine versus methylphenidate effects in depressed inpatients. *J. Clin. Psychiatry* **1993**, 54 (9), 349–355.
- LIU, B. A., MITTMANN, N., KNOWLES, S. R., SHEAR, N. H., Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. *CMAJ* **1996**, 155 (5), 519–527.
- LIU, X., SAHUD, M. A., Glycoprotein IIb/IIIa complex is the target in mirtazapine-induced immune thrombocytopenia. *Blood Cells Mol. Dis.* **2003**, 30 (3), 241–245.
- LIU, Z. Q., CHENG, Z. N., HUANG, S. L., CHEN, X. P., OU-YANG, D. S., JIANG, C. H., ZHOU, H. H., Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br. J. Clin. Pharmacol.* **2001**, 52 (1), 96–99.
- LLERENA, A., DORADO, P., BEREZ, R., GONZALEZ, A. P., PENAS-LLEDO, E. M., Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. *Eur. J. Clin. Pharmacol.* **2004** (in press).
- LOBBEZOO, F., VAN DENDEREN, R. J., VERHEIJ, J. G., NAEIJE, M., Reports of SSRI-associated bruxism in the family physician's office. *J. Orofac. Pain* **2001**, 15 (4), 340–346.
- LONDBORG, P. D., SMITH, W. T., GLAUDIN, V., PAINTER, J. R., Short-term cotherapy with clonazepam and fluoxetine: anxiety, sleep disturbance and core symptoms of depression. *J. Affect Disord.* **2000**, 61 (1–2), 73–79.
- Longborn, P. D., GLAUDIN, V., PAINTER, J. R., Pramipexole in the treatment of markedly depressed outpatients. 39th New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, **1999**.
- LONGSTRETH, G. F., HERSHMAN, J., Trazodone-induced hepatotoxicity and leukonychia. *J. Am. Acad. Dermatol.* **1985**, 13 (1), 149–150.
- LONNQVIST, J., SIHVO, S., SYVALAHTI, E., KIVIRUUSU, O., Moclobemide and fluoxetine in atypical depression: a double-blind trial. *J. Affect Disord.* **1994**, 32 (3), 169–177.
- LOO, H., HALE, A., D'HAENEN, H., Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT (2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int. Clin. Psychopharmacol.* **2002**, 17 (5), 239–247.
- LOO, H., SAIZ-RUIZ, J., COSTA E SILVA, J. A., ANSSEAU, M., HERRINGTON, R., VASZ-SERRA, A., DILLING, H., DE RISIO, S., Efficacy and safety of tianeptine in the treatment of depressive disorders in comparison with fluoxetine. *Hum. Psychopharmacol.* **2001**, 16 (S1), S31–S38.
- LOO, H., SAIZ-RUIZ, J., COSTA E SILVA JACE, ANSSEAU, M., HERRINGTON, R., VASZ-SERRA, A., DILLING, H., DE RISIO, S., Efficacy and safety of tianeptine in the treatment of depressive disorders in comparison with fluoxetine. *J. Affect Disord.* **1999**, 56 (2–3), 109–118.
- LOO, W. J., ALEXANDROFF, A., FLANAGAN, N., Bupropion and generalized acute urti-

- caria: a further case. *Br. J. Dermatol.* **2003**, 149 (3), 660.
- LOPEZ-IBOR ALINO, J. J., AYUSO GUTIEREZ, J. L., MONTEJO IGLESIAS, M. L., RAMONS, J. L., A double-blind clinical comparison between nomifensine and amitriptyline in the treatment of endogenous depressions. *Int. Pharmacopsychiatry* **1982**, 17 (Suppl. 1), 97–105.
- LOWENTHAL, M. N., Sertraline-induced hyponatremia in an older patient. *J. Am. Geriatr. Soc.* **1999**, 47 (10), 1274.
- LU, R., HURLEY, A. D., GOURLEY, M., Dystonia induced by mirtazapine. *J. Clin. Psychiatry* **2002**, 63 (5), 452–453.
- LUSTMAN, P. J., GRIFFITH, L. S., CLOUSE, R. E., FREEDLAND, K. E., EISEN, S. A., RUBIN, E. H., CARNEY, R. M., MCGILL, J. B., Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom. Med.* **1997**, 59 (3), 241–250.
- LYKOURAS, L., AVGOUSTIDES, D., PAPAPOSTAS, Y., STEFANIS, C., Medication response to ECT-resistant melancholic patients. *Acta Psychiatr. Belg.* **1995**, 95 (3), 113–121.
- LYLIARD, R. B., STAHL, S. M., HERTZMAN, M., HARRISON, W. M., A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. *J. Clin. Psychiatry* **1997**, 58 (11), 484–491.
- MAANY, I., DHOPESH, V., Akathisia and fluoxetine. *J. Clin. Psychiatry* **1990**, 51 (5), 210–212.
- MACHER, J. P., MIRABAUD, C., A double-blind comparison of moclobemide and amineptine in the treatment of depressed out-patients. *Psychopharmacology (Berl.)* **1992**, 106 (Suppl.), S116–S117.
- MACHER, J. P., SICHEL, J. P., SERRE, C., VON FRENCKELL, R., HUCK, J. C., DEMAREZ, J. P., Double-blind placebo-controlled study of milnacipran in hospitalized patients with major depressive disorders. *Neuropsychobiology* **1989**, 22 (2), 77–82.
- MADHUSOODANAN, S., OSNOS, R., Amitriptyline induced hyponatremia: a case report. *Mt. Sinai J. Med.* **1981**, 48 (5), 431–433.
- MAES, M., LIBBRECHT, I., VAN HUNSEL, F., CAMPENS, D., MELTZER, H. Y., Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. *J. Clin. Psychopharmacol.* **1999b**, 19 (2), 177–182.
- MAES, M., SONG, C., LIN, A. H., BONACCORSO, S., KENIS, G., DE JONGH, R., BOSMANS, E., SCHARPE, S., Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacology* **1999a**, 20 (4), 370–379.
- MAES, M., VAN DE VYVERE, J., VANDOOOLAEGHE, E., BRIL, T., DEMEDTS, P., WAUTERS, A., NEELS, H., Alterations in iron metabolism and the erythron in major depression: further evidence for a chronic inflammatory process. *J. Affect. Disord.* **1996a**, 40 (1–2), 23–33.
- MAES, M., VANDOOOLAEGHE, E., DESNYDER, R., Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. *J. Affect. Disord.* **1996b**, 41 (3), 201–210.
- MAGGI, L., PALMA, E., MILEDI, R., EUSEBI, F., Effects of fluoxetine on wild and mutant neuronal alpha 7 nicotinic receptors. *Mol. Psychiatry* **1998**, 3 (4), 350–355.
- MAGGIO, R., SCARSELLI, M., NOVI, F., MILLAN, M. J., CORSINI, G. U., Potent activation of dopamine D3/D2 heterodimers by the antiparkinsonian agents, S32504, pramipexole and ropinirole. *J. Neurochem.* **2003**, 87 (3), 631–641.
- MAGYAROS, E., HARASZTI, L., The augmentation effect of pindolol on onset of action of SSRI in the treatment of depression illness. *Eur. Neuropsychopharmacol.* **2002**, 12 (3), S206.
- MAHEAUX, P., DUCROS, F., BOURQUE, J., GARON, J., CHIASSON, J. L., Fluoxetine improves insulin sensitivity in obese patients with non-insulin-dependant diabetes mellitus independently of weight loss. *Int. J. Obes. Relat. Metab. Disord.* **1997**, 21 (2), 97–102.
- MAIER, U., KOINIG, G., Andrological findings in young patients under long-term antidepressive therapy with clomipramine. *Psychopharmacology (Berl.)* **1994**, 116 (3), 357–359.
- MALESKER, M. A., SOORI, G. S., MALONE, P. M., MAHOWALD, J. A., HOUSEL, G. J., Eosinophilia associated with bupropion.

- Ann. Pharmacother.* **1995**, 29 (9), 867–869.
- MALLICK, R., ZHUANG, H. F., A comparison of venlafaxine, SSRIs, and placebo in improving fatigue in patients with major depression. Presented at the 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- MANDER, A., MCCAUSLAND, M., WORKMAN, B., FLAMER, H., CHRISTOPHIDIS, N., Fluoxetine induced dyskinesia. *Aust. NZ J. Psychiatry* **1994**, 28 (2), 328–330.
- MARANGELL, L. B., JOHNSON, C. R., KERTZ, B., ZBOYAN, H. A., MARTINEZ, J. M., Olanzapine in the treatment of apathy in previously depressed participants maintained with selective serotonin reuptake inhibitors: an open-label, flexible-dose study. *J. Clin. Psychiatry* **2002**, 63 (5), 391–395.
- MARAR, I. E., TOWERS, A. L., MULSANT, B. H., POLLOCK, B. G., AMICO, J. A., Effect of paroxetine on plasma vasopressin and water load testing in elderly individuals. *J. Geriatr. Psychiatry Neurol.* **2000**, 13 (4), 212–216.
- MARCOLI, M., MAURA, G., TORTAROLO, M., RAITERI, M., Trazodone is a potent agonist at 5-HT_{2C} receptors mediating inhibition of the N-methyl-D-aspartate/nitric oxide/cyclic GMP pathway in rat cerebellum. *J. Pharmacol. Exp. Ther.* **1998**, 285 (3), 983–986.
- MARGOLESE, H. C., CHOUINARD, G., Serotonin syndrome from addition of low-dose trazodone to nefazodone. *Am. J. Psychiatry* **2000**, 157 (6), 1022.
- MARIK, P. E., VAN HEERDEN, W., STEENKAMP, V., Fluoxetine-induced syndrome of inappropriate antidiuretic hormone excretion. *S. Afr. Med. J.* **1990**, 78 (12), 760–761.
- MARKIANOS, M., ALEVIZOS, V., STEFANIS, C., Plasma sex hormones and urinary biogenic amine metabolites during treatment of male depressed patients with the monoamine oxidase inhibitor moclobemide. *Neuroendocrinol. Lett.* **1991**, 13, 49–55.
- MARTINEZ, D., HWANG, D., MAWLAWI, O., SLIFSTEIN, M., KENT, J., SIMPSON, N., PARSEY, R. V., HASHIMOTO, T., HUANG, Y., SHINN, A., VAN HEERTUM, R., ABI-DARGHAM, A., CALTABIANO, S., MALIZIA, A., COWLEY, H., MANN, J. J., LARUELLE, M., Differential occupancy of somatodendritic and postsynaptic 5HT (1A) receptors by pindolol: a dose-occupancy study with [11C]WAY 100635 and positron emission tomography in humans. *Neuropsychopharmacology* **2001**, 24 (3), 209–229.
- MASAND, P., MURRAY, G. B., PICKETT, P., Psychostimulants in post-stroke depression. *J. Neuropsychiatry Clin. Neurosci.* **1991a**, 3 (1), 23–27.
- MASAND, P., PICKETT, P., MURRAY, G. B., Psychostimulants for secondary depression in medical illness. *Psychosomatics* **1991b**, 32 (2), 203–208.
- MASAND, P. S., ANAND, V. S., TANQUARY, J. F., Psychostimulant augmentation of second generation antidepressants: a case series. *Depress. Anxiety* **1998**, 7 (2), 89–91.
- MASAND, P. S., ASHTON, A. K., GUPTA, S., FRANK, B., Sustained-release bupropion for selective serotonin reuptake inhibitor-induced sexual dysfunction: a randomized, double-blind, placebo-controlled, parallel-group study. *Am. J. Psychiatry* **2001**, 158 (5), 805–807.
- MASAND, P. S., GUPTA, S., Selective serotonin-reuptake inhibitors: an update. *Harv. Rev. Psychiatry* **1999**, 7 (2), 69–84.
- MASKALL, D. D., LAM, R. W., Midodrine for TCA-induced orthostatic hypotension. *J. Psychiatry Neurosci.* **1993**, 18 (5), 276–277.
- MASSANA, J., Reboxetine versus fluoxetine: an overview of efficacy and tolerability. *J. Clin. Psychiatry* **1998**, 59 (Suppl. 14), 8–10.
- MASSANA, J., MOLLER, H. J., BURROWS, G. D., MONTENEGRO, R. M., Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. *Int. Clin. Psychopharmacol.* **1999**, 14 (2), 73–80.
- MATTOX, J. H., BUCKMAN, M. T., BERNSTEIN, J., PATHAK, D., KELLNER, R., Dopamine agonists for reducing depression associated with hyperprolactinemia. *J. Reprod. Med.* **1986**, 31 (8), 694–698.
- MAURA, G., MARCOLI, M., PEPICELLI, O., ROSU, C., VIOLA, C., RAITERI, M., Serotonin inhibition of the NMDA receptor/nitric oxide/cyclic GMP pathway in human neocortex slices: involvement of 5-HT (2C) and 5-HT (1A) receptors. *Br. J. Pharmacol.* **2000**, 130 (8), 1853–1858.

- MAURI, M. C., LAINI, V., CERVERI, G., SCALVINI, M. E., VOLONTERI, L. S., REGISPANI, F., MALVINI, L., MANFRE, S., BOSCATI, L., PANZA, G., Clinical outcome and tolerability of sertraline in major depression: a study with plasma levels. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, 26 (3), 597–601.
- MAWHINNEY, M., COLE, D., AZZARO, A. J., Daily transdermal administration of selegiline to guinea-pigs preferentially inhibits monoamine oxidase activity in brain when compared with intestinal and hepatic tissues. *J. Pharm. Pharmacol.* **2003**, 55 (1), 27–34.
- MBAYA, P., Safety and efficacy of high dose of venlafaxine XL in treatment resistant major depression. *Hum. Psychopharmacol.* **2002**, 17 (7), 335–339.
- MCCOLLOM, R. A., ELBE, D. H., RITCHIE, A. H., Bupropion-induced serum sickness-like reaction. *Ann. Pharmacother.* **2000**, 34 (4), 471–473.
- MCCORMICK, S., OLIN, J., BROTMAN, A. W., Reversal of fluoxetine-induced anorgasmia by cyproheptadine in two patients. *J. Clin. Psychiatry* **1990**, 51 (9), 383–384.
- MCCOWEN, K. C., GARBER, J. R., SPARK, R., Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N. Engl. J. Med.* **1997**, 337 (14), 1010–1011.
- MCCRACKEN, J., KOSANIN, R., Trazodone administration during ECT associated with cardiac conduction abnormality. *Am. J. Psychiatry* **1984**, 141 (11), 1488–1489.
- MCCUE, R. E., JOSEPH, M., Venlafaxine- and trazodone-induced serotonin syndrome. *Am. J. Psychiatry* **2001**, 158 (12), 2088–2089.
- MCFARLANE, A., KAMATH, M. V., FALLEN, E. L., MALCOLM, V., CHERIAN, F., NORMAN, G., Effect of sertraline on the recovery rate of cardiac autonomic function in depressed patients after acute myocardial infarction. *Am. Heart J.* **2001**, 142 (4), 617–623.
- MCGILL, J. B., Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosom. Med.* **1997**, 59 (3), 241–250.
- MCGRATH, P. J., BLOOD, D. K., STEWART, J. W., HARRISON, W., QUITKIN, F. M., TRICAMO, E., MARKOWITZ, J., A comparative study of the electrocardiographic effects of phenelzine, tricyclic antidepressants, mianserin, and placebo. *J. Clin. Psychopharmacol.* **1987b**, 7 (5), 335–339.
- MCGRATH, P. J., FAVA, M., NIERENBERG, A. A., STEWART, J. W., ALPERT, J. E., Bupropion SR for relapses of MDD during or after fluoxetine treatment. 42nd Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, **2002**.
- MCGRATH, P. J., STEWART, J. W., HARRISON, W., QUITKIN, F. M., Treatment of tricyclic refractory depression with a monoamine oxidase inhibitor antidepressant. *Psychopharmacol. Bull.* **1987a**, 23 (1), 169–172.
- MCGRATH, P. J., STEWART, J. W., HARRISON, W. M., OCEPEK-WELIKSON, K., RABKIN, J. G., NUNES, E. N., WAGER, S. G., TRICAMO, E., QUITKIN, F. M., KLEIN, D. F., Predictive value of symptoms of atypical depression for differential drug treatment outcome. *J. Clin. Psychopharmacol.* **1992**, 12 (3), 197–202.
- MCGRATH, P. J., STEWART, J. W., NUNES, E. V., OCEPEK-WELIKSON, K., RABKIN, J. G., QUITKIN, F. M., KLEIN, D. F., A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *Am. J. Psychiatry* **1993**, 150 (1), 118–123.
- MCGRATH, P. J., STEWART, J. W., QUITKIN, F. M., WAGER, S., JENKINS, S. W., ARCHIBALD, D. G., STRINGFELLOW, J. C., ROBINSON, D. S., Gepirone treatment of atypical depression: preliminary evidence of serotonergic involvement. *J. Clin. Psychopharmacol.* **1994**, 14 (5), 347–352.
- MEDINA, C. A., Clitoral priapism: a rare condition presenting as a cause of vulvar pain. *Obstet. Gynecol.* **2002**, 100 (5 Pt 2), 1089–1091.
- MEKLER, G., WOGGON, B., A case of serotonin syndrome caused by venlafaxine and lithium. *Pharmacopsychiatry* **1997**, 30 (6), 272–273.
- MELTZER, H. Y., PIYAKALMALA, S., SCHYVE, P., FANG, V. S., Lack of effect of tricyclic antidepressants on serum prolactin levels. *Psychopharmacology (Berl.)* **1977**, 51 (2), 185–187.
- MELTZER, H. Y., YOUNG, M., METZ, J., FANG, V. S., SCHYVE, P. M., ARORA, R. C., Extrapyrmidal side effects and increased

- serum prolactin following fluoxetine, a new antidepressant. *J. Neural Transm.* **1979**, 45 (2), 165–175.
- MENDIS, N., HANWELLA, D. R., WEERASINGHE, C., ILLESINGHE, D. S., DE SILVA, D., A double-blind comparative study: amineptine (Survector 100) versus imipramine. *Clin. Neuropharmacol.* **1989**, 12 (Suppl. 2), S58–S65.
- MENZA, M. A., Withdrawal syndrome in a depressed patient treated with trazodone. *Am. J. Psychiatry* **1986**, 143 (9), 1195.
- MERCIER, M. A., STEWART, J. W., QUITKIN, F. M., A pilot sequential study of cognitive therapy and pharmacotherapy of atypical depression. *J. Clin. Psychiatry* **1992**, 53 (5), 166–170.
- MERCKE, Y., SHENG, H., KHAN, T., LIPPMANN, S., Hair loss in psychopharmacology. *Ann. Clin. Psychiatry* **2000**, 12 (1), 35–42.
- MERCURI, N. B., CALABRESI, P., Bernardi G. The electrophysiological actions of dopamine and dopaminergic drugs on neurons of the substantia nigra pars compacta and ventral tegmental area. *Life Sci.* **1992**, 51 (10), 711–718.
- MERIDETH, C. H., FEIGHNER, J. P., HENDRICKSON, G., A double-blind comparative evaluation of the efficacy and safety of nomifensine, imipramine, and placebo in depressed geriatric outpatients. *J. Clin. Psychiatry* **1984**, 45 (4 Pt 2), 73–77.
- MEYER, J. H., CHO, R., KENNEDY, S., KAPUR, S., The effects of single dose nefazodone and paroxetine upon 5-HT_{2A} binding potential in humans using [18F]-setoperone PET. *Psychopharmacology (Berl.)* **1999**, 144 (3), 279–281.
- MEYER, J. H., GOULDING, V. S., WILSON, A. A., HUSSEY, D., CHRISTENSEN, B. K., HOULE, S., Bupropion occupancy of the dopamine transporter is low during clinical treatment. *Psychopharmacology (Berl.)* **2002**, 163 (1), 102–105.
- MEYER, J. H., WILSON, A. A., GINOVART, N., GOULDING, V., HUSSEY, D., HOOD, K., HOULE, S., Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: a [(11)C]DASB PET imaging study. *Am. J. Psychiatry* **2001**, 158 (11), 1843–1849.
- MEYERS, B. S., MATTIS, S., GABRIELE, M., KAKUMA, T., Effects of nortriptyline on memory self-assessment and performance in recovered elderly depressives. *Psychopharmacol. Bull.* **1991**, 27 (3), 295–299.
- MEYERS, S., Use of neurotransmitter precursors for treatment of depression. *Altern. Med. Rev.* **2000**, 5 (1), 64–71.
- MEYNAAR, I. A., PEETERS, A. J., MULDER, A. H., OTTERVANGER, J. P., Syndrome of inappropriate ADH secretion attributed to the serotonin re-uptake inhibitors, venlafaxine and paroxetine. *Neth. J. Med.* **1997**, 50 (6), 243–245.
- MICHAEL, A., O'DONNELL, E. A., Fluoxetine-induced sexual dysfunction reversed by trazodone. *Can. J. Psychiatry* **2000**, 45 (9), 847–848.
- MICHAEL, A., TUBBE, P. A., PRASEEDOM, A., Sertraline-induced anorgasmia reversed by nefazodone. *Br. J. Psychiatry* **1999**, 175, 491.
- MICHALETS, E. L., WILLIAMS, C. R., Drug interactions with cisapride: clinical implications. *Clin. Pharmacokinet.* **2000**, 39 (1), 49–75.
- MICHELSON, D., AMSTERDAM, J., APTER, J., FAVA, M., LONDBORG, P., TAMURA, R., PAGH, L., Hormonal markers of stress response following interruption of selective serotonin reuptake inhibitor treatment. *Psychoneuroendocrinology* **2000**, 25 (2), 169–177.
- MICHELSON, D., AMSTERDAM, J. D., QUITKIN, F. M., REIMHERR, F. W., ROSENBAUM, J. F., ZAJECKA, J., SUNDELL, K. L., KIM, Y., BEASLEY, C. M. JR., Changes in weight during a 1-year trial of fluoxetine. *Am. J. Psychiatry* **1999**, 156 (8), 1170–1176.
- MICHELSON, D., BANCROFT, J., TARGUM, S., KIM, Y., TEPNER, R., Female sexual dysfunction associated with antidepressant administration: a randomized, placebo-controlled study of pharmacologic intervention. *Am. J. Psychiatry* **2000b**, 157 (2), 239–243.
- MICHELSON, D., FAVA, M., AMSTERDAM, J., APTER, J., LONDBORG, P., TAMURA, R., TEPNER, R. G., Interruption of selective serotonin reuptake inhibitor treatment. Double-blind, placebo-controlled trial. *Br. J. Psychiatry* **2000a**, 176, 363–368.
- MICHELSON, D., KOCIBAN, K., TAMURA, R., MORRISON, M. F., Mirtazapine, yohimbine or olanzapine augmentation therapy for serotonin reuptake-associated

- female sexual dysfunction: a randomized, placebo controlled trial. *J. Psychiatr. Res.* **2002**, 36 (3), 147–152.
- MICHELSON, D., PAGE, S. W., CASEY, R., TRUCKSESS, M. W., LOVE, L. A., MILSTIEN, S., WILSON, C., MASSAQUOI, S. G., CROFFORD, L. J., HALLETT, M., An eosinophilia–myalgia syndrome related disorder associated with exposure to L-5-hydroxytryptophan. *J. Rheumatol.* **1994**, 21 (12), 2261–2265.
- MIHARA, K., KONDO, T., SUZUKI, A., YASUI-FURUKORI, N., ONO, S., OTANI, K., KANEKO, S., Effects of genetic polymorphism of CYP1A2 inducibility on the steady-state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine in depressed Japanese patients. *Pharmacol. Toxicol.* **2001**, 88 (5), 267–270.
- MIHARA, K., OTANI, K., SUZUKI, A., YASUI, N., NAKANO, H., MENG, X., OHKUBO, T., NAGASAKI, T., KANEKO, S., TSUCHIDA, S., SUGAWARA, K., GONZALEZ, F. J., Relationship between the CYP2D6 genotype and the steady-state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine. *Psychopharmacology (Berl.)* **1997**, 133 (1), 95–98.
- MILLAN, M. J., GOBERT, A., LEJEUNE, F., DEKEYNE, A., NEWMAN-TANCREDI, A., PASTEAU, V., RIVET, J. M., CUSSAC, D., The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine_{2c} receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J. Pharmacol. Exp. Ther.* **2003**, 306 (3), 954–964.
- MILLER, D. K., SUMITHRAN, S. P., DWOSKIN, L. P., Bupropion inhibits nicotine-evoked [(3)H]overflow from rat striatal slices preloaded with [(3)H]dopamine and from rat hippocampal slices preloaded with [(3)H]norepinephrine. *J. Pharmacol. Exp. Ther.* **2002b**, 302 (3), 1113–1122.
- MILLER, D. K., WONG, E. H., CHESNUT, M. D., DWOSKIN, L. P., Reboxetine: functional inhibition of monoamine transporters and nicotinic acetylcholine receptors. *J. Pharmacol. Exp. Ther.* **2002a**, 302 (2), 687–695.
- MILLER, L., GRIFFITH, J., A comparison of bupropion, dextroamphetamine, and placebo in mixed-substance abusers. *Psychopharmacology (Berl.)* **1983**, 80 (3), 199–205.
- MILLER, M., Depression after cardiac transplant treated with interpersonal psychotherapy and paroxetine. *Am. J. Psychother.* **2002**, 56 (4), 555–561.
- MILNES, J. T., CROCIANI, O., ARCANGELI, A., HANCOX, J. C., WITCHEL, H. J., Blockade of HERG potassium currents by fluvoxamine: incomplete attenuation by S6 mutations at F656 or Y652. *Br. J. Pharmacol.* **2003**, 139 (5), 887–898.
- MING, M. E., BHAWAN, J., STEFANATO, C. M., MCCALMONT, T. H., COHEN, L. M., Imipramine-induced hyperpigmentation: four cases and a review of the literature. *J. Am. Acad. Dermatol.* **1999**, 40 (2 Pt 1), 159–166.
- MIRANDA, H., ORTIZ, G., FIGUEROA, S., PEREZ, C. M., SUAREZ, E., Depression scores following migraine treatment in patients attending a specialized center for headache and neurology. *Headache* **2001**, 41 (7), 680–684.
- MISCHOULON, D., DOUGHERTY, D. D., BOTTONARI, K. A., GRESHAM, R. L., SONAWALLA, S. B., FISCHMAN, A. J., FAVA, M., An open pilot study of nefazodone in depression with anger attacks: relationship between clinical response and receptor binding. *Psychiatry Res.* **2002**, 116 (3), 151–161.
- MISCHOULON, D., KRAMER, L., FAVA, S., SELHUB, J., MASCARINI, A., PERLIS, R. H., ALPERT, J. E., FAVA, M., Prevalence of MTHFR C677T and methionine synthase A2756G polymorphisms in major depression, and impact on response to fluoxetine treatment. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003**.
- MISCHOULON, D., NIERENBERG, A. A., KIZILBASH, L., ROSENBAUM, J. F., FAVA, M., Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. *Can. J. Psychiatry* **2000b**, 45 (5), 476–481.
- MISCHOULON, D., OPITZ, G., KELLY, K., FAVA, M., ROSENBAUM, J. F., A pilot study on the effectiveness of nefazodone in depressed outpatients with or without a

- history of SSRI treatment failure. 40th Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, 2000a.
- MITCHELL, P. B., SCHWEITZER, I., BURROWS, G., JOHNSON, G., POLONOWITA, A., Efficacy of venlafaxine and predictors of response in a prospective open-label study of patients with treatment-resistant major depression. *J. Clin. Psychopharmacol.* **2000**, 20 (4), 483–487.
- MOCHIZUKI, D., TSUJITA, R., YAMADA, S., KAWASAKI, K., OTSUKA, Y., HASHIMOTO, S., HATTORI, T., KITAMURA, Y., MIKI, N., Neurochemical and behavioural characterization of milnacipran, a serotonin and noradrenaline reuptake inhibitor in rats. *Psychopharmacology (Berl.)* **2002**, 162 (3), 323–332.
- MODELL, J. G., KATHOLI, C. R., MODELL, J. D., DePALMA, R. L., Comparative sexual side effects of bupropion, fluoxetine, paroxetine, and sertraline. *Clin. Pharmacol. Ther.* **1997**, 61 (4), 476–487.
- MOHR, D. C., BOUDEWYN, A. C., GOODKIN, D. E., BOSTROM, A., EPSTEIN, L., Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *J. Consult. Clin. Psychol.* **2001a**, 69 (6), 942–949.
- MOHR, D. C., GOODKIN, D. E., ISLAR, J., HAUSER, S. L., GENAIN, C. P., Treatment of depression is associated with suppression of nonspecific and antigen-specific T (H)1 responses in multiple sclerosis. *Arch. Neurol.* **2001b**, 58 (7), 1081–1086.
- MOHR, D. C., HART, S. L., GOLDBERG, A., Effects of treatment for depression on fatigue in multiple sclerosis. *Psychosom. Med.* **2003**, 65 (4), 542–547.
- MOK, J., SWANN, I., Diagnosis of pheochromocytoma after ingestion of imipramine. *Arch. Dis. Child* **1978**, 53 (8), 676–677.
- MOLL, E., NEUMANN, N., SCHMID-BURGK, W., STABL, M., AMREIN, R., Safety and efficacy during long-term treatment with moclobemide. *Clin. Neuropharmacol.* **1994**, 17 (Suppl. 1), S74–S87.
- MOLLER, H. J., KASPER, S., MULLER, H., KISSLING, W., FUGER, J., RUHRMANN, S., A controlled study of the efficacy and safety of mianserin and amitriptyline in depressive inpatients. *Pharmacopsychiatry* **1995**, 28 (6), 249–252.
- MOLLER, H. J., RIEHL, T., DIETZFELBINGER, T., WERNICKE, T., A controlled study of the efficacy and safety of mianserin and maprotiline in outpatients with major depression. *Int. Clin. Psychopharmacol.* **1991**, 6 (3), 179–192.
- MONTALBETTI, D. J., ZIS, A. P., Cholinergic rebound following trazodone withdrawal? *J. Clin. Psychopharmacol.* **1988**, 8 (1), 73.
- MONTASTRUC, J. L., PELAT, M., VERWAERDE, P., BREFEL-COURBON, C., TRAN, M. A., BLIN, O., RASCOL, O., SENARD, J. M., Fluoxetine in orthostatic hypotension of Parkinson's disease: a clinical and experimental pilot study. *Fund. Clin. Pharmacol.* **1998**, 12 (4), 398–402.
- MONTEJO, A. L., LLORCA, G., IZQUIERDO, J. A., RICO-VILLADEMOROS, F., Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. *J. Clin. Psychiatry* **2001**, 62 (Suppl. 3), 10–21.
- MONTELEONE, P., CATAPANO, F., TORTORELLA, A., DI MARTINO, S., MAJ, M., Plasma melatonin and cortisol circadian patterns in patients with obsessive-compulsive disorder before and after fluoxetine treatment. *Psychoneuroendocrinology* **1995**, 20 (7), 763–770.
- MONTES, J. M., FERRANDO, L., SAIZ-RUIZ, J., Remission in major depression with two antidepressant mechanisms: results from a naturalistic study. *J. Affect Disord.* **2004** (in press).
- MONTGOMERY, S. A., Safety of agomelatine in the treatment of depression: Absence of discontinuation symptoms. *Eur. Neuro-psychopharmacol.* **2003**, 13 (4), S210.
- MONTGOMERY, S., FERGUSON, J. M., SCHWARTZ, G. E., The antidepressant efficacy of reboxetine in patients with severe depression. *J. Clin. Psychopharmacol.* **2003**, 23 (1), 45–50.
- MOONSAMMY, G., BLOB, L. F., SHAROKY, M., VANBEDBERG, C. M., Azzaro AJ, Safety of selegiline transdermal system in long-term prevention of relapse of depression. 43rd Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, **2003**.

- MOOSA, M. Y., PANZ, V. R., JEENAH, F. Y., JOFFE, B. I., African women with depression: the effect of imipramine and fluoxetine on body mass index and leptin secretion. *J. Clin. Psychopharmacol.* **2003**, *23* (6), 549–552.
- MOREAU, X., AZORIN, J. M., LEJEUNE, P. J., JEANNINGROS, R., Red blood cell tri-iodothyronine uptake in unipolar major depression: effect of a chronic antidepressant treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2000**, *24* (1), 23–35.
- MORRISON, J., REMICK, R. A., LEUNG, M., WRIXON, K. J., BEBB, R. A., Galactorrhea induced by paroxetine. *Can. J. Psychiatry* **2001**, *46* (1), 88–89.
- MORROW, G. R., HICKOK, J. T., ROSCOE, J. A., RAUBERTAS, R. F., ANDREWS, P. L., FLYNN, P. J., HYNES, H. E., BANERJEE, T. K., KIRSHNER, J. J., KING, D. K., Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the university of Rochester cancer center community clinical oncology program. *J. Clin. Oncol.* **2003**, *21* (24), 4635–4641.
- MORROW, G. R., HICKOK, J. T., ROSENTHAL, S. N., Progress in reducing nausea and emesis. Comparisons of ondansetron (Zofran), granisetron (Kytril), and tropisetron (Navoban). *Cancer* **1995**, *76* (3), 343–357.
- MOVIG, K. L., JANSSEN, M. W., DE WAAL MALEFIJT, J., KABEL, P. J., LEUFKENS, H. G., EGBERTS, A. C., Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch. Intern. Med.* **2003**, *163* (19), 2354–2358.
- MUCK-SELER, D., PIVAC, N., SAGUD, M., JAKOVljeVIC, M., MIHALJEVIC-PELES, A., The effects of paroxetine and tianeptine on peripheral biochemical markers in major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, *26* (7–8), 1235–1243.
- MULLER, D. J., SCHULZE, T. G., MACCIARDI, F., OHLRAUN, S., GROSS, M. M., SCHERK, H., NEIDT, H., SYAGAILO, Y. V., GRASSLE, M., NOTHEN, M. M., MAIER, W., LESCH, K. P., RIETSCHEL, M., Moclobemide response in depressed patients: association study with a functional polymorphism in the monoamine oxidase A promoter. *Pharmacopsychiatry* **2002**, *35* (4), 157–158.
- MULLER, J. C., PRYER, W. W., GIBBONS, J. E., et al. Depression and anxiety occurring during Rauwolfia therapy. *JAMA* **1955**, *159*, 836–839.
- MULSANT, B. H., POLLOCK, B. G., NEBES, R. D., MILLER, M. D., LITTLE, J. T., STACK, J., HOUCK, P. R., BENSASI, S., MAZUMDAR, S., REYNOLDS, C. F. 3RD, A double-blind randomized comparison of nortriptyline and paroxetine in the treatment of late-life depression: 6-week outcome. *J. Clin. Psychiatry* **1999**, *60* (Suppl. 20), 16–20.
- MUNJACK, D. J., The treatment of phenelzine-induced hypotension with salt tablets: case report. *J. Clin. Psychiatry* **1984**, *45* (2), 89–90.
- MURPHY, D. L., TAMARKIN, L., SUNDERLAND, T., GARRICK, N. A., COHEN, R. M., Human plasma melatonin is elevated during treatment with the monoamine oxidase inhibitors clorgyline and tranylcypromine but not deprenyl. *Psychiatry Res.* **1986**, *17* (2), 119–127.
- MURPHY, G. M., KREMER, C., RODRIGUES, H. E., SCHATZBERG, A. F., Pharmacogenetics of antidepressant medication intolerance. *Am. J. Psychiatry* **2003**, *160* (10), 1830–1835.
- MUSSELMAN, D. L., LAWSON, D. H., GUMNICK, J. F., MANATUNGA, A. K., PENNA, S., GOODKIN, R. S., GREINER, K., NEMEROFF, C. B., MILLER, A. H., Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med.* **2001**, *344* (13), 961–966.
- NAKAYAMA, T., SUHARA, T., OKUBO, Y., ICHIMIYA, T., YASUNO, F., MAEDA, J., TAKANO, A., SAIJO, T., SUZUKI, K., In vivo drug action of tandospirone at 5-HT_{1A} receptor examined using positron emission tomography and neuroendocrine response. *Psychopharmacology (Berl.)* **2002**, *165* (1), 37–42.
- NAPPI, G., SANDRINI, G., GRANELLA, F., RUIZ, L., CERUTTI, G., FACCHINETTI, F., BLANDINI, F., MANZONI, G. C., A new 5-HT₂ antagonist (ritanserin) in the treatment of chronic headache with depression. A double-blind study vs amitriptyline. *Headache* **1990**, *30* (7), 439–444.
- NARUSHIMA, K., KOSIER, J. T., ROBINSON, R. G., Preventing poststroke depression:

- a 12-week double-blind randomized treatment trial and 21-month follow-up. *J. Nerv. Ment. Dis.* **2002**, 190 (5), 296–303.
- NATELSON, B. H., CHEU, J., HILL, N., BERGEN, M., KORN, L., DENNY, T., DAHL, K., Single-blind, placebo phase-in trial of two escalating doses of selegiline in the chronic fatigue syndrome. *Neuropsychobiology* **1998**, 37 (3), 150–154.
- NATELSON, B. H., CHEU, J., PAREJA, J., ELLIS, S. P., POLICASTRO, T., FINDLEY, T. W., Randomized, double blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndrome. *Psychopharmacology (Berl.)* **1996**, 124 (3), 226–230.
- NAVARRO, V., GASTO, C., TORRES, X., MARCOS, T., PINTOR, L., Citalopram versus nortriptyline in late-life depression: a 12-week randomized single-blind study. *Acta Psychiatr. Scand.* **2001**, 103 (6), 435–440.
- NEELY, J. L., Tonic clonic seizures and tachycardia induced by fluoxetine (Prozac) overdose. *W. V. Med. J.* **1998**, 94 (5), 283–285.
- NELSON, E. B., KECK, P. E. JR., MCELROY, S. L., Resolution of fluoxetine-induced sexual dysfunction with the 5-HT₃ antagonist granisetron. *J. Clin. Psychiatry* **1997**, 58 (11), 496–497.
- NELSON, E. B., SHAH, V. N., WEIGE, J. A., KECK, P. E. JR., A placebo-controlled, crossover trial of granisetron in SRI-induced sexual dysfunction. *J. Clin. Psychiatry* **2001**, 62 (6), 469–473.
- NELSON, J. C., Safety and tolerability of the new antidepressants. *J. Clin. Psychiatry* **1997**, 58 (Suppl. 6), 26–31.
- NELSON, J. C., KENNEDY, J. S., POLLOCK, B. G., LAGHRISSE-THODE, F., NARAYAN, M., NOBLER, M. S., ROBIN, D. W., GERGEL, I., MCCAFFERTY, J., ROOSE, S., Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. *Am. J. Psychiatry* **1999**, 156 (7), 1024–1028.
- NELSON, J. C., MAZURE, C. M., BOWERS, M. B., et al. A preliminary open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Arch. Gen. Psychiatry* **1991**, 48, 303–307.
- NELSON, J. C., MAZURE, C. M., JATLOW, P. I., BOWERS, M. B. JR., PRICE, L. H., Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biol. Psychiatry* **2004**, 55 (3), 296–300.
- NEMEROFF, C. B., EVANS, D. L., GYULAI, L., SACHS, G. S., BOWDEN, C. L., GERGEL, I. P., OAKES, R., PITTS, C. D., Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am. J. Psychiatry* **2001**, 158 (6), 906–912.
- NEUSCH, C., SCHNIERLE, S., MOSER, A., Selegiline induces dopamine release through ATP-sensitive potassium channels in the rat caudate-putamen *in vitro*. *Neurochem. Int.* **1997**, 31 (2), 307–311.
- NEWMAN, J. R., EWING, S. E., MCCOLL, R. D., BORUS, J. S., NIERENBERG, A. A., PAVA, J., FAVA, M., Tridimensional personality questionnaire and treatment response in major depressive disorder: a negative study. *J. Affect. Disord.* **2000**, 57 (1–3), 241–247.
- NEWTON, R. E., MARUNYCZ, J. D., ALDERDICE, M. T., NAPOLIello, M. J., Review of the side-effect profile of buspirone. *Am. J. Med.* **1986**, 80 (3B), 17–21.
- NICHOLAS, L. M., FORD, A. L., ESPOSITO, S. M., EKSTROM, R. D., GOLDEN, R. N., The effects of mirtazapine on plasma lipid profiles in healthy subjects. *J. Clin. Psychiatry* **2003**, 64 (8), 883–889.
- NIELSEN, J. L., Plasma prolactin during treatment with nortriptyline. *Neuropsychobiology* **1980**, 6 (1), 52–55.
- NIERENBERG, A. A., ADLER, L. A., PESELOW, E., ZORNBERG, G., ROSENTHAL, M., Trazodone for antidepressant-associated insomnia. *Am. J. Psychiatry* **1994a**, 151 (7), 1069–1072.
- NIERENBERG, A. A., COLE, J. O., GLASS, L., Possible trazodone potentiation of fluoxetine: a case series. *J. Clin. Psychiatry* **1992**, 53 (3), 83–85.
- NIERENBERG, A. A., FEIGHNER, J. P., RUDOLPH, R., COLE, J. O., SULLIVAN, J., Venlafaxine for treatment-resistant unipolar depression. *J. Clin. Psychopharmacol.* **1994b**, 14 (6), 419–423.
- NIERENBERG, A. A., KECK, P. E. JR., Management of monoamine oxidase inhibitor-associated insomnia with

- trazodone. *J. Clin. Psychopharmacol.* **1989**, *9* (1), 42–45.
- NIERENBERG, A. A., KREMER, C., REIMITZ, P., Mirtazapine and the onset of antidepressant action: Survival function analysis-response. *Eur. Neuropsychopharmacol.* **2000**, *10* (3), S265.
- NIERENBERG, A. A., PAPAPOSTAS, G. I., PETERSEN, T., KELLY, K. E., IACOVIELLO, B. M., WORTHINGTON, J. J., TEDLOW, J., ALPERT, J. E., FAVA, M., Nortriptyline for treatment-resistant depression. *J. Clin. Psychiatry* **2003**, *64* (1), 35–39.
- NINAN, P., HASSMAN, H., MCMANUS, F. C., GLASS, S. J., SCIAMANNA, A., Initiating modafinil with SSRI enhances degree and onset of therapeutic effects in depression. 43rd Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, **2003**.
- NISIJIMA, K., SHIMIZU, M., ABE, T., ISHIGURO, T., A case of serotonin syndrome induced by concomitant treatment with low-dose trazodone and amitriptyline and lithium. *Int. Clin. Psychopharmacol.* **1996**, *11* (4), 289–290.
- NISOLI, E., CARRUBA, M. O., A benefit-risk assessment of sibutramine in the management of obesity. *Drug Saf.* **2003**, *26* (14), 1027–1048.
- NOFZINGER, E. A., REYNOLDS, C. F. 3RD, THASE, M. E., FRANK, E., JENNINGS, J. R., FASICZKA, A. L., SULLIVAN, L. R., KUPFER, D. J., REM sleep enhancement by bupropion in depressed men. *Am. J. Psychiatry* **1995**, *152* (2), 274–276.
- NOLEN, W. A., Tranylcypromine in depression resistant to cyclic antidepressants. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1989**, *13* (1–2), 155–158.
- NOLEN, W. A., HAFFMANS, P. M., BOUVY, P. F., DUIVENVOORDEN, H. J., Monoamine oxidase inhibitors in resistant major depression. A double-blind comparison of brofaromine and tranylcypromine in patients resistant to tricyclic antidepressants. *J. Affect Disord.* **1993**, *28* (3), 189–197.
- NOLEN, W. A., VAN DE PUTTE, J. J., DIJKEN, W. A., KAMP, J. S., BLANSJAAR, B. A., KRAMER, H. J., HAFFMANS, J., Treatment strategy in depression II, MAO inhibitors in depression resistant to cyclic antidepressants: two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatr. Scand.* **1988**, *78* (6), 676–683.
- NOMIKOS, G. G., DAMSMA, G., WENKSTERN, D., FIBIGER, H. C., Acute effects of bupropion on extracellular dopamine concentrations in rat striatum and nucleus accumbens studied by in vivo microdialysis. *Neuropsychopharmacology* **1989**, *2* (4), 273–279.
- NONACS, R., COHEN, L. S., Assessment and treatment of depression during pregnancy: an update. *Psychiatr. Clin. North Am.* **2003**, *26* (3), 547–562.
- NORDGREN, L., VON SCHEELE, C., Nortriptyline and pituitary–thyroid function in affective disorder. *Pharmacopsychiatry* **1981**, *14* (2), 61–65.
- NORDIN, C., SIWERS, B., BERTILSSON, L., Bromocriptine treatment of depressive disorders. Clinical and biochemical effects. *Acta Psychiatr. Scand.* **1981**, *64* (1), 25–33.
- NOVOTNY, V., FALTUS, F., First signs of improvement with tianeptine in the treatment of depression: An analysis of a double-blind study versus fluoxetine. *Eur. Neuropsychopharmacol.* **2003**, *13* (4), S230.
- NOVOTNY, V., FALTUS, F., Tianeptine and fluoxetine in major depression: a 6-week randomised double-blind study. *Hum. Psychopharmacol.* **2002**, *17* (6), 299–303.
- NUNEZ, E., LOPEZ-CORCUERA, B., VAZQUEZ, J., GIMENEZ, C., ARAGON, C., Differential effects of the tricyclic antidepressant amoxapine on glycine uptake mediated by the recombinant GLYT1 and GLYT2 glycine transporters. *Br. J. Pharmacol.* **2000**, *129* (1), 200–206.
- NURNBERG, H. G., HENSLEY, P. L., GELENBERG, A. J., FAVA, M., LAURIELLO, J., PAINE, S., Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. *JAMA* **2003**, *289* (1), 56–64.
- O'KANE, M., WILES, P. G., WALES, J. K., fluoxetine in the treatment of obese type 2 diabetic patients. *Diabetic Med.* **1994**, *11*, 105–110.
- O'BRIEN, S., MCKEON, P., O'REGAN, M., A comparative study of the electrocardiographic effects of tranylcypromine and

- amitriptyline when prescribed singly and in combination. *Int. Clin. Psychopharmacol.* **1991**, 6 (1), 11–17.
- ODEH, M., BENY, A., OLIVEN, A., Severe symptomatic hyponatremia during citalopram therapy. *Am. J. Med. Sci.* **2001**, 321 (2), 159–160.
- O'GRADY, P., CARNEY, P. A., Recurrent life-threatening thrombocytopenia in a patient with chronic "Parstelin" dependence. *Ir. Med. J.* **1997**, 90 (1), 25.
- OHARA, K., TANABU, S., ISHIBASHI, K., IKEMOTO, K., YOSHIDA, K., SHIBUYA, H., CYP2D6*10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. *Eur. J. Clin. Pharmacol.* **2003**, 58 (10), 659–661.
- OKE, A., ADHIYAMAN, V., AZIZ, K., ROSS, A., Dose-dependent seizure activity associated with fluoxetine therapy. *QJM* **2001**, 94 (2), 113–114.
- OKUN, M., WATTS, R. L., Depression associated with Parkinson's disease: clinical features and treatment. *Neurology* **2002**, 58 (4 Suppl. 1), 563–570.
- OLIN, J., MASAND, P., Psychostimulants for depression in hospitalized cancer patients. *Psychosomatics* **1996**, 37 (1), 57–62.
- OLIVERA, A. A., A case of paroxetine-induced akathisia. *Biol. Psychiatry* **1996**, 39 (10), 910.
- OLIVERA, A. O., Sertraline and akathisia: spontaneous resolution. *Biol. Psychiatry* **1997**, 41 (2), 241–242.
- OLUSI, S. O., FIDO, A. A., Serum lipid concentrations in patients with major depressive disorder. *Biol. Psychiatry* **1996**, 40 (11), 1128–1131.
- O'MALLEY, P. G., JACKSON, J. L., SANTORO, J., TOMKINS, G., BALDEN, E., KROENKE K., Antidepressant therapy for unexplained symptoms and symptom syndromes. *J. Fam. Pract.* **1999**, 48 (12), 980–990.
- ONG, S. B., LEE, C. T., A double-blind comparison of nomifensine and amitriptyline in the treatment of depression. *Acta Psychiatr. Scand.* **1981**, 63 (3), 198–207.
- ONO, K., IWANAGA, Y., MANNAMI, T., KOKUBO, Y., TOMOIKE, H., KOMAMURA, K., SHIOJI, K., YASUI, N., TAGO, N., IWAI, N., Epidemiological evidence of an association between SLC6A2 gene polymorphism and hypertension. *Hypertens. Res.* **2003**, 26 (9), 685–689.
- OPBROEK, A., DELGADO, P. L., LAUKES, C., MCGAHUEY, C., KATSANIS, J., MORENO, F. A., MANBER, R., Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *Int. J. Neuropsychopharmacol.* **2002**, 5 (2), 147–151.
- OPLER, L. A., Sertraline and akathisia. *Am. J. Psychiatry* **1994**, 151 (4), 620–621.
- ORAL, E. T., TANELI, B., TUNCA, Z., AKDEMIR, A., VAHIP, S., DOGAN, O., SOFUOGLU, S., DILBAZ, N., KIRPINA, I., ULUG, B., LEVENT, B. A., UNAL, S., UZKUTLU, S., Efficacy and acceptability of tianeptine versus sertraline: a multicenter, double blind, controlled study. *Eur. Neuropsychopharmacol.* **2001**, 11 (3), S206.
- OREN, D. A., MOUL, D. E., SCHWARTZ, P. J., WEHR, T. A., ROSENTHAL, N. E., A controlled trial of levodopa plus carbidopa in the treatment of winter seasonal affective disorder: a test of the dopamine hypothesis. *J. Clin. Psychopharmacol.* **1994**, 14 (3), 196–200.
- O'ROURKE, D., WURTMAN, J. J., WURTMAN, R. J., CHEBLI, R., GLEASON, R., Treatment of seasonal depression with d-fenfluramine. *J. Clin. Psychiatry* **1989**, 50 (9), 343–347.
- OSHIKA, T., Ocular adverse effects of neuropsychiatric agents. Incidence and management. *Drug Saf.* **1995**, 12 (4), 256–263.
- OSTROFF, R. B., NELSON, C. J., Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J. Clin. Psychiatry* **1999**, 60, 256–259.
- OSWALD, P., SOUERY, D., MENDLEWICZ, J., Fluvoxamine-induced hyperglycaemia in a diabetic patient with comorbid depression. *Int. J. Neuropsychopharmacol.* **2003**, 6 (1), 85–87.
- OTANI, K., YASUI, N., KANEKO, S., ISHIDA, M., OHKUBO, T., OSANAI, T., SUGAWARA, K., FUKUSHIMA, Y., Trazodone treatment increases plasma prolactin concentrations in depressed patients. *Int. Clin. Psychopharmacol.* **1995**, 10 (2), 115–117.
- OTTON, S. V., BALL, S. E., CHEUNG, S. W., INABA, T., RUDOLPH, R. L., SELLERS, E. M., Venlafaxine oxidation in vitro is catalysed by CYP2D6. *Br. J. Clin. Pharmacol.* **1996**, 41 (2), 149–156.
- OUELLET, D., HSU, A., QIAN, J., LAMM, J. E., CAVANAUGH, J. H., LEONARD, J. M.,

- GRANNEMAN, G. R., Effect of fluoxetine on pharmacokinetics of ritonavir. *Antimicrob. Agents Chemother.* **1998**, *42* (12), 3107–3112.
- OWENS, M. J., KNIGHT, D. L., NEMEROFF, C. B., Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. *Biol. Psychiatry* **2001**, *50* (5), 345–350.
- PACE-SCHOTT, E. F., GERSH, T., SILVESTRI, R., STICKGOLD, R., SALZMAN, C., HOBSON, J. A., SSRI treatment suppresses dream recall frequency but increases subjective dream intensity in normal subjects. *J. Sleep Res.* **2001**, *10* (2), 129–142.
- PAE, C. U., KIM, Y. J., WON, W. Y., KIM, H. J., LEE, S., LEE, C. U., LEE, S. J., KIM, D. W., LEE, C., MIN, W. S., KIM, C. C., PAIK, I. H., SERRETTI, A., Paroxetine in the treatment of depressed patients with haematological malignancy: an open-label study. *Hum. Psychopharmacol.* **2004**, *19* (1), 25–29.
- PAES DE SOUSA, M., TROPA, J., Evaluation of the efficacy of amineptine in a population of 1,229 depressed patients: results of a multicenter study carried out by 135 general practitioners. *Clin. Neuropharmacol.* **1989**, *12* (Suppl. 2), S77–S86.
- PAI, V. B., KELLY, M. W., Bruising associated with the use of fluoxetine. *Ann. Pharmacother.* **1996**, *30* (7–8), 786–788.
- PALLADINO, A. JR., Adverse reactions to abrupt discontinuation of phenelzine. *J. Clin. Psychopharmacol.* **1983**, *3* (3), 206–207.
- PAN, J. J., SHEN, W. W., Serotonin syndrome induced by low-dose venlafaxine. *Ann. Pharmacother.* **2003**, *37* (2), 209–211.
- PANCRAZIO, J. J., KAMATCHI, G. L., ROSCOE, A. K., LYNCH, C. 3RD, Inhibition of neuronal Na⁺ channels by antidepressant drugs. *J. Pharmacol. Exp. Ther.* **1998**, *284* (1), 208–214.
- PANDE, A. C., BIRKETT, M., FECHNER-BATES, S., HASKETT, R. F., GREDEN, J. F., Fluoxetine versus phenelzine in atypical depression. *Biol. Psychiatry* **1996**, *40* (10), 1017–1020.
- PAPAKOSTAS, G. I., ALPERT, J. E., FAVA, M., S-adenosyl-methionine in depression: a comprehensive review of the literature. *Curr. Psychiatry Rep.* **2003d**, *5* (6), 460–466.
- PAPAKOSTAS, G. I., ONGUR, D., IOSIFESCU, D. V., MISCHOULON, D., FAVA, M., Cholesterol in mood and anxiety disorders: review of the literature and new hypotheses. *European Neuropsychopharmacology* **2004b** (in press).
- PAPAKOSTAS, G. I., PETERSEN, T., DENNINGER, J., TOSSANI, E., ALPERT, J. E., NIERENBERG, A. A., FAVA, M., Time to onset of clinical response and psychosocial functioning in the treatment of major depressive disorder. 157th Annual Meeting of the American Psychiatric Association, New York, New York, **2003a**.
- PAPAKOSTAS, G. I., PETERSEN, T., IOSIFESCU, D. V., ALPERT, J. E., NIERENBERG, A. A., FAVA, M., Somatic symptoms as predictors of time to onset of response to fluoxetine in major depressive disorder. *J. Clin. Psychiatry* **2004a** (in press).
- PAPAKOSTAS, G. I., PETERSEN, T., MONTOYA, H., NIERENBERG, A. A., ALPERT, J. E., FAVA, M., Treatment-related adverse events and outcome in a clinical trial of fluoxetine for depression. *Ann. Clin. Psychiatry* **2003e**, *15* (3–4), 187–192.
- PAPAKOSTAS, G. I., PETERSEN, T., NIERENBERG, A. A., MURAKAMI, J. L., ALPERT, J. E., ROSENBAUM, J. F., FAVA, M., Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *J. Clin. Psychiatry* **2004c** (in press).
- PAPAKOSTAS, G. I., PETERSEN, T., PAVA, J. A., GREEN, C. H., ALPERT, J. E., NIERENBERG, A. A., ROSENBAUM, J. F., FAVA, M., Hopelessness as a predictor of response to fluoxetine in major depressive disorder. *J. Clin. Psychopharmacol.* **2004d** (in press).
- PAPAKOSTAS, G. I., PETERSEN, T., RYAN, J., ROSENBAUM, J. F., ALPERT, J. E., FAVA, M., Serum folate, vitamin B12 and homocysteine in major depression: predictors of time to onset of response to fluoxetine. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003c**.
- PAPAKOSTAS, G. I., PETERSEN, T., WORTHINGTON, J. J., ROFFI, P. A., ALPERT, J. E., FAVA, M., NIERENBERG, A. A., A pilot, open study of sertraline in outpatients with treatment-resistant depression (TRD) or with a history of TRD who responded but later relapsed.

- Int. Clin. Psychopharmacol.* **2003b**, 18 (5), 293–296.
- PAPAKOSTAS, Y. G., MARKIANOS, M., ZERVAS, I. M., THEODOROPOULOU, M., VAIDAKIS, N., DARAS, M., Administration of citalopram before ECT: seizure duration and hormone responses. *J. ECT* **2000**, 16 (4), 356–360.
- PARIS, P. A., SAUCIER, J. R., ECG conduction delays associated with massive bupropion overdose. *J. Toxicol. Clin. Toxicol.* **1998**, 36 (6), 595–598.
- PARKER, W. A., Imipramine-induced syndrome of inappropriate antidiuretic hormone secretion. *Drug Intell. Clin. Pharm.* **1984**, 18 (11), 890–894.
- PASINI, A., TORTORELLA, A., GALE, K., Anti-convulsant effect of intranigral fluoxetine. *Brain Res.* **1992**, 593 (2), 287–290.
- PAYKEL, E. S., ROWAN, P. R., PARKER, R. R., BHAT, A. V., Response to phenelzine and amitriptyline in subtypes of outpatient depression. *Arch. Gen. Psychiatry* **1982**, 39 (9), 1041–1049.
- PAZZAGLI, M., GIOVANNINI, M. G., PEPEU, G., Trazodone increases extracellular serotonin levels in the frontal cortex of rats. *Eur. J. Pharmacol.* **1999** Nov. 3, 383 (3), 249–257.
- PAZZELLA, et al. **2001**.
- PEABODY, C. A., Trazodone withdrawal and formication. *J. Clin. Psychiatry* **1987**, 48 (9), 385.
- PEETERS, F. P., DE VRIES, M. W., VISSINK, A., Risks for oral health with the use of antidepressants. *Gen. Hosp. Psychiatry* **1998**, 20 (3), 150–154.
- PEETERS, M., MALOTEAUX, J. M., HERMANS, E., Distinct effects of amantadine and memantine on dopaminergic transmission in the rat striatum. *Neurosci. Lett.* **2003**, 343 (3), 205–209.
- PELOSO, P. M., BAILLIE, C., Serum sickness-like reaction with bupropion. *JAMA* **1999**, 282 (19), 1817.
- PENNINGS, E. J., VERKES, R. J., DE KONING, J., BOMMELE, J. J., JANSEN, G. S., VERMEIJ, P., Tranylcypromine intoxication with malignant hyperthermia, delirium, and thrombocytopenia. *J. Clin. Psychopharmacol.* **1997**, 17 (5), 430–432.
- PEREZ, V., GILABERTE, I., FARIES, D., ALVAREZ, E., ARTIGAS, F., Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. *Lancet* **1997**, 349 (9065), 1594–1597.
- PEREZ, V., SOLER, J., PUIGDEMONT, D., ALVAREZ, E., ARTIGAS, F., A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Grup de Recerca en Trastorns Afectius. *Arch. Gen. Psychiatry* **1999**, 56 (4), 375–379.
- PERLIS, R. H., MISCHOULON, D., SMOLLER, J. W., WAN, Y. J., LAMON-FAVA, S., LIN, K. M., ROSENBAUM, J. F., FAVA, M., Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. *Biol. Psychiatry* **2003**, 54 (9), 879–883.
- PERRY, N. K., Venlafaxine-induced serotonin syndrome with relapse following amitriptyline. *Postgrad. Med. J.* **2000**, 76 (894), 254–256.
- PERRY, P. J., ZEILMANN, C., ARNDT, S., Tricyclic antidepressant concentrations in plasma: an estimate of their sensitivity and specificity as a predictor of response. *J. Clin. Psychopharmacol.* **1994**, 14 (4), 230–240.
- PERUCCA, E., MARCHIONI, E., SORAGNA, D., SAVOLDI, F., Fluoxetine-induced movement disorders and deficient CYP2D6 enzyme activity. *Mov. Disord.* **1997**, 12 (4), 624–625.
- PERUGI, G., TONI, C., RUFFOLO, G., FRARE, F., AKISKAL, H., Adjunctive dopamine agonists in treatment-resistant bipolar II depression: an open case series. *Pharmacopsychiatry* **2001**, 34 (4), 137–141.
- PESTALITY, P., RIHMER, Z., KISS, H. G., Moclobemide-amitriptyline combination therapy in treatment-resistant depression. *Eur. Neuropsychopharmacol.* **2003**, 13 (4), S275.
- PETER, H., TABRIZIAN, S., HAND, I., Serum cholesterol in patients with obsessive compulsive disorder during treatment with behavior therapy and SSRI or placebo. *Int. J. Psychiatry Med.* **2000**, 30 (1), 27–39.
- PETERSEN, T., DORDING, C., NEAULT, N. B., KORNBLUH, R., ALPERT, J. E., NIERENBERG, A. A., ROSENBAUM, J. F., FAVA, M., A survey of prescribing practices in the treatment of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002a**, 26 (1), 177–187.

- PETERSEN, T., PAPAKOSTAS, G. I., BOTTONARI, K., IACOVIELLO, B., ALPERT, J. E., FAVA, M., NIERENBERG, A. A., NEO-FFI factor scores as predictors of clinical response to fluoxetine in depressed outpatients. *Psychiatry Res.* **2002b**, *109* (1), 9–16.
- PETERSON, J. C., POLLACK, R. W., MAHONEY, J. J., FULLER, T. J., Inappropriate antidiuretic hormone secondary to a monoamine oxidase inhibitor. *JAMA* **1978** Apr. 3, *239* (14), 1422–1423.
- PETERSON, M. C., Reversible galactorrhea and prolactin elevation related to fluoxetine use. *Mayo Clin. Proc.* **2001**, *76* (2), 215–216.
- PETTY, K. J., Hyperglycemia associated with paroxetine. *Ann. Intern. Med.* **1996**, *125* (9), 782.
- PEZZELLA, G., MOSLINGER-GEHMAYR, R., CONTU, A., Treatment of depression in patients with breast cancer: a comparison between paroxetine and amitriptyline. *Breast Cancer Res. Treat.* **2001**, *70* (1), 1–10.
- PHILIPP, M., TILLER, J. W., BAIER, D., KOHNEN, R., Comparison of moclobemide with selective serotonin reuptake inhibitors (SSRIs) on sexual function in depressed adults. The Australian and German Study Groups. *Eur. Neuropsychopharmacol.* **2000**, *10* (5), 305–314.
- PICKETT, P., MASAND, P., MURRAY, G. B., Psychostimulant treatment of geriatric depressive disorders secondary to medical illness. *J. Geriatr. Psychiatry Neurol.* **1990**, *3* (3), 146–151.
- PIERCEY, M. F., SMITH, M. W., LUM-RAGAN, J. T., Excitation of noradrenergic cell firing by 5-hydroxytryptamine_{1A} agonists correlates with dopamine antagonist properties. *J. Pharmacol. Exp. Ther.* **1994**, *268* (3), 1297–1303.
- PIERCEY, M. F., Pharmacology of pramipexole, a dopamine D₃-preferring agonist useful in treating Parkinson's disease. *Clin. Neuropharmacol.* **1998**, *21* (3), 141–151.
- PIERRE, J. M., GUZE, B. H., Benztrapine for venlafaxine-induced night sweats. *J. Clin. Psychopharmacol.* **2000**, *20* (2), 269.
- PISANI, F., OTERI, G., COSTA, C., DI RAIMONDO, G., DI PERRI, R., Effects of psychotropic drugs on seizure threshold. *Drug Saf.* **2002**, *25* (2), 91–110.
- PISANI, F., SPINA, E., OTERI, G., Antidepressant drugs and seizure susceptibility: from in vitro data to clinical practice. *Epilepsia* **1999**, *40* (Suppl. 10), 548–556.
- PITCHOT, W., ANSSEAU, M., Venlafaxine-induced hair loss. *Am. J. Psychiatry* **2001**, *158* (7), 1159–1160.
- PLAISANT, F., DOMMERGUES, M. A., SPEDDING, M., CECHELLI, R., BRILLAUD, J., KATO, G., MUNOZ, C., GRESSENS, P., Neuroprotective properties of tianeptine: interactions with cytokines. *Neuropharmacology* **2003**, *44* (6), 801–809.
- POHL, R., BALON, R., JAYARAMAN, A., DOLL, R. G., YERAGANI, V., Effect of fluoxetine, pemoline and placebo on heart period and QT variability in normal humans. *J. Psychosom. Res.* **2003**, *55* (3), 247–251.
- POIRIER, M. F., BOYER, P., Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. Venlafaxine and paroxetine in treatment-resistant depression. *Br. J. Psychiatry* **1999**, *175*, 12–16.
- POLDINGER, W., STREICHENWEIN, S. M., A clinical trial comparing nomifensine and nortriptyline. *Int. Pharmacopsychiatry* **1982**, *17* (Suppl. 1), 106–115.
- POLLAK, P. T., MUKHERJEE, S. D., FRASER, A. D., Sertraline-induced hypoglycemia. *Ann. Pharmacother.* **2001**, *35* (11), 1371–1374.
- POLLOCK, B. G., FERRELL, R. E., MULSANT, B. H., MAZUMDAR, S., MILLER, M., SWEET, R. A., DAVIS, S., KIRSHNER, M. A., HOUCK, P. R., STACK, J. A., REYNOLDS, C. F., KUPFER, D. J., Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. *Neuropsychopharmacology* **2000**, *23* (5), 587–590.
- POLLOCK, B. G., PEREL, J. M., PARADIS, C. F., FASICZKA, A. L., REYNOLDS, C. F. 3RD, Metabolic and physiologic consequences of nortriptyline treatment in the elderly. *Psychopharmacol. Bull.* **1994**, *30* (2), 145–150.
- POLLOCK, B. G., SWEET, R. A., KIRSHNER, M., REYNOLDS, C. F. 3RD, Bupropion plasma levels and CYP2D6 phenotype. *Ther. Drug Monit.* **1996**, *18* (5), 581–585.
- POMARA, N., TUN, H., HERNANDO, R., DE LA PENA, C., WESNES, K., COOPER, T., APOE

- polymorphism and anticholinergic toxicity in the elderly. 41st Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, 2001.
- POST, R. M., GERNER, R. H., CARMAN, J. S., GILLIN, J. C., JIMERSON, D. C., GOODWIN, F. K., BUNNEY, W. E. JR., Effects of a dopamine agonist piribedil in depressed patients: relationship of pretreatment homovanillic acid to antidepressant response. *Arch. Gen. Psychiatry* 1978, 35 (5), 609–615.
- POTTER VAN LOON, B. J., Fluoxetine increases insulin action in obese nondiabetic and in obese non-insulin-dependant diabetic individuals. *Int. J. Obes.* 1992, 16, 79–85.
- POTTER, W. Z., ZAHARKO, D. S., BECK, L. V., Possible role of hydrazine group in hypoglycemia associated with the use of certain monoamine-oxidase inhibitors (MAOI's). *Diabetes* 1969, 18 (8), 538–541.
- POUZET, B., SB-258741: a 5-HT₇ receptor antagonist of potential clinical interest. *CNS Drug Rev.* 2002, 8 (1), 90–100.
- POYUROVSKY, M., SCHNEIDMAN, M., WEIZMAN, A., Successful treatment of fluoxetine-induced dystonia with low-dose mianserin. *Mov. Disord.* 1997, 12 (6), 1102–1105.
- PRASHER, V. P., Seizures associated with fluoxetine therapy. *Seizure* 1993, 2 (4), 315–317.
- PRENDIVILLE, S., GALE, K., Anticonvulsant effect of fluoxetine on focally evoked limbic motor seizures in rats. *Epilepsia* 1993, 34 (2), 381–384.
- PRESKORN, S. H., Antidepressant response and plasma concentrations of bupropion. *J. Clin. Psychiatry* 1983, 44 (5 Pt 2), 137–139.
- PRETI, A., Tomoxetine (Eli Lilly & Co). *Curr Opin Invest Drugs* 2002, 3 (2), 272–277.
- PRICE, J., GRUNHAUS, L. J., Treatment of clomipramine-induced anorgasmia with yohimbine: a case report. *J. Clin. Psychiatry* 1990, 51 (1), 32–33.
- PRICE, L. H., CHARNEY, D. S., DELGADO, P. L., HENINGER, G. R., Fenfluramine augmentation in tricyclic-refractory depression. *J. Clin. Psychopharmacol.* 1990, 10 (5), 312–317.
- PRIOR, F. H., ISBISTER, G. K., DAWSON, A. H., WHYTE, I. M., Serotonin toxicity with therapeutic doses of dexamphetamine and venlafaxine. *Med. J. Aust.* 2002, 176 (5), 240–241.
- PRISKORN, M., SIDHU, J. S., LARSEN, F., DAVIS, J. D., KHAN, A. Z., ROLAN, P. E., Investigation of multiple dose citalopram on the pharmacokinetics and pharmacodynamics of racemic warfarin. *Br. J. Clin. Pharmacol.* 1997, 44 (2), 199–202.
- PULLAR, I. A., CARNEY, S. L., COLVIN, E. M., LUCAITES, V. L., NELSON, D. L., WEDLEY, S., LY367265, an inhibitor of the 5-hydroxytryptamine transporter and 5-hydroxytryptamine (2A) receptor antagonist: a comparison with the antidepressant, nefazodone. *Eur. J. Pharmacol.* 2000, 407 (1–2), 39–46.
- QUITKIN, F. M., LIEBOWITZ, M. R., STEWART, J. W., McGRATH, P. J., HARRISON, W., RABKIN, J. G., MARKOWITZ, J., DAVIES, S. O., l-Deprenyl in atypical depressives. *Arch. Gen. Psychiatry* 1984, 41 (8), 777–781.
- QUITKIN, F. M., McGRATH, P. J., STEWART, J. W., HARRISON, W., TRICAMO, E., WAGER, S. G., OCEPEK-WELIKSON, K., NUNES, E., RABKIN, J. G., KLEIN, D. F., Atypical depression, panic attacks, and response to imipramine and phenelzine. A replication. *Arch. Gen. Psychiatry* 1990, 47 (10), 935–941.
- QUITKIN, F. M., McGRATH, P. J., STEWART, J. W., HARRISON, W., WAGER, S. G., NUNES, E., RABKIN, J. G., TRICAMO, E., MARKOWITZ, J., KLEIN, D. F., Phenelzine and imipramine in mood reactive depressives. Further delineation of the syndrome of atypical depression. *Arch. Gen. Psychiatry* 1989, 46 (9), 787–793.
- QUITKIN, F. M., STEWART, J. W., McGRATH, P. J., LIEBOWITZ, M. R., HARRISON, W. M., TRICAMO, E., KLEIN, D. F., RABKIN, J. G., MARKOWITZ, J. S., WAGER, S. G., Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. *Am. J. Psychiatry* 1988, 145 (3), 306–311.
- QUITKIN, F. M., STEWART, J. W., McGRATH, P. J., TRICAMO, E., RABKIN, J. G., OCEPEK-WELIKSON, K., NUNES, E., HARRISON, W., KLEIN, D. F., Columbia atypical depression: a subgroup of depressives with better response to MAOI than to

- tricyclic antidepressants or placebo. *Br. J. Psychiatry (Suppl.)* **1993**, (21), 30–34.
- RABINER, E. A., BHAGWAGAR, Z., GUNN, R. N., SARGENT, P. A., BENCH, C. J., COWEN, P. J., GRASBY, P. M., Pindolol augmentation of selective serotonin reuptake inhibitors: PET evidence that the dose used in clinical trials is too low. *Am. J. Psychiatry* **2001**, 158 (12), 2080–2082.
- RABKIN, J. G., WAGNER, G. J., RABKIN, R., Fluoxetine treatment for depression in patients with HIV and AIDS: a randomized, placebo-controlled trial. *Am. J. Psychiatry* **1999**, 156 (1), 101–107.
- RAJAGOPALAN, M., LITTLE, J., Discontinuation symptoms with nefazodone. *Aust. NZ J. Psychiatry* **1999**, 33 (4), 594–597.
- RAJU, G. V., KUMAR, T. C., KHANNA, S., Seizures associated with sertraline. *Can. J. Psychiatry* **2000**, 45 (5), 491.
- RAMAEKERS, J. G., Antidepressants and driver impairment: empirical evidence from a standard on-the-road test. *J. Clin. Psychiatry* **2003**, 64 (1), 20–29.
- RAMASUBBU, R., Switching to moclobemide to reverse fluoxetine-induced sexual dysfunction in patients with depression. *J. Psychiatry Neurosci.* **1999**, 24 (1), 45–50.
- RAMPELLO, L., CHIECHIO, S., RAFFAELE, R., VECCHIO, I., NICOLETTI, F., The SSRI, citalopram, improves bradykinesia in patients with Parkinson's disease treated with L-dopa. *Clin. Neuropharmacol.* **2002**, 25 (1), 21–24.
- RAMPELLO, L., NICOLETTI, G., RAFFAELE, R., Dopaminergic hypothesis for retarded depression: a symptom profile for predicting therapeutic responses. *Acta Psychiatr. Scand.* **1991**, 84 (6), 552–554.
- RAMPELLO, L., NICOLETTI, G., RAFFAELE, R., DRAGO, F., Comparative effects of amitriptyline and amineptine in patients affected by anxious depression. *Neuropsychobiology* **1995**, 31 (3), 130–134.
- RANIERI, P., FRANZONI, S., ROZZINI, R., TRABUCCHI, M., Venlafaxine-induced reset osmostat syndrome: case of a 79-year-old depressed woman. *J. Geriatr. Psychiatry Neurol.* **1997**, 10 (2), 75–78.
- RANIERI, P., FRANZONI, S., TRABUCCHI, M., Reboxetine and hyponatremia. *N. Engl. J. Med.* **2000**, 342 (3), 215–216.
- RAO, R., Serotonergic syndrome with trazodone. *Hosp. Med.* **1998**, 59 (1), 79.
- RAPAPORT, M., GHARABAWI, G., CANUSO, C., LASSER, R., LOESCHER, A., Preliminary results from the ARISe-RD (Risperidone Augmentation in Resistant Depression) Trial. American Psychiatric Association Annual Meeting, San Francisco, **2003**.
- RAPAPORT, M., WILCOX, C., HEISER, J., LONDBORG, P., SCHWARTZ, G., Reboxetine augmentation of fluoxetine for patients with major depressive disorder: an 8-week open-label study. *Eur. Neuro-psychopharmacol.* **2002**, 12 (3), S205.
- RASKIN, J., GOLDSTEIN, D. J., MALLINCKRODT, C. H., FERGUSON, M. B., Duloxetine in the long-term treatment of major depressive disorder. *J. Clin. Psychiatry* **2003**, 64 (10), 1237–1244.
- RASMUSSEN, A., LUNDE, M., POULSEN, D. L., SORENSEN, K., QVITZAU, S., BECH, P., A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. *Psychosomatics* **2003**, 44 (3), 216–221.
- RASMUSSEN, S. L., OVERO, K. F., TANGHOJ, P., Cardiac safety of citalopram: prospective trials and retrospective analyses. *J. Clin. Psychopharmacol.* **1999**, 19 (5), 407–415.
- RAUSCH, J. L., JOHNSON, M. E., FEI, Y. J., LI, J. Q., SHENDARKAR, N., HOBBY, H. M., GANAPATHY, V., LEIBACH, F. H., Initial conditions of serotonin transporter kinetics and genotype: influence on SSRI treatment trial outcome. *Biol. Psychiatry* **2002**, 51 (9), 723–732.
- RAUSCH, J. L., PAVLINAC, D. M., NEWMAN, P. E., Complete heart block following a single dose of trazodone. *Am. J. Psychiatry* **1984**, 141 (11), 1472–1473.
- RAY, W. A., FOUGHT, R. L., DECKER, M. D., Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *Am. J. Epidemiol.* **1992**, 136 (7), 873–883.
- RAY, W. A., GRIFFIN, M. R., MALCOLM, E., Cyclic antidepressants and the risk of hip fracture. *Arch. Intern. Med.* **1991**, 151 (4), 754–756.
- RAZAVI, D., KORMOSS, N., COLLARD, A., FARVACQUES, C., DELVAUX, N., Comparative study of the efficacy and safety of trazodone versus clorazepate in the treatment of adjustment disorders in cancer patients: a pilot study. *J. Int. Med. Res.* **1999**, 27 (6), 264–272.

- RECCOPPA, L., WELCH, W. A., WARE, M. R., Acute dystonia and fluoxetine. *J. Clin. Psychiatry* **1990**, *51* (11), 487.
- REEVES, R. R., BULLEN, J. A., Serotonin syndrome produced by paroxetine and low-dose trazodone. *Psychosomatics* **1995**, *36* (2), 159–160.
- REICHMANN, H., BRECHT, M. H., KOSTER, J., KRAUS, P. H., LEMKE, M. R., Pramipexole in routine clinical practice: a prospective observational trial in Parkinson's disease. *CNS Drugs* **2003**, *17* (13), 965–973.
- REKTOROVA, I., REKTOR, I., BARES, M., DOSTAL, V., EHLE, E., FANFRDLOVA, Z., FIEDLER, J., KLAJBLOVA, H., KULIST'AK, P., RESSNER, P., SVATOVA, J., URBANEK, K., VELISKOVA, J., Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. *Eur. J. Neurol.* **2003**, *10* (4), 399–406.
- RENSHAW, P. F., GUIMARAES, A. R., FAVA, M., ROSENBAUM, J. F., PEARLMAN, J. D., FLOOD, J. G., PUPOLO, P. R., CLANCY, K., GONZALEZ, R. G., Accumulation of fluoxetine and norfluoxetine in human brain during therapeutic administration. *Am. J. Psychiatry* **1992**, *149* (11), 1592–1594.
- RETTMAN, K. S., MCCLINTOCK, C., Hepatotoxicity after short-term trazodone therapy. *Ann. Pharmacother.* **2001**, *35* (12), 1559–1561.
- REYNAERT, C., JANNE, P., ZDANOWICZ, N., MIGNON, A., Efficacy of venlafaxine in depressed patients after switching from prior SSRI treatment. *Eur. Neuropsychopharmacol.* **2000**, *10* (3), S241.
- REYNOLDS, R. D., Sertraline-induced anorgasmia treated with intermittent nefazodone. *J. Clin. Psychiatry* **1997**, *58* (2), 89.
- RICHARD, I. H., KURLAN, R., TANNER, C., FACTOR, S., HUBBLE, J., SUCHOWERSKY, O., WATERS, C., Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. *Neurology* **1997**, *48* (4), 1070–1107.
- RICHELSON, E., NELSON, A., Antagonism by antidepressants of neurotransmitter receptors of normal human brain *in vitro*. *J. Pharm. Exp. Ther.* **1984**, *230*, 94–102.
- RICHELSON, E., SOUDER, T., Binding of antipsychotic drugs to human brain receptors, focus on newer generation compounds. *Life Sci.* **2000**, *24*, 68 (1), 29–39.
- RICKELS, K., AMSTERDAM, J., CLARY, C., HASSMAN, J., LONDON, J., PUZZUOLI, G., SCHWEIZER, E., Buspirone in depressed outpatients: a controlled study. *Psychopharmacol. Bull.* **1990**, *26* (2), 163–167.
- RICKELS, K., AMSTERDAM, J. D., CLARY, C., PUZZUOLI, G., SCHWEIZER, E., Buspirone in major depression: a controlled study. *J. Clin. Psychiatry* **1991**, *52* (1), 34–38.
- RICKELS, K., DERIVAN, A., KUNZ, N., PALLAY, A., SCHWEIZER, E., Zalospiroline in major depression: a placebo-controlled multicenter study. *J. Clin. Psychopharmacol.* **1996**, *16* (3), 212–217.
- RIDDLE, M. A., BROWN, N., DZUBINSKI, D., JETMALANI, A. N., LAW, Y., WOOLSTON, J. L., Fluoxetine overdose in an adolescent. *J. Am. Acad. Child Adolesc. Psychiatry* **1989**, *28* (4), 587–588.
- RIMELE, T. J., HENRY, D. E., LEE, D. K., GEIGER, G., HEASLIP, R. J., GRIMES, D., Tissue-dependent alpha adrenoceptor activity of buspirone and related compounds. *J. Pharmacol. Exp. Ther.* **1987**, *241* (3), 771–778.
- RISPAIL, Y., SCHMITT, L., BERLAN, M., MONTASTRUC, J. L., MONTASTRUC, P., Yohimbine increases salivary secretion in depressed patients treated with tricyclic antidepressants. *Eur. J. Clin. Pharmacol.* **1990**, *39* (4), 425–426.
- ROBERTS, C., WATSON, J., PRICE, G. W., MIDDLEMISS, D. N., SB-236057-A: a selective 5-HT_{1B} receptor inverse agonist. *CNS Drug Rev.* **2001**, *7* (4), 433–444.
- ROBERTS, R. L., JOYCE, P. R., MULDER, R. T., BEGG, E. J., KENNEDY, M. A., A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. *Pharmacogenomics J.* **2002**, *2* (3), 191–196.
- ROBERTS, R. L., MULDER, R. T., JOYCE, P. R., LUTY, S. E., KENNEDY, M. A., No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. *Hum. Psychopharmacol.* **2004**, *19* (1), 17–23.

- ROBINSON, D. S., RICKELS, K., FEIGHNER, J., FABRE, L. F. JR., GAMMANS, R. E., SHROTRIYA, R. C., ALMS, D. R., ANDARY, J. J., MESSINA, M. E., Clinical effects of the 5-HT_{1A} partial agonists in depression: a composite analysis of bupirone in the treatment of depression. *J. Clin. Psychopharmacol.* **1990**, 10 (3 Suppl.), 67S–76S.
- ROBINSON, R. G., SCHULTZ, S. K., CASTILLO, C., KOPEL, T., KOSIER, J. T., NEWMAN, R. M., CURDUE, K., PETRACCA, G., STARKSTEIN, S. E., Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. *Am. J. Psychiatry* **2000**, 157 (3), 351–359.
- ROCCA, P., FONZO, V., RAVIZZA, L., ROCCA, G., SCOTTA, M., ZANALDA, E., BOGETTO, F., A comparison of paroxetine and amisulpride in the treatment of dysthymic disorder. *J. Affect Disord.* **2002a**, 70 (3), 313–317.
- ROCCA, P., MARCHIARO, L., RASETTI, R., RIVOIRA, E., BOGETTO, F., A comparison of paroxetine versus paroxetine plus amisulpride in the treatment of dysthymic disorder: efficacy and psychosocial outcomes. *Psychiatry Res.* **2002b**, 112 (2), 145–152.
- ROCCATAGLIATA, G., MURIALDO, G., ALBANO, C., GIOVALE, M., ZAULI, C., POLLERI, A., Neuroendocrinological and clinical data upon trazodone treatment in depressed patients. *Neuropsychobiology* **1982**, 8 (5), 259–268.
- RODRIGUES, A. M., RADOMINSKI, R. B., SUPILY HDE, L., DE ALMEIDA, S. M., NICLEWICZ, P. A., BOGUSZEWSKI, C. L., The cerebrospinal fluid/serum leptin ratio during pharmacological therapy for obesity. *J. Clin. Endocrinol. Metab.* **2002**, 87 (4), 1621–1626.
- ROGDE, S., HILBERG, T., TEIGE, B., Fatal combined intoxication with new antidepressants. Human cases and an experimental study of postmortem moclobemide redistribution. *Forensic Sci. Int.* **1999**, 100 (1–2), 109–116.
- ROGOZ, Z., DIABOGA, D., DZIEDZICKA-WASYLEWSKA, M., Effect of combined treatment with imipramine and amantadine on the central dopamine D₂ and D₃ receptors in rats. *J. Physiol. Pharmacol.* **2003a**, 54 (2), 257–270.
- ROGÓZ, Z., KUBERA, M., BASTA-KAIM, A., LASON, W., DUDEK, D., WRÓBEL, A., ZIEBA, A., Effect of combined treatment with imipramine and amantadine in patients with drug-resistant unipolar depression – clinical and immunological studies. Citation: *Eur. Neuropsychopharmacol.* **2003b**, 13 (4), S207.
- ROLLEMA, H., LU, Y., SCHMIDT, A. W., SPROUSE, J. S., ZORN, S. H., 5-HT (1A) receptor activation contributes to ziprasidone-induced dopamine release in the rat prefrontal cortex. *Biol. Psychiatry* **2000**, 48 (3), 229–237.
- ROMANELLI, F., ADLER, D. A., BUNGAY, K. M., Possible paroxetine-induced bruxism. *Ann. Pharmacother.* **1996**, 30 (11), 1246–1248.
- ROOSE, S. P., DALACK, G. W., GLASSMAN, A. H., WOODRING, S., WALSH, B. T., GIARDINA, E. G., Cardiovascular effects of bupropion in depressed patients with heart disease. *Am. J. Psychiatry* **1991**, 148 (4), 512–516.
- ROOSE, S. P., GLASSMAN, A. H., ATTIA, E., WOODRING, S., Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am. J. Psychiatry* **1994**, 151 (12), 1735–1739.
- ROOSE, S. P., GLASSMAN, A. H., ATTIA, E., WOODRING, S., GIARDINA, E. G., BIGGER, J. T. JR., Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am. J. Psychiatry* **1998a**, 155 (5), 660–665.
- ROOSE, S. P., GLASSMAN, A. H., GIARDINA, E. G., JOHNSON, L. L., WALSH, B. T., BIGGER, J. T. JR., Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. *J. Clin. Psychopharmacol.* **1987b**, 7 (4), 247–251.
- ROOSE, S. P., GLASSMAN, A. H., GIARDINA, E. G., WALSH, B. T., WOODRING, S., BIGGER, J. T., Tricyclic antidepressants in depressed patients with cardiac conduction disease. *Arch. Gen. Psychiatry* **1987a**, 44 (3), 273–275.
- ROOSE, S. P., LAGHRISSE-THODE, F., KENNEDY, J. S., NELSON, J. C., BIGGER, J. T. JR., POLLOCK, B. G., GAFFNEY, A., NARAYAN, M., FINKEL, M. S., McCAFFERTY, J., GERGEL, I., Comparison of paroxetine and nortriptyline in depressed patients

- with ischemic heart disease. *JAMA* **1998b**, 279 (4), 287–291.
- ROSEBOOM, P. H., KALIN, N. H., Neuropharmacology of venlafaxine. *Depress. Anxiety* **2000**, 12 (Suppl. 1), 20–29.
- ROSENBAUM, J. F., FAVA, M., HOOG, S. L., ASCROFT, R. C., KREBS, W. B., Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol. Psychiatry* **1998**, 44 (2), 77–87.
- ROSENBAUM, J. F., ZAJECKA, J., Clinical management of antidepressant discontinuation. *J. Clin. Psychiatry* **1997**, 58 (Suppl. 7), 37–40.
- ROSENSTEIN, D. L., NELSON, J. C., JACOBS, S. C., Seizures associated with antidepressants: a review. *J. Clin. Psychiatry* **1993**, 54 (8), 289–299.
- ROTHENHAUSLER, H. B., EHRENTAUF, S., VON DEGENFELD, G., WEIS, M., TICHY, M., KILGER, E., STOLL, C., SCHELLING, G., KAPFFHAMMER, H. P., Treatment of depression with methylphenidate in patients difficult to wean from mechanical ventilation in the intensive care unit. *J. Clin. Psychiatry* **2000**, 61 (10), 750–755.
- ROTHMAN, R. B., BAUMANN, M. H., Serotonin releasing agents. Neurochemical, therapeutic and adverse effects. *Pharmacol. Biochem. Behav.* **2002**, 71 (4), 825–836.
- ROTHSCHILD, A. J., Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. *Am. J. Psychiatry* **1995**, 152 (10), 1514–1516.
- ROTHSCHILD, R., QUITKIN, H. M., QUITKIN, F. M., STEWART, J. W., OCEPEK-WELIKSON, K., McGRATH, P. J., TRICAMO, E., A double-blind placebo-controlled comparison of phenelzine and imipramine in the treatment of bulimia in atypical depressives. *Int. J. Eat Disord.* **1994**, 15 (1), 1–9.
- ROUILLON, F., WARNER, B., PEZOUS, N., BISSERBE, J. C., Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. Milnacipran recurrence prevention study group. *Int. Clin. Psychopharmacol.* **2000a**, 15 (3), 133–140.
- ROWLAND, D. L., MYERS, L., CULVER, A., DAVIDSON, J. M., Bupropion and sexual function: a placebo-controlled prospective study on diabetic men with erectile dysfunction. *J. Clin. Psychopharmacol.* **1997**, 17 (5), 350–357.
- ROWLAND, M. J., BRANSOME, E. D. JR., HENDRY, L. B., Hypoglycemia caused by selegiline, an antiparkinsonian drug: can such side effects be predicted? *J. Clin. Pharmacol.* **1994**, 34 (1), 80–85.
- ROXANAS, M. G., MACHADO, J. F., Serotonin syndrome in combined moclobemide and venlafaxine ingestion. *Med. J. Aust.* **1998**, 168 (10), 523–524.
- ROXANAS, M. G., Mirtazapine-induced hyponatraemia. *Med. J. Aust.* **2003**, 179 (8), 453–454.
- RUBIO, G., SAN, L., LOPEZ-MUNOZ, F., ALAMO, C., Reboxetine adjunct for partial or nonresponders to antidepressant treatment. *J. Affect Disord.* **2004** (in press).
- RUDOLPH, R. L., DERIVAN, A. T., The safety and tolerability of venlafaxine hydrochloride: analysis of the clinical trials database. The safety and tolerability of venlafaxine hydrochloride: analysis of the clinical trials database. *J. Clin. Psychopharmacol.* **1996**, 16 (3 Suppl. 2), 54S–59S.
- RUETER, L. E., BLIER, P., Electrophysiological examination of the effects of sustained flibanserin administration on serotonin receptors in rat brain. *Br. J. Pharmacol.* **1999**, 126 (3), 627–638.
- RUGGIERI, S., DENARO, A., MECO, G., CARTA, A., STOCCHI, F., AGNOLI, A., Multicenter trial of L-deprenyl in Parkinson's disease. *Ital. J. Neurol. Sci.* **1986**, 7 (1), 133–137.
- RUSH, A. J., ARMITAGE, R., GILLIN, J. C., YONKERS, K. A., WINOKUR, A., MOLDOFSKY, H., VOGEL, G. W., KAPLITA, S. B., FLEMING, J. B., MONTPLAISIR, J., ERMAN, M. K., ALBALA, B. J., MCQUADE, R. D., Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. *Biol. Psychiatry* **1998**, 44 (1), 3–14.
- RUSH, A. J., BATEY, S. R., DONAHUE, R. M., ASCHER, J. A., CARMODY, T. J., METZ, A., Does pretreatment anxiety predict response to either bupropion SR or sertraline? *J. Affect Disord.* **2001**, 64 (1), 81–87.
- RUSH, A. J., SCHMID, R., HAIGHT, B., ZISOOK, S., ROCKETT, C., CARMODY, T., Does pretreatment anxiety or insomnia predict acute response to bupropion SR? *Eur.*

- Neuropsychopharmacol.* **2003**, *13* (4), S253.
- RUSSELL, J. L., Relatively low doses of cispripide in the treatment of nausea in patients treated with venlafaxine for treatment-refractory depression. *J. Clin. Psychopharmacol.* **1996**, *16* (1), 35–37.
- RUSO, S., BOON, J. C., KORF, J., HAAGSM, E. B., Mirtazapine for the treatment of interferon-induced psychopathology. *Gen. Hosp. Psychiatry* **2003**, *25*, 497.
- RYE, D. B., DIHENIA, B., BLIWISE, D. L., Reversal of atypical depression, sleepiness, and REM-sleep propensity in narcolepsy with bupropion. *Depress. Anxiety* **1998**, *7* (2), 92–95.
- SABELLI, H. C., FAWCETT, J., GUSOVSKY, F., JAVAD, J. I., WYNN, P., EDWARDS, J., JEFFRIES, H., KRAVITZ, H., Clinical studies on the phenylethylamine hypothesis of affective disorder: urine and blood phenylacetic acid and phenylalanine dietary supplements. *J. Clin. Psychiatry* **1986**, *47* (2), 66–70.
- SACHDEV, M., MILLER, W. C., RYAN, T., JOLLIS, J. G., Effect of fenfluramine-derivative diet pills on cardiac valves: a meta-analysis of observational studies. *Am. Heart J.* **2002**, *144* (6), 1065–1073.
- SAENZ DE TEJADA, I., WARE, J. C., BLANCO, R., PITTARD, J. T., NADIG, P. W., AZADZOI, K. M., KRANE, R. J., GOLDSTEIN, I., Pathophysiology of prolonged penile erection associated with trazodone use. *J. Urol.* **1991**, *145* (1), 60–64.
- SAGUD, M., PIVAC, N., MUCK-SELER, D., JAKOVljeVIC, M., MIHALJEVIC-PELES, A., KORSIC, M., Effects of sertraline treatment on plasma cortisol, prolactin and thyroid hormones in female depressed patients. *Neuropsychobiology* **2002**, *45* (3), 139–143.
- SAIZ-RUIZ, J., IBANEZ, A., DIAZ-MARSA, M., ARIAS, F., PADIN, J., MARTIN-CARRASCO, M., MONTES, J. M., FERRANDO, L., CARRASCO, J. L., MARTIN-BALLESTEROS, E., JORDA, L., CHAMORRO, L., Efficacy of venlafaxine in major depression resistant to selective serotonin reuptake inhibitors. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, *26* (6), 1129–1134.
- SALAH, R. S., CAMERON, O. G., Pilocarpine for anticholinergic adverse effects associated with desipramine treatment. *Am. J. Psychiatry* **1996**, *153* (4), 579.
- SALIN-PASCUAL, R. J., GALICIA-POLO, L., DRUCKER-COLIN, R., Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. *J. Clin. Psychiatry* **1997**, *58* (8), 348–350.
- SALOMON, R. M., RIPLEY, B., KENNEDY, J. S., JOHNSON, B., SCHMIDT, D., ZEITZER, J. M., NISHINO, S., Mignot E Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects. *Biol. Psychiatry* **2003**, *54* (2), 96–104.
- SALZMAN, C., JIMMERSON, D., VASILE, R., WATSKY, E., GERBER, J., Response to SSRI antidepressants correlates with reduction in plasma HVA: pilot study. *Biol. Psychiatry* **1993**, *34* (8), 569–571.
- SAMBUNARIS, A., HESSELINK, J. K., PINDER, R., PANAGIDES, J., STAHL, S. M., Development of new antidepressants. *J. Clin. Psychiatry* **1997**, *58* (Suppl. 6), 40–53.
- SANCHEZ, C., HYTTTEL, J., Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. *Cell Mol. Neurobiol.* **1999**, *19* (4), 467–489.
- SANDOR, P., BAKER, B., IRVINE, J., DORIAN, P., MCKESSOK, D., MENDLOWITZ, S., Effectiveness of fluoxetine and doxepin in treatment of melancholia in depressed patients. *Depress. Anxiety* **1998**, *7* (2), 69–72.
- SANNICANDRO, T. J., FARRAR, M. C., MARKOWITZ, J. S., Selective serotonin reuptake inhibitor-induced rash: case report and review of the literature. *Pharmacotherapy* **2002**, *22* (4), 516–518.
- SANSONE, R. A., SANSONE, L. A., Sertraline-induced hyperglycemia: case report. *Int. J. Psychiatry Med.* **2003**, *33* (1), 103–105.
- SAPER, J. R., LAKE, A. E., TEPPER, S. J., Nefazodone for chronic daily headache prophylaxis: an open-label study. *Headache* **2001**, *41* (5), 465–474.
- SARAF, M., SCHRADER, G., Seizure associated with sertraline. *Aust. NZ J. Psychiatry* **1999**, *33* (6), 944–945.
- SARGENT, P. A., SHARPLEY, A. L., WILLIAMS, C., GOODALL, E. M., COWEN, P. J., 5-HT_{2C} receptor activation decreases appetite and body weight in obese subjects. *Psychopharmacology (Berl.)* **1997**, *133* (3), 309–312.
- SAUNDERS, C., FERRER, J. V., SHI, L., CHEN, J., MERRILL, G., LAMB, M. E.,

- LEEB-LUNDBERG, L. M., CARVELLI, L., JAVITCH, J. A., GALLI, A., Amphetamine-induced loss of human dopamine transporter activity: an internalization-dependent and cocaine-sensitive mechanism. *Proc. Natl. Acad. Sci. USA* **2000**, *97* (12), 6850–6855.
- SAYAL, K. S., DUNCAN-McCONNELL, D. A., McCONNELL, H. W., TAYLOR, D. M., Psychotropic interactions with warfarin. *Acta Psychiatr. Scand.* **2000**, *102* (4), 250–255.
- SCARZELLA, L., SCARZELLA, R., MAILLAND, F., BERGAMASCO, B., Amineptine in the management of the depressive syndromes. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1985**, *9* (4), 429–439.
- SCHACHTER, M., PARKES, J. D., Fluvoxamine and clomipramine in the treatment of cataplexy. *J. Neurol. Neurosurg. Psychiatry* **1980**, *43* (2), 171–174.
- SCHATTNER, A., SKURNIK, Y., Fluoxetine-induced SIADH. *J. Am. Geriatr. Soc.* **1996**, *44* (11), 1413.
- SCHATZBERG, A. F., KREMER, C., RODRIGUES, H. E., MURPHY, G. M. JR., Mirtazapine vs. Paroxetine Study Group. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am. J. Geriatr. Psychiatry* **2002**, *10* (5), 541–550.
- SCHECHESTER, J. O., Treatment of dis-equilibrium and nausea in the SRI discontinuation syndrome. *J. Clin. Psychiatry* **1998**, *59* (8), 431–432.
- SCHILDKRAUT, J. J., The catecholamine hypothesis of affective disorders: a review of the supporting evidence. *Am. J. Psychiatry* **1965**, *122*, 509–521.
- SCHINKEL, A. H., MOL, C. A., WAGENAAR, E., VAN DEEMTER, L., SMIT, J. J., BORST, P., Multidrug resistance and the role of P-glycoprotein knockout mice. *Eur. J. Cancer* **1995**, *31A* (7–8), 1295–1298.
- SCHINKEL, A. H., WAGENAAR, E., MOL, C. A., VAN DEEMTER, L., P-glycoprotein in the blood–brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. *J. Clin. Invest.* **1996**, *97* (11), 2517–2524.
- SCHIWY, W., HEATH, W. R., DELINI-STULA, A., Therapeutic and side-effect profile of a selective and reversible MAO-A inhibitor, brofaromine. Results of dose-finding trials in depressed patients. *J. Neural Transm. Suppl.* **1989**, *28*, 33–44.
- SCHLIENGER, J. L., KAPFER, M. T., SINGER, L., STEPHAN, F., The action of clomipramine on thyroid function. *Horm. Metab. Res.* **1980**, *12* (9), 481–482.
- SCHLOSSER, R., WETZEL, H., DORR, H., ROSSBACH, W., HIEMKE, C., BENKERT, O., Effects of subchronic paroxetine administration on night-time endocrinological profiles in healthy male volunteers. *Psychoneuroendocrinology* **2000**, *25* (4), 377–388.
- SCHMAUSS, M., KAPFFHAMMER, H. P., MEYER, P., HOFF, P., Combined MAO-inhibitor and tri- (tetra) cyclic antidepressant treatment in therapy resistant depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1988a**, *12* (4), 523–532.
- SCHMAUSS, M., LAAKMANN, G., DIETERLE, D., Effects of alpha 2-receptor blockade in addition to tricyclic antidepressants in therapy-resistant depression. *J. Clin. Psychopharmacol.* **1988b**, *8* (2), 108–111.
- SCHNEIER, F. R., GARFINKEL, R., KENNEDY, B., CAMPEAS, R., FALLON, B., MARSHALL, R., O'DONNELL, L., HOGAN, T., LIEBOWITZ, M. R., Ondansetron in the treatment of panic disorder. *Anxiety* **1996**, *2* (4), 199–202.
- SCHRAMM, T. M., LAW FORD, B. R., MACDONALD, G. A., COOKSLEY, W. G., Sertraline treatment of interferon-alfa-induced depressive disorder. *Med. J. Aust.* **2000**, *173* (7), 359–361.
- SCHREIBER, S., BACKER, M. M., HERMAN, I., SHAMIR, D., BONIEL, T., PICK, C. G., The antinociceptive effect of trazodone in mice is mediated through both mu-opioid and serotonergic mechanisms. *Behav. Brain Res.* **2000**, *114* (1–2), 51–56.
- SCHUTTE, A. J., Vester-Blokland E: Factor analysis on onset of therapeutic effect of mirtazapine fast dissolving tablets versus sertraline. *Eur. Neuropsychopharmacol.* **2003**, *13* (4), S250.
- SCHWARTZ, G. E., SUCH, P., SCHATZBERG, A., The reboxetine study group. Reboxetine vs. venlafaxine in the treatment of severe major depression. 42nd Annual New Clinical Drug Evaluation Unit meeting, Boca Raton, Florida, **2002**.
- SCHWEITZER, I., BURROWS, G., TUCKWELL, V., POLONOWITA, A., FLYNN, P., GEORGE, T.,

- THEODOROS, M., MITCHELL, P., Sustained response to open-label venlafaxine in drug-resistant major depression. *J. Clin. Psychopharmacol.* **2001**, *21* (2), 185–189.
- SCRIABINE, A., Psychiatric drug discovery and development. Princeton, NJ, USA, June 23–24, *CNS Drug Rev.* **2003**, *9* (3), 319–326.
- SEEMAN, P., TALLERICO, T., Antipsychotic drugs which elicit little or no parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors. *Mol. Psychiatry* **1998**, *3* (2), 123–134.
- SEGRAVES, R. T., KAVOUSSI, R., HUGHES, A. R., BATEY, S. R., JOHNSTON, J. A., DONAHUE, R., ASCHER, J. A., Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. *J. Clin. Psychopharmacol.* **2000**, *20* (2), 122–128.
- SEIBYL, J. P., KRYSTAL, J. H., PRICE, L. H., CHARNEY, D. S., Use of yohimbine to counteract nortriptyline-induced orthostatic hypotension. *J. Clin. Psychopharmacol.* **1989**, *9* (1), 67–68.
- SEIDMAN, S. N., PESCE, V. C., ROOSE, S. P., High-dose sildenafil citrate for selective serotonin reuptake inhibitor-associated ejaculatory delay: open clinical trial. *J. Clin. Psychiatry* **2003**, *64* (6), 721–725.
- SEREBRUANY, V. L., GLASSMAN, A. H., MALININ, A. I., NEMEROFF, C. B., MUSSELMAN, D. L., VAN ZYL, L. T., FINKEL, M. S., KRISHNAN, K. R., GAFFNEY, M., HARRISON, W., CALIFF, R. M., O'CONNOR, C. M., Sertraline AntiDepressant Heart Attack Randomized Trial Study Group. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation* **2003**, *108* (8), 939–944.
- SERRETTI, A., LORENZI, C., CUSIN, C., ZANARDI, R., LATTUADA, E., ROSSINI, D., LILLI, R., PIROVANO, A., CATALANO, M., SMERALDI, E., SSRIs antidepressant activity is influenced by G beta 3 variants. *Eur. Neuropsychopharmacol.* **2003**, *13* (2), 117–122.
- SERRETTI, A., ZANARDI, R., CUSIN, C., ROSSINI, D., LILLI, R., LORENZI, C., LATTUADA, E., SMERALDI, E., No association between dopamine D (2) and D (4) receptor gene variants and antidepressant activity of two selective serotonin reuptake inhibitors. *Psychiatry Res.* **2001c**, *104* (3), 195–203.
- SERRETTI, A., ZANARDI, R., CUSIN, C., ROSSINI, D., LORENZI, C., SMERALDI, E., Tryptophan hydroxylase gene associated with paroxetine antidepressant activity. *Eur. Neuropsychopharmacol.* **2001b**, *11* (5), 375–380.
- SERRETTI, A., ZANARDI, R., ROSSINI, D., CUSIN, C., LILLI, R., SMERALDI, E., Influence of tryptophan hydroxylase and serotonin transporter genes on fluvoxamine antidepressant activity. *Mol. Psychiatry* **2001a**, *6* (5), 586–592.
- SETTLE, E. C. JR., Akathisia and sertraline. *J. Clin. Psychiatry* **1993**, *54* (8), 321.
- SETTLE, E. C., STAHL, S. M., BATEY, S. R., JOHNSTON, J. A., ASCHER, J. A., Safety profile of sustained-release bupropion in depression: results of three clinical trials. *Clin. Ther.* **1999**, *21* (3), 454–463.
- SHAPIRA, B., KINDLER, S., LERER, B., Medication outcome in ECT-resistant depression. *Convuls. Ther.* **1988**, *4* (3), 192–198.
- SHAPIRO, P. A., LESPERANCE, F., FRASURE-SMITH, N., O'CONNOR, C. M., BAKER, B., JIANG, J. W., DORIAN, P., HARRISON, W., GLASSMAN, A. H., An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (the SADHAT Trial). Sertraline Anti-Depressant Heart Attack Trial. *Am. Heart J.* **1999**, *137* (6), 1100–1106.
- SHAW, K., TURNER, J., DEL MAR, C., Are tryptophan and 5-hydroxytryptophan effective treatments for depression? A meta-analysis. *Aust. NZ J. Psychiatry* **2002a**, *36* (4), 488–491.
- SHAW, K., TURNER, J., DEL MAR, C., Tryptophan and 5-hydroxytryptophan for depression. *Cochrane Database Syst. Rev.* **2002b**, (1), CD003198.
- SHELTON, R. C., TOLLEFSON, G. D., TOHEN, M., STAHL, S., GANNON, K. S., JACOBS, T. G., BURAS, W. R., BYMASTER, F. P., ZHANG, W., SPENCER, K. A., FELDMAN, P. D., MELTZER, H. Y., A novel Augmen-

- tation strategy for Treating Resistant Major Depression. *Am. J. Psychiatry* **2001**, *158* (1), 131–134.
- SHELTON, R. C., WINN, S., EKHATORE, N., LOOSEN, P. T., The effects of antidepressants on the thyroid axis in depression. *Biol. Psychiatry* **1993**, *33* (2), 120–126.
- SHIAH, I. S., YATHAM, L. N., SRISURAPANONT, M., LAM, R. W., TAM, E. M., ZIS, A. P., Does the addition of pindolol accelerate the response to electroconvulsive therapy in patients with major depression? A double-blind, placebo-controlled pilot study. *J. Clin. Psychopharmacol.* **2000**, *20* (3), 373–378.
- SHIHABUDDIN, L., RAPPORT, D., Sertraline and extrapyramidal side effects. *Am. J. Psychiatry* **1994**, *151* (2), 288.
- SHORE, P. A., SILVER, S. L., BRODIE, B. B., Interaction of reserpine, serotonin, and lysergic acid diethylamine in brain. *Science* **1955**, *122*, 284–285.
- SHRIVASTAVA, R. K., COHN, C., CROWDER, J., DAVIDSON, J., DUNNER, D., FEIGHNER, J., KIEV, A., PATRICK, R., Long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression. *J. Clin. Psychopharmacol.* **1994**, *14* (5), 322–329.
- SHRIVASTAVA, R. K., SHRIVASTAVA, S., OVERWEG, N., SCHMITT, M., Amantadine in the treatment of sexual dysfunction associated with selective serotonin reuptake inhibitors. *J. Clin. Psychopharmacol.* **1995**, *15* (1), 83–84.
- SIDDIQUI, M. A., KHAN, I. A., Nefazodone-associated torsade de pointes. *Int. J. Cardiol.* **2004**, *93* (1), 85–86.
- SIMON, G. E., HEILIGENSTEIN, J. H., GROTHAUS, L., KATON, W., REVICKI, D., Should anxiety and insomnia influence antidepressant selection: a randomized comparison of fluoxetine and imipramine. *J. Clin. Psychiatry* **1998**, *59* (2), 49–55.
- SINDRUP, S. H., JENSEN, T. S., Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* **1999**, *83* (3), 389–400.
- SINGER, P. P., JONES, G. R., An uncommon fatality due to moclobemide and paroxetine. *J. Anal. Toxicol.* **1997**, *21* (6), 518–520.
- SLAWSON, M. H., TACCOGNO, J. L., FOLTZ, R. L., MOODY, D. E., Quantitative analysis of selegiline and three metabolites (N-desmethyl-selegiline, methamphetamine, and amphetamine) in human plasma by high-performance liquid chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry. *J. Anal. Toxicol.* **2002**, *26* (7), 430–437.
- SLEMMER, J. E., MARTIN, B. R., DAMAJ, M. I., Bupropion is a nicotinic antagonist. *J. Pharmacol. Exp. Ther.* **2000**, *295* (1), 321–327.
- SMALL, J. G., KELLAMS, J. J., DENNIS, J. L., MILSTEIN, V., Comparison of molidone and tranlycypromine in the treatment of refractory depression. *J. Clin. Pharmacol.* **1981**, *21* (8–9), 351–358.
- SMERALDI, E., ZANARDI, R., BENEDETTI, F., DI BELLA, D., PEREZ, J., CATALANO, M., Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Mol. Psychiatry* **1998**, *3*, 508–511.
- SMERALDI, E., Amisulpride versus fluoxetine in patients with dysthymia or major depression in partial remission: a double-blind, comparative study. *J. Affect Disord.* **1998**, *48* (1), 47–56.
- SMITH, D. L., WENEGRAT, B. G., A case report of serotonin syndrome associated with combined nefazodone and fluoxetine. *J. Clin. Psychiatry* **2000**, *61* (2), 146.
- SMITH, W. T., LONDBORG, P. D., GLAUDIN, V., PAINTER, J. R., Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. *Am. J. Psychiatry* **1998**, *155* (10), 1339–1345.
- SMULEVICH, A. B., DROBIJEV, M. Y., ILINA, N. A., Mirtazapine in treatment of depression in patients with ischaemic heart disease. *Eur. Neuropsychopharmacol.* **2001**, *11* (3), S205.
- SOGAARD, J., LANE, R., LATIMER, P., BEHNKE, K., CHRISTIANSEN, P. E., NIELSEN, B., RAVINDRAN, A. V., REESAL, R. T., GOODWIN, D. P., A 12-week study comparing moclobemide and sertraline in the treatment of outpatients with atypical depression. *J. Psychopharmacol.* **1999**, *13* (4), 406–414.
- SOMMER, M., DIETERICH, A., KRAUSE, C., RUTHER, E., WILTFANG, J., Subclinical

- pancreatitis related to mirtazapine – a case report. *Pharmacopsychiatry* **2001**, 34 (4), 158–159.
- SONAWALLA, S., CHAKRABORTY, N., PARIKH, R., Treatment of major depression and anxiety with the selective serotonin re-uptake enhancer tianeptine in the outpatient psychiatric care setting of India. *J. Indian Med. Assoc.* **2003**, 101 (2), 116–117, 124.
- SONAWALLA, S. B., DECECCO, L. M., GORDON, J. A., TEDLOW, J. R., MISCHOULON, D., ROSENBAUM, J. F., FAVA, M., Cholesterol levels decrease with fluoxetine treatment of MDD. 154th Annual Meeting of the American Psychiatric Association, New Orleans, Louisiana, **2001b**.
- SONAWALLA, S. B., HUTCHINS, A. C., DELGADO, M. L., JOHNSON, M. W., WORTHINGTON, J. J., ALPERT, J. E., FAVA, M., Onset of response to fluoxetine as assessed by the symptom questionnaire. American Psychiatric Association Annual Meeting, New Orleans, **2001a**.
- SONAWALLA, S. B., PAPAPOSTAS, G. I., PETERSEN, T. J., YEUNG, A. S., SMITH, M. M., SICKINGER, A. H., GORDON, J., ISRAEL, J. A., TEDLOW, J. R., LAMON-FAVA, S., FAVA, M., Elevated cholesterol levels associated with nonresponse to fluoxetine treatment in major depressive disorder. *Psychosomatics* **2002**, 43 (4), 310–316.
- SONNTAG, A., ROTHE, B., GULDNER, J., YASSOURIDIS, A., HOLDSBOER, F., STEIGER, A., Trimipramine and imipramine exert different effects on the sleep EEG and on nocturnal hormone secretion during treatment of major depression. *Depression* **1996**, 4 (1), 1–13.
- SORKIN, E. M., HEEL, R. C., Guanfacine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of hypertension. *Drugs* **1986**, 31 (4), 301–336.
- SPIER, S. A., Use of bupropion with SRIs and venlafaxine. *Depress. Anxiety* **1998**, 7 (2), 73–75.
- SPIGSET, O., HEDENMALM, K., DAHL, M. L., WIHOLM, B. E., DAHLQVIST, R., Seizures and myoclonus associated with antidepressant treatment: assessment of potential risk factors, including CYP2D6 and CYP2C19 polymorphisms, and treatment with CYP2D6 inhibitors. *Acta Psychiatr. Scand.* **1997**, 96 (5), 379–384.
- SPIGSET, O., MJORNDAL, T., The effect of fluvoxamine on serum prolactin and serum sodium concentrations: relation to platelet 5-HT_{2A} receptor status. *J. Clin. Psychopharmacol.* **1997**, 17 (4), 292–297.
- SPIGSET, O., Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. *Drug Saf.* **1999**, 20 (3), 277–287.
- SPINA, E., BIRGERSSON, C., VON BAHR, C., ERICSSON, O., MELLSTROM, B., STEINER, E., SJOQVIST, F., Phenotypic consistency in hydroxylation of desmethylimipramine and debrisoquine in healthy subjects and in human liver microsomes. *Clin. Pharmacol. Ther.* **1984**, 36 (5), 677–682.
- SPIVEY, K. M., WAIT, C. M., Perioperative seizures and fluvoxamine. *Br. J. Anaesth.* **1993**, 71 (2), 321.
- SPORN, J., GHAEMI, S. N., SAMBUR, M. R., RANKIN, M. A., RECHT, J., SACHS, G. S., ROSENBAUM, J. F., FAVA, M., Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. *Ann. Clin. Psychiatry* **2000**, 12 (3), 137–140.
- STABL, M., KASAS, A., BLAJEV, B., BAJETTA, G., ZOCHLING, R., HOLDSBOER-TRACHSLER, E., REALINI, R., SCHAUBLIN-LOIDL, M., A double-blind comparison of moclobemide and thioridazine versus moclobemide and placebo in the treatment of refractory, severe depression. *J. Clin. Psychopharmacol.* **1995**, 15 (4 Suppl. 2), 41S–45S.
- STAHL, S. M., KAISER, L., ROESCHEN, J., KEPPEL HESSELINK, J. M., ORAZEM, J., Effectiveness of ipsapirone, a 5-HT_{1A} partial agonist, in major depressive disorder: support for the role of 5-HT_{1A} receptors in the mechanism of action of serotonergic antidepressants. *Int. J. Neuropsychopharmacol.* **1998**, 1 (1), 11–18.
- STANISLAV, S. W., CHILDS, N. L., Dystonia associated with sertraline. *J. Clin. Psychopharmacol.* **1999**, 19 (1), 98–100.
- STAUFENBERG, E. F., TANTAM, D., Malignant hyperpyrexia syndrome in combined treatment. *Br. J. Psychiatry* **1989**, 154, 577–578.
- STEELE, T. E., HOWELL, E. F., Cyproheptadine for imipramine-induced anorgasmia.

- J. Clin. Psychopharmacol.* **1986**, 6 (5), 326–327.
- STEEN, A., DEN BOER, J. A., A double-blind six months comparative study of milnacipran and clomipramine in major depressive disorder. *Int. Clin. Psychopharmacol.* **1997**, 12 (5), 269–281.
- STEFANIS, C. N., ALEVIZOS, B., MARKIANOS, M., HATZIMANOLIS, J., Effect of moclobemide on clinical and neurochemical variables in depressed patients (preliminary findings). *J. Neural Transm. Suppl.* **1988**, 26, 87–95.
- STEIGER, A., BENKERT, O., HOLSBOER, F., Effects of long-term treatment with the MAO-A inhibitor moclobemide on sleep EEG and nocturnal hormonal secretion in normal men. *Neuropsychobiology* **1994**, 30 (2–3), 101–105.
- STEIGER, A., HOLSBOER, F., BENKERT, O., Effects of brofaremine (CGP 11 305A), a short-acting, reversible, and selective inhibitor of MAO-A on sleep, nocturnal penile tumescence and nocturnal hormonal secretion in three healthy volunteers. *Psychopharmacology (Berl.)* **1987**, 92 (1), 110–114.
- STEIGER, A., HOLSBOER, F., Nocturnal secretion of prolactin and cortisol and the sleep EEG in patients with major endogenous depression during an acute episode and after full remission. *Psychiatry Res.* **1997**, 72 (2), 81–88.
- STEINER, W., FONTAINE, R., Toxic reaction following the combined administration of fluoxetine and L-tryptophan: five case reports. *Biol. Psychiatry* **1986**, 21 (11), 1067–1071.
- STERN, W. C., HARTO-TRUAX, N., BAUER, N., Efficacy of bupropion in tricyclic-resistant or intolerant patients. *J. Clin. Psychiatry* **1983**, 44 (5 Pt 2), 148–152.
- STERNBACH, H., Venlafaxine-induced galactorrhea. *J. Clin. Psychopharmacol.* **2003**, 23 (1), 109–110.
- STEUR, E. N., Increase of Parkinson disability after fluoxetine medication. *Neurology* **1993**, 43 (1), 211–213.
- STEWART, D. E., Hepatic adverse reactions associated with nefazodone. *Can. J. Psychiatry* **2002**, 47 (4), 375–377.
- STEWART, J. W., HALBREICH, U., Plasma melatonin levels in depressed patients before and after treatment with antidepressant medication. *Biol. Psychiatry* **1989**, 25 (1), 33–38.
- STEWART, J. W., HARRISON, W., QUITKIN, F., LIEBOWITZ, M. R., Phenelzine-induced pyridoxine deficiency. *J. Clin. Psychopharmacol.* **1984**, 4 (4), 225–226.
- STEWART, J. W., McGRATH, P. J., QUITKIN, F. M., HARRISON, W., MARKOWITZ, J., WAGER, S., LIEBOWITZ, M. R., Relevance of DMS-III depressive subtype and chronicity of antidepressant efficacy in atypical depression. Differential response to phenelzine, imipramine, and placebo. *Arch. Gen. Psychiatry* **1989**, 46 (12), 1080–1087.
- STEWART, J. W., McGRATH, P. J., QUITKIN, F. M., Can mildly depressed outpatients with atypical depression benefit from antidepressants? *Am. J. Psychiatry* **1992**, 149 (5), 615–619.
- STEWART, J. W., McGRATH, P. J., QUITKIN, F. M., Do age of onset and course of illness predict different treatment outcome among DSM IV depressive disorders with atypical features? *Neuropsychopharmacology* **2002**, 26 (2), 237–245.
- STINSON, J. C., MURPHY, C. M., ANDREWS, J. F., TOMKIN, G. H., An assessment of the thermogenic effects of fluoxetine in obese subjects. *Int. J. Obes.* **1992**, 16, 391–395.
- STOLL, A. L., PILLAY, S. S., DIAMOND, L., WORKUM, S. B., COLE, J. O., Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J. Clin. Psychiatry* **1996**, 57 (2), 72–76.
- STORMER, E., VON MOLTKE, L. L., PERLOFF, M. D., GREENBLATT, D. J., P-glycoprotein interactions of nefazodone and trazodone in cell culture. *J. Clin. Pharmacol.* **2001**, 41 (7), 708–714.
- STRAUSS, W. L., DAGER, S. R., Magnetization transfer of fluoxetine in the human brain using fluorine magnetic resonance spectroscopy. *Biol. Psychiatry* **2001**, 49 (9), 798–802.
- STRAUSS, W. L., LAYTON, M. E., DAGER, S. R., Brain elimination half-life of fluvoxamine measured by ¹⁹F magnetic resonance spectroscopy. *Am. J. Psychiatry* **1998**, 155 (3), 380–384.
- STRAUSS, W. L., LAYTON, M. E., HAYES, C. E., DAGER, S. R., ¹⁹F magnetic resonance

- spectroscopy investigation *in vivo* of acute and steady-state brain fluvoxamine levels in obsessive-compulsive disorder. *Am. J. Psychiatry* **1997**, *154* (4), 516–522.
- STRAUSS, W. L., UNIS, A. S., COWAN, C., DAWSON, G., DAGER, S. R., Fluorine magnetic resonance spectroscopy measurement of brain fluvoxamine and fluoxetine in pediatric patients treated for pervasive developmental disorders. *Am. J. Psychiatry* **2002**, *159* (5), 755–760.
- STRAYHORN, J. M., NASH, J. L., Frightening dreams and dosage schedule of tricyclic and neuroleptic drugs *J. Nerv. Ment. Dis.* **1978**, *166* (12), 878–880.
- STRIK, J. J., HONIG, A., LOUSBERG, R., CHERIEX, E. C., VAN PRAAG, H. M., Cardiac side-effects of two selective serotonin reuptake inhibitors in middle-aged and elderly depressed patients. *Int. Clin. Psychopharmacol.* **1998**, *13* (6), 263–267.
- STRIK, J. J., HONIG, A., LOUSBERG, R., LOUSBERG, A. H., CHERIEX, E. C., TUYNMAN-QUA, H. G., KUIJPERS, P. M., WELLENS, H. J., VAN PRAAG, H. M., Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. *Psychosom. Med.* **2000**, *62* (6), 783–789.
- STROUSE, T. B., FAIRBANKS, L. A., SKOTZKO, C. E., FAWZY, F. I., Fluoxetine and cyclosporine in organ transplantation. Failure to detect significant drug interactions or adverse clinical events in depressed organ recipients. *Psychosomatics* **1996**, *37* (1), 23–30.
- STRYJER, R., STROUS, R. D., SHAKED, G., BAR, F., FELDMAN, B., KOTLER, M., POLAK, L., ROSENZWAIG, S., WEIZMAN, A., Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int. Clin. Psychopharmacol.* **2003**, *18* (2), 93–96.
- SUCKOW, R. F., ZHANG, M. F., COOPER, T. B., Enantiomeric determination of the phenylmorpholinol metabolite of bupropion in human plasma using coupled achiral–chiral liquid chromatography. *Biomed. Chromatogr.* **1997**, *11* (3), 174–179.
- SUHARA, T., TAKANO, A., SUDO, Y., ICHIMIYA, T., INOUE, M., YASUNO, F., IKOMA, Y., OKUBO, Y., High levels of serotonin transporter occupancy with low-dose clomipramine in comparative occupancy study with fluvoxamine using positron emission tomography. *Arch. Gen. Psychiatry* **2003**, *60* (4), 386–391.
- SUNDERLAND, T., COHEN, R. M., MOLCHAN, S., LAWLOR, B. A., MELLOW, A. M., NEWHOUSE, P. A., TARIOT, P. N., MUELLER, E. A., MURPHY, D. L., High-dose selegiline in treatment-resistant older depressive patients. *Arch. Gen. Psychiatry* **1994**, *51* (8), 607–615.
- SUSSMAN, N., GINSBERG, D. L., BIKOFF, J., Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. *J. Clin. Psychiatry* **2001**, *62* (4), 256–260.
- SUZUKI, E., YOSHIDA, Y., SHIBUYA, A., MIYAOKA, H., Nitric oxide involvement in depression during interferon-alpha therapy. *Int. J. Neuropsychopharmacol.* **2003**, *6* (4), 415–419.
- SWENSON, J. R., O'CONNOR, C. M., BARTON, D., VAN ZYL, L. T., SWEDBERG, K., FORMAN, L. M., GAFFNEY, M., GLASSMAN, A. H., Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group. Influence of depression and effect of treatment with sertraline on quality of life after hospitalization for acute coronary syndrome. *Am. J. Cardiol.* **2003**, *92* (11), 1271–1276.
- SZABADI, E., Doxazosin for reboxetine-induced urinary hesitancy. *Br. J. Psychiatry* **1998**, *173*, 441–442.
- SZABO, Z., ARGYELAN, M., KANYO, B., JUHASZ, A., KOVACS, Z. S., PAVICS, L., JANKA, Z., The effects of bupropion on the activity of dopamine transporter in depression – preliminary results. *Eur. Neuropsychopharmacol.* **2003**, *13* (4), S210.
- SZELENYI, A., ALBRECHT, J., Tranylcypromine abuse associated with an isolated thrombocytopenia. *Pharmacopsychiatry* **1998**, *31* (6), 238–240.
- TAKAHASHI, H., YOSHIDA, K., HIGUCHI, H., SHIMIZU, T., INOUE, T., KOYAMA, T., Addition of a dopamine agonist, cabergoline, to a serotonin–noradrenalin reuptake inhibitor, milnacipran as a therapeutic option in the treatment of refractory depression: two case reports.

- Clin. Neuropharmacol.* **2003**, 26 (5), 230–232.
- TAKAHASHI, H., YOSHIDA, K., ITO, K., SATO, K., KAMATA, M., HIGUCHI, H., SHIMIZU, T., ITO, K., INOUE, K., TEZUKA, T., SUZUKI, T., OHKUBO, T., SUGAWARA, K., No association between the serotonergic polymorphisms and incidence of nausea induced by fluvoxamine treatment. *Eur. Neuropsychopharmacol.* **2002**, 12 (5), 477–481.
- TAMAM, L., OZPOYRAZ, N., Discontinuation symptoms associated with nefazodone. *J. Psychopharmacol.* **2003**, 17 (4), 447–450.
- TANI, K., TAKEI, N., KAWAI, M., SUZUKI, K., SEKINE, Y., TOYODA, T., MINABE, Y., MORI, N., Augmentation of milnacipran by risperidone in treatment for major depression. *Int. J. Neuropsychopharmacol.* **2004**, 7 (1), 55–58.
- TAVORMINA, G., COREA, S., CITRON, A., Reboxetine utilization as an add-on therapy to SSRI in treatment-resistant depression. *Eur. Neuropsychopharmacol.* **2002**, 12 (3), S178.
- TAYLOR, D. P., CARTER, R. B., EISON, A. S., MULLINS, U. L., SMITH, H. L., TORRENTE, J. R., WRIGHT, R. N., Yocca, F. D., Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. *J. Clin. Psychiatry* **1995**, 56 (Suppl. 6), 3–11.
- TAYLOR, F. B., PRATHER, M. R., The efficacy of nefazodone augmentation for treatment-resistant depression with anxiety symptoms or anxiety disorder. *Depress. Anxiety* **2003**, 18 (2), 83–88.
- TAYLOR, F. B., RUSSO, J., Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. *J. Clin. Psychopharmacol.* **2001**, 21 (2), 223–228.
- TERSTAPPEN, G. C., PELLACANI, A., ALDEGHERI, L., GRAZIANI, F., CARIGNANI, C., PULA, G., VIRGINIO, C., The antidepressant fluoxetine blocks the human small conductance calcium-activated potassium channels SK1, SK2 and SK3. *Neurosci. Lett* **2003**, 346 (1–2), 85–88.
- TESCHEMACHER, A. G., SEWARD, E. P., HANCOX, J. C., WITCHEL, H. J., Inhibition of the current of heterologously expressed HERG potassium channels by imipramine and amitriptyline. *Br. J. Pharmacol.* **1999**, 128 (2), 479–485.
- TESEI, S., ANTONINI, A., CANESI, M., ZECCHINELLI, A., MARIANI, C. B., PEZZOLI, G., Tolerability of paroxetine in Parkinson's disease: a prospective study. *Mov. Disord.* **2000**, 15 (5), 986–989.
- THASE, M., FAVA, M., HOLLANDER, S., BOYLE, K., GUBERTINI, M., Analysis of gepirone-ER on the Bech-6 and Individual HamD-17 Item Scores. 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, **2003a**.
- THASE, M. E., Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *J. Clin. Psychiatry* **1998**, 59 (10), 502–508.
- THASE, M. E., BARTLETT, C., Reboxetine does not cause weight gain during long-term therapy. *Eur. Neuropsychopharmacol.* **2001**, 11 (3), S215.
- THASE, M. E., BLOMGREN, S. L., BIRKETT, M. A., APTER, J. T., TEPNER, R. G., Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. *J. Clin. Psychiatry* **1997**, 58 (1), 16–21.
- THASE, M. E., FERGUSON, J. M., LYDIARD, R. B., WILCOX, C. S., Citalopram treatment of paroxetine-intolerant depressed patients. *Depress. Anxiety* **2002b**, 16 (3), 128–133.
- THASE, M. E., FRANK, E., MALLINGER, A. G., HAMER, T., KUPFER, D. J., Treatment of imipramine-resistant recurrent depression, III: Efficacy of monoamine oxidase inhibitors. *J. Clin. Psychiatry* **1992**, 53 (1), 5–11.
- THASE, M. E., HAIGHT, B., ROCKETT, C., ASGHARIAN, A., MODELL, M., Lack of effect of bupropion SR on blood pressure in hypertensive patients. 43rd Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, **2003c**.
- THASE, M. E., KREMER, C., RODRIGUES, H., Mirtazapine versus sertraline after SSRI non-response. Presented at the 41st Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, Florida, **2001**.
- THASE, M. E., RUSH, A. J., HOWLAND, R. H., KORNSTEIN, S. G., KOCSIS, J. H., GELENBERG, A. J., SCHATZBERG, A. F., KORAN, L. M., KELLER, M. B., RUSSELL, J. M., HIRSCHFELD, R. M., LAVANGE, L. M., KLEIN, D. N., FAWCETT, J.,

- HARRISON, W., Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch. Gen. Psychiatry* **2002a**, *59* (3), 233–239.
- THASE, M. E., TRIVEDI, M. H., RUSH, A. J., MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* **1995**, *12* (3), 185–219.
- THASE, M. E., WANG, Y., RICHARD, N., MITTON, M., HAIGHT, B., GOODALE, E., Remission rates following therapy with bupropion or selective serotonin reuptake inhibitors. *Eur. Neuropsychopharmacol.* **2003b**, *13* (4), S259.
- THAYSEN, P., BJERRE, M., KRAGH-SØRENSEN, P., MØLLER, M., PETERSEN, O. L., KRISTENSEN, C. B., GRAM, L. F., Cardiovascular effect of imipramine and nortriptyline in elderly patients. *Psychopharmacology (Berl.)* **1981**, *74* (4), 360–364.
- THEDENAT, B., LOCHE, F., ALBES, B., MARGUERY, M. C., BAZEX, J., Acute generalized exanthematous pustulosis with photodistribution pattern induced by sertraline. *Dermatology* **2001**, *203* (1), 87–88.
- THEOHAR, C., FISCHER-CORNELISSEN, K., BROSCHE, H., FISCHER, E., PETROVIC, D., A comparative, multicenter trial between bromocriptine and amitriptyline in the treatment of endogenous depression. *Arzneimittelforschung* **1982**, *32*, 783–787.
- THIRUMALAI, S. S., SHUBIN, R. A., The use of citalopram in resistant cataplexy. *Sleep Med.* **2000**, *1* (4), 313–316.
- THOMAS, D., GUT, B., WENDT-NORDAHL, G., KIEHN, J., The antidepressant drug fluoxetine is an inhibitor of human ether-a-go-go-related gene (HERG) potassium channels. *J. Pharmacol. Exp. Ther.* **2002**, *300* (2), 543–548.
- THOMPSON, J. W. JR., WARE, M. R., BLASHFIELD, R. K., Psychotropic medication and priapism: a comprehensive review. *J. Clin. Psychiatry* **1990**, *51* (10), 430–433.
- TIGNOL, J., PUJOL-DOMENECH, J., CHARTRES, J. P., LEGER, J. M., PLETAN, Y., TONELLI, I., TOURNOUX, A., PEZOUS, N., Double-blind study of the efficacy and safety of milnacipran and imipramine in elderly patients with major depressive episode. *Acta Psychiatr. Scand.* **1998**, *97* (2), 157–165.
- TIMMINGS, P., LAMONT, D., Intrahepatic cholestasis associated with moclobemide leading to death. *Lancet* **1996**, *347* (9003), 762–763.
- TIPERMAS, A., GILMAN, H. E., RUSSAKOFF, L. M., A case report of leukopenia associated with phenelzine. *Am. J. Psychiatry* **1984**, *141* (6), 806–807.
- TOME, M. B., ISAAC, M. T., HARTE, R., HOLLAND, C., Paroxetine and pindolol: a randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. *Int. Clin. Psychopharmacol.* **1997**, *12* (2), 81–89.
- TOOFANNY, N., MADDENS, M. E., Reversible penile priapism associated with nefazodone. *J. Am. Geriatr. Soc.* **2002**, *50* (9), 1610–1611.
- TRABERT, W., HOHAGEN, F., WINKELMANN, G., BERGER, M., A seizure, and electroencephalographic signs of a lowered seizure threshold, associated with fluvoxamine treatment of obsessive-compulsive disorder. *Pharmacopsychiatry* **1995**, *28* (3), 95–97.
- TRESCOLI-SERRANO, C., SMITH, N. K., Sertraline-induced agranulocytosis. *Postgrad. Med. J.* **1996**, *72* (849), 446.
- TRIPATHI, A., GREENBERGER, P. A., Bupropion hydrochloride induced serum sickness-like reaction. *Ann. Allergy Asthma Immunol.* **1999**, *83* (2), 165–166.
- TRIVEDI, M. H., RUSH, A. J., CARMODY, T. J., DONAHUE, R. M., BOLDEN-WATSON, C., HOUSER, T. L., METZ, A., Do bupropion SR and sertraline differ in their effects on anxiety in depressed patients? *J. Clin. Psychiatry* **2001**, *62* (10), 776–781.
- TRUE, B. L., PERRY, P. J., BURNS, E. A., Profound hypoglycemia with the addition of a tricyclic antidepressant to maintenance sulfonylurea therapy. *Am. J. Psychiatry* **1987**, *144* (9), 1220–1221.
- TSAT, S. J., CHENG, C. Y., YU, Y. W., CHEN, T. J., HONG, C. J., Association study of a brain-derived neurotrophic-factor genetic polymorphism and major depressive disorders, symptomatology, and antidepressant response. *Am. J. Med. Genet.* **2003**, *123B* (1), 19–22.
- TSAPAKIS, E. M., CHECKLEY, S., KERWIN, R. W., ATTCHISON, K. J., Association between the serotonin transporter linked polymorphic region gene (5HTTLPR)

- and response to tricyclic antidepressants (TCAs). *Eur. Neuropsychopharmacol.* **2003**, *13* (4), S250.
- TURKEL, S. B., NADALA, J. G., WINCOR, M. Z., Possible serotonin syndrome in association with 5-HT (3) antagonist agents. *Psychosomatics* **2001**, *42* (3), 258–260.
- TYRER, P., Clinical effects of abrupt withdrawal from tri-cyclic antidepressants and monoamine oxidase inhibitors after long-term treatment. *J. Affect Disord.* **1984**, *6* (1), 1–7.
- UBOGU, E. E., KATIRJI, B., Mirtazapine-induced serotonin syndrome. *Clin. Neuropharmacol.* **2003**, *26* (2), 54–57.
- UEDA, N., YOSHIMURA, R., SHINKAI, K., TERAU, T., NAKAMURA, J. L., Characteristics of fluvoxamine-induced nausea. *Psychiatry Res.* **2001**, *104* (3), 259–264.
- UHR, M., GRAUER, M. T., HOLSBOER, F., Differential enhancement of antidepressant penetration into the brain in mice with abcb1ab (mdr1ab) P-glycoprotein gene disruption. *Biol. Psychiatry* **2003**, *54* (8), 840–846.
- UHR, M., GRAUER, M. T., abcb1ab P-glycoprotein is involved in the uptake of citalopram and trimipramine into the brain of mice. *J. Psychiatr. Res.* **2003**, *37* (3), 179–185.
- UHR, M., STECKLER, T., YASSOURIDIS, A., HOLSBOER, F., Penetration of amitriptyline, but not of fluoxetine, into brain is enhanced in mice with blood–brain barrier deficiency due to mdr1a P-glycoprotein gene disruption. *Neuropsychopharmacology* **2000**, *22* (4), 380–387.
- URBAN, R. J., VELDHUIS, J. D., A selective serotonin reuptake inhibitor, fluoxetine hydrochloride, modulates the pulsatile release of prolactin in postmenopausal women. *Am. J. Obstet. Gynecol.* **1991**, *164* (1 Pt 1), 147–152.
- VAN AMERONGEN, M., MANCINI, C., PIPE, B., CAMPBELL, M., OAKMAN, J., Topiramate treatment for SSRI-induced weight gain in anxiety disorders. *J. Clin. Psychiatry* **2002**, *63* (11), 981–984.
- VAN AMERONGEN, A. P., FERREY, G., TOURNOUX, A., A randomised, double-blind comparison of milnacipran and imipramine in the treatment of depression. *J. Affect Disord.* **2002**, *72* (1), 21–31.
- VAN AMERONGEN, P., Double-blind clinical trial of the antidepressant action of amineptine. *Curr. Med. Res. Opin.* **1979**, *6* (2), 93–100.
- VAN DE MERWE, T. J., SILVERSTONE, T., ANKIER, S. I., WARRINGTON, S. J., TURNER, P., A double-blind non-crossover placebo-controlled study between group comparison of trazodone and amitriptyline on cardiovascular function in major depressive disorder. *Psychopathology* **1984**, *17* (Suppl. 2), 64–76.
- VAN DE VIJVER, D. A., ROOS, R. A., JANSEN, P. A., PORSIUS, A. J., DE BOER, A., Start of a selective serotonin reuptake inhibitor (SSRI) and increase of antiparkinsonian drug treatment in patients on levodopa. *Br. J. Clin. Pharmacol.* **2002**, *54* (2), 168–170.
- VAN DER FLIER, S., VESTER-BLOKLAND, E., Sexual function of patients with major depression treated with mirtazapine fast dissolving tablets or sertraline. *Eur. Neuropsychopharmacol.* **2003**, *13* (4), S251.
- VAN PRAAG, H. M., Management of depression with serotonin precursors. *Biol. Psychiatry* **1981**, *16* (3), 291–310.
- VAN PRAAG, H. M., LEMUS, C., KAHN, R., The pitfalls of serotonin precursors as challengers in hormonal probes of central serotonin activity. *Psychopharmacol. Bull.* **1986**, *22* (3), 565–570.
- VAN WALRAVEN, C., MAMDANI, M. M., WELLS, P. S., Williams JI Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* **2001**, *323* (7314), 655–658.
- VANPEE, D., LALOYLAUX, P., GILLET, J. B., Seizure and hyponatraemia after overdose of trazadone. *Am. J. Emerg. Med.* **1999**, *17* (4), 430–431.
- VAUTERIN, C., Bazot M.A double-blind controlled trial of amineptine versus trimipramine in depression. *Curr. Med. Res. Opin.* **1979**, *6* (2), 101–106.
- VEEFKIND, A. H., HAFFMANS, P. M., HOENCAMP, E., Venlafaxine serum levels and CYP2D6 genotype. *Ther. Drug Monit.* **2000**, *22* (2), 202–208.
- VERCOULEN, J. H., SWANINK, C. M., ZITMAN, F. G., et al. Randomized double-blind placebo-controlled study of fluoxetine in

- chronic fatigue syndrome. *Lancet* **1996**, 347 (9005), 858–861.
- VERSIONI, M., AMIN, M., CHOUINARD, G., Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. *J. Clin. Psychopharmacol.* **2000**, 20 (1), 28–34.
- VERSIONI, M., MEHILANE, L., GASZNER, P., ARNAUD-CASTIGLIONI, R., Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. *J. Clin. Psychiatry* **1999**, 60 (6), 400–406.
- VILINSKY, F. D., LUBIN, A., Severe neutropenia associated with fluoxetine hydrochloride. *Ann. Intern. Med.* **1997**, 127 (7), 573–574.
- VISSER, M., SEIDELL, J. C., KOPPESCHAAR, H. P. F., SMITS, P., The effect of fluoxetine on body weight, body composition and visceral fat accumulation. *Int. J. Obes.* **1993**, 17, 247–253.
- VITULLO, R. N., WHARTON, J. M., ALLEN, N. B., PRITCHETT, E. L., Trazodone-related exercise-induced nonsustained ventricular tachycardia. *Chest* **1990**, 98 (1), 247–248.
- VLAY, S. C., FRIEDLING, S., TRAZODONE EXACERBATION OF, V. T., *Am. Heart J.* **1983**, 106 (3), 604.
- VOLKOW, N. D., FOWLER, J. S., WANG, G., DING, Y., GATLEY, S. J., Mechanism of action of methylphenidate: insights from PET imaging studies. *J. Atten. Disord.* **2002**, 6 (Suppl. 1), S31–S43.
- VOLKOW, N. D., WANG, G. J., FISCHMAN, M. W., FOLTIN, R. W., FOWLER, J. S., ABUMRAD, N. N., VITKUN, S., LOGAN, J., GATLEY, S. J., PAPPAS, N., HITZEMANN, R., SHEA, C. E., Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* **1997**, 386 (6627), 827–830.
- VOLKOW, N. D., WANG, G. J., FOWLER, J. S., GATLEY, S. J., LOGAN, J., DING, Y. S., HITZEMANN, R., PAPPAS, N., Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am. J. Psychiatry* **1998**, 155 (10), 1325–1331.
- VOLKOW, N. D., WANG, G. J., FOWLER, J. S., LOGAN, J., GATLEY, S. J., WONG, C., HITZEMANN, R., PAPPAS, N. R., Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D (2) receptors. *J. Pharmacol. Exp. Ther.* **1999**, 291 (1), 409–415.
- VOLKOW, N. D., WANG, G. J., FOWLER, J. S., MOLINA, P. E., LOGAN, J., GATLEY, S. J., GIFFORD, A., DING, Y. S., WONG, C., PAPPAS, N. R., ZHU, W., SWANSON, J. M., Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. *Psychopharmacology (Berl.)* **2003**, 166 (3), 264–270.
- VOLZ, H. P., FALTUS, F., MAGYAR, I., MOLLER, H. J., Brofaromine in treatment-resistant depressed patients – a comparative trial versus tranilcypromine. *J. Affect Disord.* **1994**, 30 (3), 209–217.
- VON FRENCKELL, R., ANSSEAU, M., SERRE, C., SUTET, P., Pooling two controlled comparisons of milnacipran (F2207) and amitriptyline in endogenous inpatients. A new approach in dose ranging studies. *Int. Clin. Psychopharmacol.* **1990**, 5 (1), 49–56.
- VORMFELDE, S. V., BITSCH, A., MEINEKE, I., GUNDELT-REMY, U. M., GLEITER, C. H., Non-response to maprotiline caused by ultra-rapid metabolism that is different from CYP2D6? *Eur. J. Clin. Pharmacol.* **1997**, 52 (5), 387–390.
- WADE, A., CRAWFORD, G. M., ANGUS, M., WILSON, R., HAMILTON, L., A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. *Int. Clin. Psychopharmacol.* **2003**, 18 (3), 133–141.
- WAEHRENS, J., GERLACH, J., Bromocriptine and imipramine in endogenous depression. A double-blind controlled trial in out-patients. *J. Affect Disord.* **1981**, 3 (2), 193–202.
- WAGNER, G. J., RABKIN, R., Effects of dextroamphetamine on depression and fatigue in men with HIV: a double-blind, placebo-controlled trial. *J. Clin. Psychiatry* **2000**, 61 (6), 436–440.
- WAGSTAFF, A. J., FRAMPTON, J. E., CROOM, K. F., Tegaserod: a review of its use in the management of irritable bowel syndrome with constipation in women. *Drugs* **2003**, 63 (11), 1101–1120.
- WAINTRAUB, L., SEPTIEN, L., AZOULAY, P., Efficacy and safety of tianeptine in major depression: evidence from a 3-month

- controlled clinical trial versus paroxetine. *CNS Drugs* **2002**, 16 (1), 65–75.
- WALKER, L., Sertraline-induced akathisia and dystonia misinterpreted as a panic attack. *Psychiatr. Serv.* **2002**, 53 (11), 1477–1478.
- WALKER, P. W., COLE, J. O., GARDNER, E. A., HUGHES, A. R., JOHNSTON, J. A., BATEY, S. R., LINEBERRY, C. G., Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. *J. Clin. Psychiatry* **1993**, 54 (12), 459–465.
- WAN, D. D., KUNDHUR, D., SOLOMONS, K., YATHAM, L. N., LAM, R. W., Mirtazapine for treatment-resistant depression: a preliminary report. *J. Psychiatry Neurosci.* **2003**, 28 (1), 55–59.
- WANG, S. J., SU, C. F., KUO, Y. H., Fluoxetine depresses glutamate exocytosis in the rat cerebrocortical nerve terminals (synaptosomes) via inhibition of P/Q-type Ca^{2+} channels. *Synapse* **2003**, 48 (4), 170–177.
- WARE, M. R., STEWART, R. B., Seizures associated with fluoxetine therapy. *DICP* **1989**, 23 (5), 428.
- WARNOCK, C. A., AZADIAN, A. G., Cross-sensitivity between paroxetine and sertraline. *Ann. Pharmacother.* **2002**, 36 (4), 631–633.
- WARNOCK, J. K., BIGGS, F., Nefazodone-induced hypoglycemia in a diabetic patient with major depression. *Am. J. Psychiatry* **1997**, 154 (2), 288–289.
- WARNOCK, J. K., BUNDREN, J. C., MORRIS, D. W., Sertraline in the treatment of depression associated with gonadotropin-releasing hormone agonist therapy. *Biol. Psychiatry* **1998**, 43 (6), 464–465.
- WARNOCK, J. K., CLAYTON, A. H., SHAW, H. A., O'DONNELL, T., Onset of menses in two adult patients with Prader–Willi syndrome treated with fluoxetine. *Psychopharmacol. Bull.* **1995**, 31 (2), 239–242.
- WECKER, L., JAMES, S., COPELAND, N., PACHECO, M. A., Transdermal selegiline: targeted effects on monoamine oxidases in the brain. *Biol. Psychiatry* **2003**, 54 (10), 1099–1104.
- WEDIN, G. P., ODERDA, G. M., KLEIN-SCHWARTZ, W., GORMAN, R. L., Relative toxicity of cyclic antidepressants. *Ann. Emerg. Med.* **1986**, 15 (7), 797–804.
- WEIHS, K. L., SETTLE, E. C. JR., BATEY, S. R., HOUSER, T. L., DONAHUE, R. M., ASCHER, J. A., Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J. Clin. Psychiatry* **2000**, 61 (3), 196–202.
- WEILBURG, J. B., ROSENBAUM, J. F., BIEDERMAN, J., SACHS, G. S., POLLACK, M. H., KELLY, K., Fluoxetine added to non-MAOI antidepressants converts nonresponders to responders: a preliminary report. *J. Clin. Psychiatry* **1989**, 50 (12), 447–449.
- WEILBURG, J. B., ROSENBAUM, J. F., MELTZER-BRODY, S., et al. Tricyclic augmentation of fluoxetine. *Ann. Clin. Psychiatry* **1991**, 3, 209–213.
- WEINER, L. A., SMYTHE, M., CISEK, J., Serotonin syndrome secondary to phenelzine–venlafaxine interaction. *Pharmacotherapy* **1998**, 18 (2), 399–403.
- WEINREB, R. M., AURIACOMBE, M., LYNCH, K. G., CHANG, K., LEWIS, J. D., A critical review of selective serotonin reuptake inhibitor-associated bleeding: balancing the risk of treating hepatitis C-infected patients. *J. Clin. Psychiatry* **2003**, 64 (12), 1502–1510.
- WEISS, J., DORMANN, S. M., MARTIN-FACKLAM, M., KERPER, C. J., KETABI-KIYANVASH, N., HAEFELI, W. E., Inhibition of P-glycoprotein by newer antidepressants. *J. Pharmacol. Exp. Ther.* **2003**, 305 (1), 197–204.
- WEITZNER, M. A., MONCELLO, J., JACOBSEN, P. B., MINTON, S., A pilot trial of paroxetine for the treatment of hot flashes and associated symptoms in women with breast cancer. *J. Pain Symptom Manag.* **2002**, 23 (4), 337–345.
- WELLINGTON, K., PERRY, C. M., Venlafaxine extended-release: a review of its use in the management of major depression. *CNS Drugs* **2001**, 15 (8), 643–669.
- WENGER, T. L., COHN, J. B., BUSTRACK, J., Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J. Clin. Psychiatry* **1983**, 44 (5 Pt 2), 174–175.
- WERNICKE, J. F., FARIES, D., GIROD, D., BROWN, J., GAO, H., KELSEY, D., QUINTANA, H., LIPETZ, R., MICHELSON, D., HEILIGENSTEIN, J., Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Saf.* **2003**, 26 (10), 729–740.
- WERNICKE, J. F., KRATOCHVIL, C. J., Safety profile of atomoxetine in the treatment of children and adolescents with ADHD.

- J. Clin. Psychiatry* **2002**, 63 (Suppl. 12), 50–55.
- WHEATLEY, D. P., VAN MOFFAERT, M., TIMMERMAN, L., KREMER, C. M., Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. Mirtazapine-Fluoxetine Study Group. *J. Clin. Psychiatry* **1998**, 59 (6), 306–312.
- WHITE, W. B., WONG, S. H., Rapid atrial fibrillation associated with trazodone hydrochloride. *Arch. Gen. Psychiatry* **1985**, 42 (4), 424.
- WHITEMAN, P. D., PECK, A. W., FOWLE, A. S., SMITH, P., Bupropion fails to affect plasma prolactin and growth hormone in normal subjects. *Br. J. Clin. Pharmacol.* **1982**, 13 (5), 743–745.
- WHITEMAN, P. D., PECK, A. W., FOWLE, A. S., SMITH, P. R., Failure of bupropion to affect prolactin or growth hormone in man. *J. Clin. Psychiatry* **1983**, 44 (5 Pt 2), 209–210.
- WIART, L., PETIT, H., JOSEPH, P. A., MAZAUX, J. M., BARAT, M., Fluoxetine in early poststroke depression: a double-blind placebo-controlled study. *Stroke* **2000**, 31 (8), 1829–1832.
- WIDERLOV, E., WIDE, L., SJOSTROM, R., Effects of tricyclic antidepressants on human plasma levels of TSH, GH and prolactin. *Acta Psychiatr. Scand.* **1978**, 58 (5), 449–456.
- WILCOX, C. S., COHN, J. B., KATZ, B. B., MIJARES, C. P., GUARINO, J. J., PANAGIDES, J., DeFRANCISCO, D. F., A double-blind, placebo-controlled study comparing mianserin and amitriptyline in moderately depressed outpatients. *Int. Clin. Psychopharmacol.* **1994**, 9 (4), 271–279.
- WILCOX, C. S., FERGUSON, J. M., DALE, J. L., HEISER, J. F., A double-blind trial of low- and high-dose ranges of gepirone-ER compared with placebo in the treatment of depressed outpatients. *Psychopharmacol. Bull.* **1996**, 32 (3), 335–342.
- WILDE, M. I., BENFIELD, P., Tianeptine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* **1995**, 49 (3), 411–439.
- WILENS, T. E., BIEDERMAN, J., MARCH, J. S., WOLKOW, R., FINE, C. S., MILLSTEIN, R. B., FARAONE, S. V., GELLER, D., SPENCER, T. J., Absence of cardiovascular adverse effects of sertraline in children and adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* **1999**, 38 (5), 573–577.
- WILLIAMSON, B. L., KLARSKOV, K., TOMLINSON, A. J., GLEICH, G. J., NAYLOR, S., Problems with over-the-counter 5-hydroxy-L-tryptophan. *Nature Med.* **1998**, 4 (9), 983.
- WINOKUR, A., DEMARTINIS, N. A., McNALLY, D. P., GARY, E. M., CORMIER, J. L., GARY, K. A., Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. *J. Clin. Psychiatry* **2003**, 64 (10), 1224–1229.
- WINOKUR, A., GARY, K. A., RODNER, S., RAE-RED, C., FERNANDO, A. T., SZUBA, M. P., Depression, sleep physiology, and antidepressant drugs. *Depress. Anxiety* **2001**, 14 (1), 19–28.
- WINOKUR, A., SATEIA, M. J., HAYES, J. B., BAYLES-DAZET, W., MACDONALD, M. M., GARY, K. A., Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. *Biol. Psychiatry* **2000**, 48 (1), 75–78.
- WISE, M., Citalopram-induced bruxism. *Br. J. Psychiatry* **2001**, 178–182.
- WISE, S. D., Clinical studies with fluoxetine in obesity. *Am. J. Clin. Nutr.* **1992**, 55, 181S–184S.
- WISTEDT, B., AGREN, H., BJARING, B., KALLSTROM, B., LUND, M., MANSBY, J., PETERSON, L. E., ROOS, B. E., Nomifensine and amitriptyline in the treatment of depression. A multi-centre double-blind comparison. *Acta Psychiatr. Scand.* **1983**, 68 (3), 212–220.
- WOHLREICH, M. M., MALLINCKRODT, C. H., POTTS, A., LU, Y., DETKE, M. J., Efficacy of duloxetine (60 mg qd) in the treatment of painful physical symptoms in patients with major depression. 55th Institute on Psychiatric Services, Boston, MA, **2003**.
- WONG, D. T., BYMASTER, F. P., MAYLE, D. A., REID, L. R., KRUSHINSKI, J. H., ROBERTSON, D. W., LY248686, a new inhibitor of serotonin and norepinephrine uptake. *Neuropsychopharmacology* **1993**, 8 (1), 23–33.
- WONG, E. H., SONNERS, M. S., AMARA, S. G., TINHOLT, P. M., PIERCEY, M. F., HOFFMANN, W. P., HYSLOP, D. K., FRANKLIN,

- S., PORSOIT, R. D., BONSIGNORI, A., CARFAGNA, N., MCARTHUR, R. A., Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. *Biol. Psychiatry* **2000**, 47 (9), 818–829.
- WOODS, S. W., TESAR, G. E., MURRAY, G. B., CASSEM, N. H., Psychostimulant treatment of depressive disorders secondary to medical illness. *J. Clin. Psychiatry* **1986**, 47 (1), 12–15.
- WOOLFREY, S., GAMMACK, N. S., DEWAR, M. S., BROWN, P. J., Fluoxetine-warfarin interaction. *BMJ* **1993**, 307 (6898), 241.
- WOOLTORTON, E., Bupropion (Zyban, Wellbutrin SR), reports of deaths, seizures, serum sickness. *CMAJ* **2002**, 166 (1), 68.
- WORTHINGTON, J., FAVA, M., AGUSTIN, C., ALPERT, J., NIERENBERG, A. A., PAVA, J. A., ROSENBAUM, J. F., Consumption of alcohol, nicotine, and caffeine among depressed outpatients. Relationship with response to treatment. *Psychosomatics* **1996**, 37 (6), 518–522.
- WORTHINGTON, J. J. 3RD, SIMON, N. M., KORBLY, N. B., PERLIS, R. H., POLLACK, M. H., Anxiety Disorders Research Program. Ropinirole for antidepressant-induced sexual dysfunction. *Int. Clin. Psychopharmacol.* **2002**, 17 (6), 307–310.
- WORTHINGTON, J. W., FAVA, M., HUGHES, M. E., KINRYS, G. D., DORDING, C., REESE, H., POLLACK, M., Aripiprazole as an augmentor of SSRIs in mood and anxiety disorder patients. American Psychiatric Association Annual Meeting, San Francisco, **2003**.
- WYSOWSKI, D. K., CORKEN, A., GALLO-TORRES, H., TALARICO, L., RODRIGUEZ, E. M., Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. *Am. J. Gastroenterol.* **2001**, 96 (6), 1698–1703.
- YALCIN, A. U., SAHIN, G., EROL, M., BAL, C., Sertraline hydrochloride treatment for patients with hemodialysis hypotension. *Blood Purif.* **2002**, 20 (2), 150–153.
- YAMADA, K., KANBA, S., YAGI, G., ASAI, M., Herbal medicine in the treatment of fluvoxamine-induced nausea and dyspepsia. *Psychiatry Clin. Neurosci.* **1999**, 53 (6), 681.
- YAMADA, K., YAGI, G., KANBA, S., Clinical efficacy of tandospirone augmentation in patients with major depressive disorder: a randomized controlled trial. *Psychiatry Clin. Neurosci.* **2003b**, 57 (2), 183–187.
- YAMADA, K., YAGI, G., KANBA, S., Effectiveness of Gorei-san (TJ-17) for treatment of SSRI-induced nausea and dyspepsia: preliminary observations. *Clin. Neuropharmacol.* **2003a**, 26 (3), 112–114.
- YAP, K. B., Low, S. T., Interaction of fluvoxamine with warfarin in an elderly woman. *Singapore Med. J.* **1999**, 40 (7), 480–482.
- YEUNG, S. Y., MILLAR, J. A., MATHIE, A., Inhibition of neuronal KV potassium currents by the antidepressant drug, fluoxetine. *Br. J. Pharmacol.* **1999**, 128 (7), 1609–1615.
- YOLLES, J. C., ARMENTA, W. A., ALAO, A. O., Serum sickness induced by bupropion. *Ann. Pharmacother.* **1999**, 33 (9), 931–933.
- YOON, Y. R., CHA, I. J., SHON, J. H., KIM, K. A., CHA, Y. N., JANG, I. J., PARK, C. W., SHIN, S. G., FLOCKHART, D. A., SHIN, J. G., Relationship of paroxetine disposition to metoprolol metabolic ratio and CYP2D6*10 genotype of Korean subjects. *Clin. Pharmacol. Ther.* **2000**, 67 (5), 567–576.
- YOSHIDA, K., ITO, K., SATO, K., TAKAHASHI, H., KAMATA, M., HIGUCHI, H., SHIMIZU, T., ITOH, K., INOUE, K., TEZUKA, T., SUZUKI, T., OHKUBO, T., SUGAWARA, K., OTANI, K., Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002a**, 26 (2), 383–386.
- YOSHIDA, K., NAITO, S., TAKAHASHI, H., SATO, K., ITO, K., KAMATA, M., HIGUCHI, H., SHIMIZU, T., ITOH, K., INOUE, K., TEZUKA, T., SUZUKI, T., OHKUBO, T., SUGAWARA, K., OTANI, K., Monoamine oxidase: A gene polymorphism, tryptophan hydroxylase gene polymorphism and antidepressant response to fluvoxamine in Japanese patients with major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002b**, 26 (7–8), 1279–1283.
- YOSHIDA, K., NAITO, S., TAKAHASHI, H., SATO, K., ITO, K., KAMATA, M., HIGUCHI, H., SHIMIZU, T., ITOH, K., INOUE, K.,

- SUZUKI, T., OHKUBO, T., Monoamine oxidase A gene polymorphism, 5-HT 2A receptor gene polymorphism and incidence of nausea induced by fluvoxamine. *Neuropsychobiology* **2003**, *48* (1), 10–13.
- YOSHINO, T., NISIJIMA, K., KATOH, S., YUI, K., NAKAMURA, M., Tandospirone potentiates the fluoxetine-induced increases in extracellular dopamine via 5-HT (1A) receptors in the rat medial frontal cortex. *Neurochem. Int.* **2002**, *40* (4), 355–360.
- YU, A., KNELLER, B. M., RETTIE, A. E., HAINING, R. L., Expression, purification, biochemical characterization, and comparative function of human cytochrome P450 2D6.1, 2D6.2, 2D6.10, and 2D6.17 allelic isoforms. *J. Pharmacol. Exp. Ther.* **2002b**, *303* (3), 1291–1300.
- YU, Y. W., CHEN, T. J., HONG, C. J., CHEN, H. M., TSAI, S. J., Association study of the interleukin-1 beta (C-511T) genetic polymorphism with major depressive disorder, associated symptomatology, and antidepressant response. *Neuropsychopharmacology* **2003**, *28* (6), 1182–1185.
- YU, Y. W., TSAI, S. J., CHEN, T. J., LIN, C. H., HONG, C. J., Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. *Mol. Psychiatry* **2002a**, *7* (10), 1115–1119.
- ZAJECKA, J. M., JEFFRIES, H., FAWCETT, J., The efficacy of fluoxetine combined with heterocyclic antidepressant in treatment-resistant depression: a retrospective analysis. *J. Clin. Psychiatry* **1995**, *56*, 338–343.
- ZANARDI, R., ARTIGAS, F., FRANCHINI, L., SFORZINI, L., GASPERINI, M., SMERALDI, E., PEREZ, J., How long should pindolol be associated with paroxetine to improve the antidepressant response? *J. Clin. Psychopharmacol.* **1997**, *17* (6), 446–450.
- ZANARDI, R., BENEDETTI, F., DI BELLA, D., CATALANO, M., SMERALDI, E., Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *J. Clin. Psychopharmacol.* **2000**, *20* (1), 105–107.
- ZANARDI, R., SERRETTI, A., ROSSINI, D., FRANCHINI, L., CUSIN, C., LATTUADA, E., DOTOLI, D., SMERALDI, E., Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and non-delusional depression. *Biol. Psychiatry* **2001**, *50* (5), 323–330.
- ZARATE, C. A., KANDO, J. C., TOHEN, M., WEISS, M. K., COLE, J. O., Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? *J. Clin. Psychiatry* **1996**, *57* (2), 68–71.
- ZETIN, M., Combined use of trazodone and phenelzine in depression: case report. *J. Clin. Psychiatry* **1984**, *45* (4), 182–183.
- ZHANG, W., PERRY, K. W., WONG, D. T., POTTS, B. D., BAO, J., TOLLEFSON, G. D., BYMASTER, F. P., Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. *Neuropsychopharmacology* **2000**, *23* (3), 250–262.
- ZIEGLER, M., CASTRO-CALDAS, A., DEL SIGNORE, S., RASCOL, O., Efficacy of piribedil as early combination to levodopa in patients with stable Parkinson's disease: a 6-month, randomized, placebo-controlled study. *Mov. Disord.* **2003**, *18* (4), 418–425.
- ZILL, P., BAGHAI, T. C., ZWANZGER, P., SCHULE, C., MINOV, C., RIEDEL, M., NEUMEIER, K., RUPPRECHT, R., BONDY, B., Evidence for an association between a G-protein beta3-gene variant with depression and response to antidepressant treatment. *Neuroreport* **2000**, *11* (9), 1893–1897.
- ZISOOK, S., PETERKIN, J., GOGGIN, K. J., SLEDGE, P., ATKINSON, J. H., GRANT, I., Treatment of major depression in HIV-seropositive men. HIV Neurobehavioral Research Center Group. *J. Clin. Psychiatry* **1998**, *59* (5), 217–224.

7

Psychobiology of Electroshock*Max Fink***Abstract**

After 70 years inducing grand mal seizures in human beings to achieve a behavior benefit, what have we learned? Convulsive therapy (ECT) was developed as a treatment for psychosis, but clinicians quickly recognized that seizures were more broadly effective, also relieving severe depressed mood, manic excitement, suicide risk, and catatonia.

For the behavioral benefits, repeated grand mal seizures must be induced. Not all seizures are equally effective, however, and the characteristics of effective treatments are now better defined. Effective seizures are marked by bilateral electroencephalographic (EEG) brain wave changes with immediate and prolonged neuroendocrine effects. While depressed mood is the most common target, so are other abnormal behaviors. ECT also augments the benefits of psychoactive drugs, especially antipsychotic agents.

Memory effects are common but are almost always transient. They are not a practical deterrent to its use, although very frequently cited as the reason why the treatment is delayed or rejected. The memory effects are best viewed as necessary accompaniments of seizures and as similar to the bleeding that accompanies surgery.

The breadth of action of ECT argues that the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Statistical Classification of Diseases and Related Health Problems* (ICD) classification systems are unsound. A syndromal, not a disease approach, is more effective in defining psychiatric illnesses.

The mechanism of action of ECT points to the neuroendocrine system as central to its benefits. Such experience should turn neuroscience away from the present obsession with neurohumors as explanations for psychiatric illness. It also points to the failure of animal models to explain psychiatric disorders or offer clues to treatments.

The stigmatization of ECT that places it as a “last resort” therapy, and not available in many psychiatric centers, is wasteful and unethical. It guarantees years of unnecessary chronic illness and hardship for the severely mentally ill.

ECT is a remarkable model for the study of psychiatric illness and its resolution. Despite its stigmatization, it offers the best hope for advancement in neuroscience.

7.1 Introduction

The litany of treatments offered the mentally ill have been marked by zeal and opportunity, not by rational thinking. The assumed demons have been exorcised by prayer, incantation, exhortation, incense, isolation, restraint, dunking, bleeding, cupping, magnetism, and electricity. With improved surgical skills and medical bravado, 20th century patients were offered the removal of teeth, gut, sex glands, and parts of the brain. Malarial fevers, grand mal seizures induced by Metrazol, flurothyl, and electricity (ECT), and comas induced by insulin (ICT) and anesthesia (barbiturates, isoflurane) were prescribed. Metabolism was altered by injections of hormones (insulin, thyroid, sex gland extracts). Brain chemistry was changed by synthetic chemicals. At the end of the 20th century, interest again moved to magnetism (transcranial magnetic stimulation and magnetic seizure therapy) and electrical stimulation of the vagus nerve (vagus nerve stimulation (VNS)) and of the brain itself (deep brain stimulation (DBS)).

Of these invasive “treatments”, only the antipsychotic, antidepressant, and sedative drugs, lithium, and ECT have withstood scientific examination and are today seen to be useful. ECT is particularly effective in relieving depressive mood disorders [1].

Seventy years ago the Hungarian neuropathologist and psychiatrist Ladislav Meduna discovered that the repeated induction of grand mal epileptic seizures relieved the signs of dementia praecox [2–4]. This extraordinary treatment was based on the belief that a psychiatric illness could be altered by a systemic illness, a belief endorsed by demonstrations that malarial fevers relieved neurosyphilis. The award of the Nobel Prize for Medicine in 1927 acknowledged this belief.

Population studies and case reports found a rare overlap of psychosis and seizures, suggesting a biological antagonism between the seizures of epilepsy and the delusions of dementia praecox. In studies of brain glial concentrations, Ladislav Meduna observed unusually low brain glial counts in those who died with dementia praecox and high glial counts in those who died with epilepsy. He envisioned the lowered glial concentrations as a cause of psychosis and conjured the induction of seizures to replace the missing glia. Animal tests of stimulating agents led to intramuscular injections of camphor as a means to induce seizures.

Zoltan had been a patient in a catatonic state for more than 4 years at the state psychiatric hospital in Lipotmezö outside Budapest. On 23 January 1934 Meduna elicited a grand mal seizure in Zoltan who, surprisingly, survived the seizure. His catatonic behavior was unchanged. Following the model of malarial treatments then in vogue, Meduna induced seizures every 3 to 4 days, until after the fifth seizure, Zoltan’s mutism, negativism, and psychosis lifted. He spoke rationally and coherently and behaved normally. Meduna offered him two more

treatments, after which Zoltan left the hospital and remained well at follow-up 5 years later.

Meduna treated nine additional patients and reported recovery in eight [2–4]. Intramuscular camphor was replaced by intravenous Metrazol. By 1936, his work was confirmed at an international psychiatric meeting in Münsingen, Switzerland [5]. Two years later, Italian clinicians showed that electrical inductions were much easier and more assured than chemical inductions, and the modern era of electroconvulsive treatment began [6].

For two decades, ECT was the main treatment for the severely psychiatrically ill until the late 1950s when it was put aside in the wake of the enthusiasm for the newly discovered psychoactive drugs. Psychopharmacology quickly replaced ECT, insulin coma, lobotomy, and much of the psychotherapies. Reports of “pharmacotherapy-resistant” patients in the 1980s led clinicians to recall ECT to clinical use. In the interim, technical changes had improved ECT safety and efficacy, broadened its applications to illnesses beyond dementia praecox and manic depressive insanity, and developed methods to effectively and safely treat patients with systemic abnormal conditions [7, 8]. ECT is now widely used throughout the world as the treatment of last resort. (Why it is used “as the last resort” when its efficacy is clearly superior to alternative treatments is a puzzle. A persistent misrepresentation of its risks is the main contributor to its stigmatization [9–11]). For this volume, it is timely to ask what elements of ECT are central to the behavioral effects and what lessons have been learned from this experience.

7.2

A Cerebral Seizure is Essential

The repeated induction of grand mal seizures is the central event in the efficacy of the treatment. The clearest benefit is seen in ECT, in which seizures are repeatedly induced, usually three times a week. Depressive and manic mood states, psychoses of diverse origins, and motor disorders of catatonia are rapidly relieved, usually with six to 15 seizures. Seizures were also important in insulin coma and lobotomy, two discarded treatments introduced at the same time as convulsive therapy [12].

In insulin coma therapy, grand mal seizures occurred in 10% or more of the comas. For patients undergoing 50 comas, from five to 10 or more seizures were likely. Manfred Sakel, the originator of the treatment, believed seizures were unwelcome side-effects, and sought to exclude them from the treatments. Other clinicians, however, prescribed electrical-induced seizures in the midst of an ICT course that was not progressing well. The benefits of ICT probably resulted from the incidental induction of seizures, and not from the comas, nor any direct hormonal effect of insulin, nor from the persistent brain effects that followed the occasional prolonged coma, nor from any psychological process [12].

In lobotomy, seizures occurred with varying frequency depending on the type of operation. Of the patients who had two operations, 47% suffered seizures. Of those who underwent one operation, 15% experienced recurrent seizures in the Freeman–

Watts series [13]. Recurrent status epilepticus with death in status were reported [14, 15]. We lack direct studies of the role of seizures but it is probable that the benefit from lobotomy resulted from seizure induction and not from any separation or excision of brain tissues.

Throughout our experience non-convulsive methods have been proffered as replacements for ECT, to little avail. Prolonged sleep, subconvulsive “treatments”, isoflurane anesthesia, transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS) do not demonstrate an equivalent efficacy, either in populations treated or remission rates, to justify their substitution for ECT. Magnetic seizure therapy (MST), the latest replacement attempt, seeks to induce grand mal seizures using very high magnetic currents. It promises experimental success since seizure induction is the stated goal [16, 17]. The first reports describe the induced seizures to be “weak” compared to those induced by electric currents and much development work is yet to be completed before we can compare the electrical and magnetic inductions for efficacy, safety, and ease of use.

7.3

Many Behaviors are Relieved

Severely depressed mood is rapidly responsive to ECT, with remission rates from 50 to 90% [1]. Remission rates are higher for those with psychotic depression [18, 19].

The delusions of schizophrenia and psychotic manic states are relieved, often within a few weeks of treatment [20]. The grandiosity and over-activity of manic delirium, rapid cycling mania, and mixed affective states are quickly reduced [10, 21]. The motor disorders of malignant catatonia, benign stupor, retarded catatonia, and the neuroleptic malignant syndrome are dissipated [22].

In each of these experiences, the response is best measured in specific behaviors (as depressed mood, insomnia, delusion, motor rigidity, suicidal thoughts) and not as a resolution of a “disease” as codified in DSM and ICD nomenclatures. Individual symptoms or symptom clusters, not disorders or diseases, are altered by seizures. The experience with ECT argues that the artifacts of nomenclature codified in DSM and ICD are no more pertinent to the development of a science than the codification of fevers or coughs as “wet” and “dry” or the four humors of medieval learning were to our understanding of brain functions and behavior. A suggestion for a different psychiatric nomenclature is made in our analysis of catatonia as a syndrome with a defined pathophysiology and symptom pattern, varied etiology, and well-defined therapeutics [22, 23].

7.4

Not All Seizures are Equal in Efficacy

While seizures are the necessary element for a persistent behavioral effect, not all seizures are equally effective. Seizures vary in the brain patterns that are altered, their duration and symmetry, and in their termination pattern. They vary with electrode placement, dosage of stimulation, numbers and frequency of treatments, and medication use. The ictal EEG shows many patterns in its recording in modern ECT devices. The best clinical results are observed when the EEG seizure is bilateral, of sufficient duration to show runs of high voltage slow waves mixed with spikes, runs of high voltage slow waves alone, and a sharp (precise) end-point. An immediate review of the monitored EEG allows the therapist to decide whether the seizure is “effective” (and likely to be followed by anticipated behavioral effects) or “ineffective”. An “ineffective seizure” can be immediately repeated using better induction parameters under the same anesthesia. Such monitored treatment courses achieve higher remission rates than those in which such monitoring is not a feature. This is best seen in the reports by the Consortium for Research in ECT (CORE) investigators in their treatment of major depression with bilateral ECT [18]. Using EEG monitoring guidelines, their remission rates are 20% better than those reported in clinical trials based on unilateral ECT [24].

7.5

Seizures have to be Repeated for a Persistent Benefit

The behavioral effects of seizures are incremental, requiring repetition until new behaviors are expressed and stabilized. ECT is not a surgical excision that removes the defect, but more like the medical treatment of diabetes where repeated administration of insulin is needed to control serum glucose levels. Stopping an ECT course at the first sign of relief or prescribing a fixed number of treatments at the onset of the course discourages an effective treatment. Early termination insures high relapse rates. Contrast this model with treatment with psychoactive medications, where neither the duration nor dosage is determined at the time of prescription but continues as long as symptoms are detected and for weeks and even months thereafter. This tolerant attitude is not applied to ECT where limited application is the standard. Patients receiving short courses of ECT are prone to high relapse rates compared to the experience reported in research studies [25].

A leading cause of long-term morbidity of depression is the inappropriate discontinuation of treatment with medication [26]. A similar loss of benefit occurs in ECT when treatments are prematurely discontinued. We do not know for how long nor how often seizures are to be repeated nor how best to use a continuation ECT schedule to sustain a benefit. But we know that a minimum effective course of ECT is measured in months, not weeks. A National Institute of Mental Health (NIMH)-supported study comparing the benefits of continuation ECT and continua-

tion medication after a successful course of ECT in patients with unipolar depression is in progress in the CORE studies, but the results are not expected until early 2005. In that study, ECT is continued with decreasing frequency for 6 months after remission [18].

7.6

Memory Effects are Common, can be Minimized, and are not a Deterrent to its Use

The most frequent objection to inducing seizures as therapy is the fear that a persistent defect in memory will ensue, wiping out personal recollections and an individual's persona. Each seizure does elicit confusion and immediate recall that clouds the events of the treatment days. Such defects are almost always transient. Some patients do experience long-term defects in the recollection of personal memories; the severity of such losses is affected by age, health status, concurrent medications, and treatment parameters [8]. Much can be done to minimize this effect but full avoidance seems unattainable. Perhaps we should look at the immediate memory effects in ECT as comparable to blood loss in surgery. Surgical techniques limit but do not fully avoid the loss of blood. ECT techniques reduce the effects of seizures on memory but cannot fully avoid them. It is as irrational to refuse ECT for its anticipated memory effects as it would be to refuse surgery for the associated bleeding.

7.7

ECT Augments the Benefits of Psychoactive Drugs

Antipsychotic drugs reduce delusions, hallucinations, and excitement. When conventional antipsychotic drugs fail, clozapine treatment is now offered. But even with high dosages and monitoring of serum levels to assure adequate dosing, many patients do not respond and are considered "clozapine resistant". In such instances, ECT augmentation of clozapine therapy (or other antipsychotic drug therapy) elicits reductions in "positive" psychotic symptoms, over and above those generated by the medicines alone [10, 20]. A similar augmentation of antidepressant drugs by ECT is the subject of an ongoing multi-site study.

Are the mechanisms of action of seizures and drugs similar? We imagine that medications operate by altering the concentrations of neurohumors and receptors in the brain. When the same methods are applied to the study of induced seizures, the changes are inconsistent and not related to the behavioral effects [27]. Many hypotheses of the actions of seizures have been proposed, including psychological concepts focused on memory, neurophysiological concepts focused on EEG changes or a rise in seizure thresholds, and neuroendocrine concepts imagining changes in hypothalamic peptides in the brain [28]. While medications affect memory, alter the EEG and seizure thresholds, and alter neuroendocrine metabolism, the hypotheses regarding the actions of drugs ignore these changes. No parallel has

been drawn between the efficacy of medications and that of seizures in any of these mechanisms. Considering the gross nature of the augmentation studies, it is highly likely that the principal benefit of ECT augmentation studies comes from the seizures alone.

7.8 Lessons for Clinical Psychiatry

7.8.1 DSM Classification is Arbitrary and Unsound

The predictable and persistent changes in behavior with ECT compel our attention. Neither the constructs of “schizophrenia”, “major depression”, or “bipolar disorder”, nor their subtypes predict clinical outcome. We are better able to select patients for treatment by assessing syndromes or symptoms. “Catatonia”, “delusion”, “vegetative syndrome”, “melancholia”, “aggressiveness”, and “suicide risk” are definable targets that are relieved by ECT, almost regardless of their associated psychopathology, duration, or severity.

In clinical practice, the DSM and ICD classification systems are ignored in developing and applying treatment algorithms. Medications are selected from lists classified as antidepressant, antipsychotic, anxiolytic, etc. ECT is not included in these lists for at least two reasons. The breadth of ECT is so great that it is not specified as an “antidepressant” or an “antipsychotic” or an “anti-manic” agent, although it is effective for each syndrome. As medications are readily available – requiring only a pen and a preprinted prescription pad – ECT use is further disadvantaged as it requires referral to an ECT treatment center, the services of a trained ECT practitioner, and the collaboration of skilled nurses and anesthesiologists. Such hurdles discourage consideration until all else has been tried and failed.

That ECT is effective across a spectrum of syndromes supports a unitary hypothesis for the cause of the major psychiatric illnesses. Rather than envisioning psychiatric illnesses as individual entities, each with a unique biology, unique genetic, and unique family bases, we need to search for a biological dysfunction that expresses itself in many forms. This lesson was learned in the first experiments with chlorpromazine and imipramine. Although these agents were immediately touted as treating schizophrenia and depressive states, it soon became clear that the diagnostic labels helped little. When patients referred for medication were randomly assigned to receive either chlorpromazine, imipramine, or placebo regardless of the presenting diagnosis, Klein and Fink reported that these agents elicited syndromal responses and that the medicines were not active antidotes to defined psychiatric disorders [29, 30]. Chlorpromazine relieved delusions, excitement, and manic behavior, consistent with its antipsychotic designation, but it also relieved depressed mood and vegetative syndromes [29]. Imipramine relieved depression but also reduced phobia and stimulated mania and aggressiveness [30].

The diversity of the effects of psychoactive medicines makes it difficult to pigeonhole them as single entities, despite the narrow lists of acceptable targets that are defined by government marketing registrations.

The classification of psychiatric disorders by the Chinese-menu approach of the DSM is a hopeless diversion. A better model is to be seen in the syndromal or symptomatic analysis as presented in the study of catatonia [22, 23]. Catatonia, a motor disorder with more than 20 definable signs, is identified in about 10% of hospitalized psychiatrically ill patients. It is a feature of patients pigeonholed in many DSM disorders. Catatonia is responsive to anticonvulsant medicines, such as barbiturates, benzodiazepines, and carbamazepine, but also to ECT. The biology of patients with catatonia has many homogeneous features. It is more fruitful to identify the syndrome and seek to understand its biology than it is to follow the DSM or ICD classification as a subtype of schizophrenia.

A similar argument is presented for melancholia by Parker and Hadzi-Pavlovic [31] and Taylor and Fink [32]. Melancholia is best defined as a mood disorder of sudden onset, with vegetative abnormalities (such as DST, sleep EEG). Psychosis, suicide risk, and a progressive course, often with a fatal outcome, are common. Melancholia is not recognized as an entity in the DSM classification where its use as a label is restricted to that of a modifier of different disorders. A unique characteristic of melancholia is its ready resolution with ECT [33].

7.8.2

ECT Action Directs Attention to Neuroendocrine Mechanisms

The question of how seizures may affect behavior has stimulated many images that dot the literature, but only a few are credible as to the facts and none explain the connection between brain events and behavior [28, 33]. According to their targets the main themes are described as *neurohumoral*, *anticonvulsant*, *electrophysiologic*, and *neuroendocrine*. Theories of neurohumoral transmission look at ECT with the same images that are used to explain the actions of antidepressant and antipsychotic drugs. For ECT (as for medications) the changes in neurohumors after seizures are ill defined and the connection between their momentary changes and behavior eludes us.

The anticonvulsant view is based on reports that the threshold for the next induction rises with repeated seizures. This change is slow in onset, small in degree, and not associated with clinical benefits.

The electrophysiologic view relates changes in behavior to the degree and generalization of EEG slow wave activity. The correlation between brain events and behavior is well established but we lack a credible explanation of why such physiological change translates into behavior.

The neuroendocrine view starts with observations that patients who are depressed and psychotic exhibit abnormalities in neuroendocrine regulation. These normalize with successful treatment. The best documentation is for the dexamethasone suppression test and the thyrotropin-stimulating-hormone response to thyrotropin-releasing-hormone tests [28, 33]. An interest in neuroendocrine dysregulation in

patients with psychotic depression was the basis for the clinical trials of the progesterone antagonist mifepristone [34, 35]. The experiences with thyroid substances as augmenting agents in treating depression are also consistent [36]. A reasonable strategy to an understanding of psychiatric disorders is to turn the spotlight away from neurohumors to the neuroendocrine system. We have no better way to affect that system than by inducing seizures.

7.8.3

Animal Studies are Misleading

Most studies to explain the effects of chemical substances and seizures on behavior are carried out in animal species. Such experiments are inexpensive, technically unlimited, and constrained little by the ethical considerations that limit human trials. Unfortunately, for studies of brain and behavior, the differences between animals and man are so large as to make this short-cut unreliable and unproductive [37]. It is erroneous to assume that neuroendocrine regulations in animals and man are similar. Not only does the physiology of animals and man differ too widely to be bridged, the variety of specially bred animals in breeder catalogs limits generalizations even for any single species selected for study. The best opportunity for the study of brain function and behavior is in man, and it is here that the opportunities in ECT are remarkably fortuitous.

7.9

Conclusion

The remarkable benefits of inducing seizures in man are worthy of greater attention than they are being given in the clinic, in neuroscience research, and in the search for new treatments for the severely mentally ill.

The stigmatization of ECT is a wasteful episode in medical history. The treatment warrants greater attention in the clinic. The objections that patients will not accept the treatment for fear of its effects on memory is a rationalization for the poverty in our training of physicians, most of whom have limited understanding of the merits and safety of ECT. The same can be said for psychiatrists who lack training and cannot educate their patients in the benefits of the treatment when it is clearly indicated.

Many writers argue that patients refuse ECT for fear of its side-effects. That is true, but the same patients will accept major surgical procedures, removal and replacements of organs, systemic poisoning by drugs, and the toxicity of radiation to relieve cancer. Surely the side-effects of these procedures are much more horrendous than the effects of ECT. The difference in patient response to ECT and to anti-cancer treatment is the conviction of the physician and surgeon that what they are doing is for the patient's good. Alas, the same cannot be said for physicians when they recommend ECT, for they do so hesitantly and shy away from re-enforcing their recommendations at the first sign of patient concern. The fears generated by

images of electricity shocking humans, the furor of a vocal anti-psychiatry movement, and the writings and films of such authors as Thomas Szasz and Kenneth Kesey generate antipathy to ECT use. The use of formal consent procedures, educational videotapes and books, and personal reminiscences of successful outcomes encourage patients and their families to overcome these anti-ECT postures [10, 38]. The legal hurdles to limit ECT in some states are persistent deterrents, but attitudes to ECT can be improved [11].

References

- 1 UK ECT REVIEW GROUP, Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* **2003**, 36, 799–808.
- 2 MEDUNA, L., Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie: Camphor und Cardiozolkrämpfe. *Z. ges. Neurol. Psychiatr.* **1935**, 152, 235–262.
- 3 MEDUNA, L., *Die Konvulsionstherapie der Schizophrenie*. Halle: Karl Marhold, **1937**.
- 4 MEDUNA, L., Autobiography. *Convulsive Ther.* **1985**, 1, 43–57, 121–138.
- 5 KATZENELBOGEN, S., SANTEE, F., The treatment of schizophrenia. Insulin shock. Cardiozol. Sleep treatment. *Am. J. Psychiatry* **1938**, 94 (Suppl.), 1–354.
- 6 CERLETTI, U., Old and new information about electroshock. *Am. J. Psychiatry* **1950**, 107, 87–94.
- 7 AMERICAN PSYCHIATRIC ASSOCIATION, *Electroconvulsive Therapy. Recommendations for Treatment, Training and Privileging*. Washington DC: American Psychiatric Association, **1990**, **2001**.
- 8 ABRAMS, R., *Electroconvulsive Therapy*, 4th ed. New York: Oxford University Press, **2002**.
- 9 FINK, M., Impact of the anti-psychiatry movement on the revival of ECT in the U.S. *Psychiatr. Clin. North Am.* **1991**, 14, 793–801.
- 10 FINK, M., *Electroshock: Restoring the Mind*. New York: Oxford University Press, **1999**. Re-issued in paperback. *Electroshock: Healing Mental Illness*, **2002**.
- 11 OTTOSSON, J.-O., FINK, M., *A Dilemma in Ethics in Electroconvulsive Therapy*. New York: Brunner-Routledge, **2004**.
- 12 FINK, M., *A beautiful mind* and insulin coma: social constraints on psychiatric diagnosis and treatment. *Harv. Rev. Psychiatry* **2003**, 11, 284–290.
- 13 VALENSTEIN, E. S. (Ed.), *The Psychosurgery Debate*. New York, San Francisco: WH Freeman & Co., **1980**.
- 14 FREEMAN, W., WATTS, J. W., *Psychosurgery* 2nd ed. Springfield IL: CC Thomas, **1950**.
- 15 SHUTTS, D., *Lobotomy: Resort to the Knife*. New York: Van Nostrand Reinhold, **1982**.
- 16 LISANBY, S. H., SCHLAEPFER, T. E., FISCH, H.-U., SACKEIM, H. A., Magnetic seizure therapy of major depression. *Arch. Gen. Psychiatry* **2001**, 58, 303–305.
- 17 LISANBY, S. H., HUSAIN, M. M., MORALES, O. G., et al., Controlled clinical trials of the antidepressant efficacy of magnetic seizure therapy in the treatment of major depression. ACNP Meeting, San Juan PR, Dec. 7, **2003**.
- 18 PETRIDES, G., FINK, M., HUSAIN, M. M., KNAPP, R., RUSH, A. J., MUELLER, M., RUMMANS, T. A., O'CONNOR, K. M., RASMUSSEN, K. G., BERNSTEIN, H. J., BIGGS, M., BAILINE, S. H., KELLNER, C. H., ECT remission rates in psychotic versus non-psychotic depressed patients: a report from CORE. *JECT* **2001**, 17, 244–253.
- 19 BIRKENHÄGER, T. K., PLUIJMS, E. M., Lucius SAP, ECT response in delusional versus non-delusional depressed inpatients. *J. Affective Dis.* **2003**, 74, 191–195.
- 20 FINK, M., SACKEIM, H. A., ECT for schizophrenia? *Schizophrenia Bull.* **1996**, 22, 27–39.
- 21 MUKHERJEE, S., SACKEIM, H. A., SCHNUR, D. B., Electroconvulsive therapy

- of acute manic episodes: a review of 50 years' experience. *Am. J. Psychiatry* **1994**, *151*, 169–176.
- 22 FINK, M., TAYLOR, M. A., *Catatonia: A Clinician's Guide to Diagnosis and Treatment*. Cambridge, UK: Cambridge University Press, **2003**.
 - 23 TAYLOR, M. A., FINK, M., Catatonia in psychiatric classification: a home of its own. *Am. J. Psychiatry* **2003**, *160*, 1233–1241.
 - 24 SACKEIM, H. A., HASKET, R. F., Mulsant BH et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA* **2001**, *285*, 1299–1307.
 - 25 PRUDIC, J., OLFSON, M., MARCUS, S. C., FULLER, R. B., SACKEIM, H. A., The effectiveness of electroconvulsive therapy in community settings. *Biol. Psychiatry* **2004**, *55*, 301–312.
 - 26 HARVEY, B. H., MCEWEN, B. S., STEIN, D. J., Neurobiology of antidepressant withdrawal: implications for the longitudinal outcome of depression. *Biol. Psychiatry* **2004**, *55*, 301–312.
 - 27 FOCHTMANN, L., Animal studies of electroconvulsive therapy: foundations for future research. *Psychopharmacol. Bull.* **1994**, *30*, 321–444.
 - 28 FINK, M., Electroshock revisited. *Am. Scientist* **2000**, *88*, 162–167.
 - 29 KLEIN, D. F., FINK, M., Behavioral reaction patterns to phenothiazines. *Arch. Gen. Psychiatry* **1962**, *7*, 449–459.
 - 30 KLEIN, D. F., FINK, M., Psychiatric reaction patterns to imipramine (Tofranil). *Am. J. Psychiatry* **1962**, *119*, 432–438.
 - 31 PARKER, G., HADZI-PAVLOVIC, D., *Melancholia: A Disorder of Movement and Mood: A Phenomenological and Neurobiological Review*. Cambridge, UK: Cambridge University Press, **1996**.
 - 32 TAYLOR, M. A., FINK, M., *Melancholia: A Clinician's Guide*. Cambridge, UK: Cambridge University Press, **2005** (in press).
 - 33 FINK, M., *Convulsive Therapy: Theory and Practice*. New York: Raven Press, **1979**.
 - 34 BELANOFF, J. K., FLORES, B. H., KALEZHAN, M., SUND, B., SCHATZBERG, A. F., Rapid reversal of psychotic depression using mifepristone. *J. Clin. Psychopharm.* **2001**, *21*, 516–521.
 - 35 BELANOFF, J. K., ROTHSCILD, A. J., CASSIDY, F., DEBATTISTA, C., BAULIEU, E. E., SCHOLD, C., SCHATZBERG, A. F., An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol. Psychiatry* **2002**, *52*, 386–392.
 - 36 LIPTON, M. A., PRANGE, A. J., NEMEROFF, C. B., BREESE, G. R., WILSON, I. C., Thyrotropin-releasing hormone: central effects in man and animals. In: USDIN, E., HAMBURG, D. A., BARCHAS, D. (Eds.), *Neuroregulators and Psychiatric Disorders*. New York: Oxford University Press, **1977**, pp. 258–266.
 - 37 BRADLEY, P., Fink, M. (Eds.), *Anticholinergic Drugs and Brain Functions in Animals and Man. Progress in Brain Research* Vol. 28. Amsterdam: Elsevier, **1968**.
 - 38 AMERICAN PSYCHIATRIC ASSOCIATION, *Electroconvulsive Therapy*. Washington DC: APA Press, **1978**.

8

Current Prognosis of Depression

H. Brent Solvason and Alan Schatzberg

8.1

Introduction

Recent developments identifying the neurobiologic substrates of affective disorders allow us to consider the recurrence, chronicity, and disability associated with depression from a new perspective. Considered together, the empirical longitudinal data and the heuristic use of the biological basis for major depressive disorder (MDD) may help to clarify treatment options, and mobilize clinicians to fully treat a chronic disease ranked in 1990 as the fourth greatest cause of disability and premature death worldwide, and predicted by the WHO to be the number two cause of disability in women worldwide by 2020.

The occurrence of only a single major depressive episode (MDE) over an individual's lifetime is relatively uncommon. Some long-term prospective studies have suggested the rate of those who will have had only a single MDE in their lifetime may be as low as 14% [1–3]. An estimate of the number of people experiencing a recurrent episode after a first MDE is thought to be greater than 80%, although inclusion of individuals with residual or subsyndromal symptoms could make this number nearly 100% [1–10]. Chronicity of an index MDE is not uncommon, with approximately 10% of individuals still in the current MDE after 5 years [11], and 5% still depressed after 15 years [10, 12].

Much work has been done to improve the acute treatment of depression [13], and some longitudinal antidepressant maintenance studies indicate that remission may be maintained in nearly 80% of patients with recurrent major depression for up to 5 years [14–16]. Despite these relatively optimistic findings, less selected populations in community settings continue to have some symptoms after acute treatment and during long-term follow-up [17]. The presence of these so-called “residual symptoms”, implies an absence of complete remission of symptoms following acute treatment, a circumstance placing patients at high risk for full syndromic relapse [17, 18]. While the emphasis in acute treatment is now on attaining remission, the implications for identification and treatment of residual symptoms, the chronicity of major depressive disorder, and the clear disability

associated with even minor symptoms has not yet been integrated into the standard of care [19].

8.2

The “Course of Illness” Concept of Recurrent Major Depression

Depression is a highly recurrent illness with disabling symptoms even between full syndromic episodes. It has been suggested that highly recurrent MDD can cause progressive changes in brain structures, which translate clinically into an apparent course of illness, characterized by increasing independence from external stressors, greater likelihood of having residual symptoms, and an increased probability of becoming ill with a full syndromic relapse, increasing psychosocial disability, and treatment resistance (Table 8.1).

This hypothesis is the organizing principle behind this review of the course and prognosis of depression. We posit that early in the course of illness (one to three major depressive episodes), the illness will be characterized by responsiveness to single-agent treatments or supportive psychotherapy, be preceded by significant psychosocial stressors, be more likely to completely remit without inter-interval residual symptoms, and be less likely to lead to chronicity.

Late in the course of illness (six to nine episodes) we expect that there is increasing treatment resistance; successful treatments will require more than one mechanism of action, or more than one drug or both, will demonstrate an increasing independence from external stressors, more inter-interval residual symptoms, less well-time between episodes, greater likelihood of chronicity and greater disability (Table 8.2). We will review the prognosis of depression and then determine whether the insights provided by our current understanding of the neurobiology of depression helps to organize prospective data on the course of illness, and what the treatment implications may be for this model of the longitudinal course of depression.

8.2.1

Kindling and Course of Illness in Recurrent Depression

Recent advances in the neurobiology of depression allow us to review and reframe the concept of symptom expression, and review the concern that maladaptive plastic changes occur in the brain with each major depressive episode. Some have posited that the course of illness of affective disorders may be partly modeled on animal kindling studies [20]. Similarly, sensitization provides a model for long-term plastic change that is irreversible, and chronically alters the behavioral response of rats to stimulants [21]. Both models have in common one theme: recurrent exposures to a stimulus may irreversibly change the regulation of prefrontal, subcortical, and limbic structures, resulting in a new behavioral phenotype. Kindling, in particular, models the “course of illness” of affective disorders, by highlighting the association between initial provoked seizures, followed by spontaneous seizures, leading to

Table 8.1 Definition of concepts in progression of illness in major depression**Network**

The symptoms of depression are the result of dysregulated connected networks that regulate mood and anxiety. See text for implicated neuroanatomical structures. Each of these structures may be thought of as a “node” whose normal functioning is required for the maintenance of the asymptomatic state.

Dysfunction

Dysregulation at one node has the capacity to dysregulate communication within the distributed network, resulting in symptoms of depression.

Treatment resistance

Dysfunction at some key nodes may be associated with more severe symptoms, and when present at multiple nodes, may affect the severity and response to treatment. The involvement of multiple subsystems or nodes would likely require drug treatments with multiple mechanisms of action and possibly longer periods of treatment to achieve complete remission.

Progression of illness

Each episode of depression results in long-lasting changes in vulnerable nodes, and in highly connected proximal structures. This has the effect of making the system prone to dysregulation because of the sensitizing effects of prior depressive episodes and/or neuronal endangerment or death.

Decreasing well-interval

Increasing nodal and network dysfunction due to recurrent mood episodes reduces the overall compliance of the system, and when the system is under duress, reduces its adaptability and capacity to correct or re-regulate activity. This instability may lead to spontaneous symptom appearance or syndromic illness. This translates clinically into a pattern of a decreasing well interval after multiple prior major depressive episodes.

Treatment refractoriness

The implication of the plastic change occurring in the distributed network regulating mood with recurrent episodes is that a course of illness for depression may be defined. This translates into an illness that is more difficult to treat after increasing multiple prior episodes.

Early (one to three episodes)

Symptoms are more likely to respond to single mechanism medications or supportive psychotherapy, be preceded by significant psychosocial stressors, not lead to chronicity, and remit fully after the episode has passed.

Late (six to nine episodes)

Treatment will likely require multiple medications, mechanisms of action, or both, and will likely be followed by: continued residual symptoms or chronicity of syndromic or minor syndromic illness, a decreased well-interval between episodes, an increased likelihood of having a subsequent episode, and increasing independence from psychosocial stressors as precipitants.

Table 8.2 Hypothesis: the prognosis of major depression**Recurrent episodes of depression sensitize networks regulating mood resulting in:**

More frequent relapses
Greater independence from external stressors
Greater symptom burden and disability between syndromic MDE
Decreased well-time between episodes
Greater treatment resistance
Subtle cognitive and motor abnormalities

progressive escape from control by anticonvulsant medications, ultimately leading to refractory uncontrolled spontaneous seizures; e.g. the illness progresses and becomes resistant to treatment over time.

8.2.2

Symptom Expression in Recurrent Depression

In a manner completely analogous to other neurologic illness such as aphasia, dysfunction of a connected network results in symptoms. The production of speech requires multiple areas working coordinately to link thought, syntax, and motor function to produce either verbal or written language. A single lesion in Broca's motor area of the prefrontal cortex if small enough, will result in a pure motor aphemia, or if somewhat larger, a Broca's aphasia. The network of structures subserving the production of speech can be interrupted by disrupting function at a single point. Further, the degree of dysfunction (aphemia versus aphasia) is proportional to extent of the lesion. In a parallel manner, the appearance of symptoms of depression such as sadness, loss of interest, anergia, appetitive and sleep disturbances, concentration and attentional deficits, ruminative thought processes with negativistic or guilt content, hopelessness and suicidality would be the consequence of the dysregulation of a distributed network of neuroanatomical structures regulating mood. Based on the model of aphasia, we might expect the severity of symptom to represent the extent of dysregulation and the number of structures affected.

8.2.3

Limbic–Prefrontal Circuits Regulate Mood

There are a number of limbic, subcortical, and prefrontal cortical structures implicated in the regulation of mood and anxiety. These structures include the dorsolateral, orbitofrontal, and the anterior cingulate prefrontal cortices; subcortical structures such as the caudate, nucleus accumbens, globus pallidus, and medial dorsal thalamus; limbic structures such as the hippocampus, amygdala, bed nucleus of the stria terminalis, and hypothalamus. It has been suggested that these structures are coordinately connected and are responsible for the normal regulation of mood. They all share the property that their intrinsic activity and presumably connectivity may be modulated by ascending innervation from the locus ceruleus (norepinephrine), ventral tegmental area (dopamine), and raphe nuclei (serotonin). Histaminergic innervation from the tuberomammillary nucleus has important modulatory effects in the prefrontal cortices.

The neurobiologic consequences of dysregulation in the context of recurrent depression appear to be maladaptive plastic changes occurring within the distributed network. This may include changes in synaptic connections, cytoarchitecture, and gene expression [22]. It has also been suggested that neuronal endangerment and death may also be a consequence of repeated major depressive episodes. This has the worrisome implication that some of the plastic changes occurring with recurrent

depressive episodes and the dysregulation of the connected network may impair neuronal survival (for a review see [23]). Whether such changes are persistent or truly irreversible has not yet been clarified.

Referring back to the sensitization and kindling models, the possibility exists that these plastic changes in the distributed network regulating mood and occurring with multiple recurrences, may make it more likely that characteristics of the depressive illness and the underlying neurobiology change over time. This “course of illness” concept would suggest that the brain in the first episode and after an individual has had six or more recurrences may be vastly different. The functional change over multiple recurrences will be detected by the instability seen in the network, that is it can become spontaneously dysregulated.

An additional feature of this hypothesis is directly related to the subcortical processing of prefrontal cortical domains. Output from the anterior cingulate and orbitofrontal cortex is partly processed through the ventral striatum (nucleus accumbens) and the dorsal striatum (caudate and putamen). These prefrontal efferents are anatomically discrete and are organized topographically in the dorsal striatum, through the globus pallidus internus and the mediodorsal thalamus (direct pathway). In addition, working memory subserved by the dorsolateral prefrontal cortex, and motor output from the pre-motor planning area and motor strip are also processed through the dorsal striatum and overlap to a certain extent with those connected to prefrontal structures implicated in mood regulation.

If the hypothesis that recurrent mood episodes are responsible for maladaptive plastic changes in connected structures, then we might expect the dorsal striatum to be modified late in the course of depressive illness. This would be borne out by documenting changes in neurocognitive testing of prefrontal or subcortical function. We would also anticipate fine motor abnormalities developing in some sensitive individuals over time.

Finally, as we consider the longitudinal course of depression, the underlying neurobiology, note the potential neurophysiologic and structural changes occurring over multiple episodes and demonstrate how the illness worsens after multiple episodes, we are impressed by the magnitude of the problem of managing this illness. We confront an illness that has a high prevalence worldwide, is inadequately treated even in the United States, and given the current literature could be argued to have the hallmarks of a progressive neurologic illness. This review becomes yet one more article emphasizing the chronic nature of this illness, highlighting the imperative to integrate the long-term course of this illness into current treatment algorithms.

We will review the longitudinal course of depression by examining prognostic factors related to the duration, severity, and chronicity of an index major depressive episode, risk factors for recurrence once remission has been established, and changes that occur over multiple recurrences in terms of symptoms, disability, independence from stressors and likelihood of future recurrence, gender effects, and the effect of comorbidity and substance abuse.

8.3

Course of an Index Major Depressive Episode

The National Institutes of Health Collaborative Program on the Psychobiology of Depression—Clinical Studies (CDS) was intended to be a large multi-site prospective trial examining factors associated with remission and relapse of major depression, and now has yielded published reports on follow-up for as long as 15 years. In one such report, 431 subjects were followed from their index major depressive episode (MDE); 50% recovered within 6 months and then the rate of remission declined rapidly. The likelihood of recovery in the next prospectively observed month was 15% in the first 3 months, but then declined to 1–2% over years 3 to 5 of follow-up. The critical point from this study was the impact of chronicity; these authors noted that the longer patients were ill, the less likely it became that remission would be achieved [10].

There was also a consistent relationship between the current level of depressive symptomatology and the likelihood of remission. Subjects with dysthymia, minor depression or moderate depression were 18 times more likely to begin to recover compared to those with severe symptoms. This suggested to the authors that patients improved in a step-wise manner from their MDE. This view of symptom expression in major depression as existing on a continuum from as few as two (as is described for minor depression), or seven to nine symptoms in a severe MDE is supported by longitudinal data [24], and was the main finding from a review of the data in 1996 by leaders in this area [25].

Many subjects in the CDS study with a chronic course had ongoing subsyndromal depressive symptoms, and disability more consistent with dysthymia or minor depression [10]. The course and prognosis associated with these subsyndromal symptoms will be reviewed below.

The pattern of recovery from a major depressive episode varies greatly across studies, although a median of 20 weeks was found in the CDS cohort, which supported similar durations in samples from Angst's prospective studies in Switzerland [1–4]. In a separate analysis of the CDS among patients that remained unipolar, a change in the length of an MDE after a number of prospectively followed recurrences was not observed. The median duration after the first MDE was 21 weeks, after the second 20 weeks, after the third 19 weeks, and the fourth and fifth episodes were 20 weeks each [26]. This study characterized prospectively observed episodes, though some subjects had retrospectively reported prior MDEs before entry to the study. The authors cautioned that this may have obscured the actual number of prior episodes due to reporting this, and thereby affecting the appearance of changes in duration of illness over the first few episodes.

To compare rates by gender within the CDS, 96 males, and 101 females were followed who were diagnosed with having their first MDE. Included within this cohort were men (5%) and women (12%) with psychotic features. Data were collected prospectively for up to 15 years. Most of these subjects were recruited while hospitalized for their index MDE, indicating a higher level of severity in the index episode than a cohort recruited only from an outpatient population. Of these

individuals, 91% of males and 90% of females remitted within 5 years, and 100% of males and 94% of women remitted by 10 years. The first prospective relapse occurred within 1 year for 21% of men and 31% of women. By 10 years 68% of men and 78% of women had relapsed. Four men and two women committed suicide during the follow-up period, and 14 men and eight women died of medical causes. A common and discouraging note from nearly all longitudinal studies was that most subjects did not receive antidepressant treatment during the prospectively followed period [27]. These data did support a higher risk of relapse in the first 6 months for women, although the relapse risk became equal by the first year.

Among the CDS cohort as a whole Keller and Boland reported a recovery rate of 80% by 2 years, 88% by 5 years, 93% by 7 years, and 94% by 15 years [11]. While the level of chronicity in this significant minority of patients was striking, there is limited data that suggest that the risk of chronicity may be independent of remission from the prior episode. Keller reported that in the first prospectively followed MDE in subjects with a prior MDE, the rate of chronic unremitting depression was 8% [11]. This would imply that in highly recurrent cohorts, for example after four recurrent MDE, conservatively there could be greater than 20% of the original cohort with chronic depression after 5 years, with the proportion of chronically-ill individuals increasing arithmetically over time. In another analysis of the CDS cohort 258 patients with ongoing depressive symptoms in a prospectively followed MDE were monitored over 10 years and the probability of recovery decreased with every year after onset. The weighted probability of recovery was 38% in the second year, 27% in the third year, and 16% in the fourth year [28]. These data highlight the highly recurrent nature of depression in this cohort and the strongly high risk of chronicity appearing over time.

Predictors of chronicity in a study of 95 subjects followed for 3.5 years (defined as having no 2 month period without symptoms of depression during follow-up) were, younger age at the onset of the first psychiatric disorder, more severe depression at baseline, and more psychopathology [29]. Genetic factors may also affect the time to recovery from an MDE. A study of 1030 female–female twin pairs from a population-based twin registry identified multiple environmental and temperamental factors correlated to the time to recovery, but also noted a genetic risk for chronicity. There appeared to be a modest effect of genetic risk in depressive episodes overall, but a more robust effect when considering later phases of a depressive episode and MDEs of longer duration [30, 31]. In a follow-up study there was a significant effect of duration of the worst MDE and the risk of illness in the co-twin, suggesting a relationship between genetic risk and chronicity [32].

Residual symptoms after recovery from an index MDE has been thought to be associated with more disability between MDEs, and to be prognostic for higher relapse susceptibility [33, 34]. A cohort from the CDS prospective trial reported on 82 patients with residual symptoms, and a relatively asymptomatic group of 155 subjects all followed for at least 10 years. These patients were assessed using a Psychiatric Rating Scale (PRS) with a “1” indicating a complete return to the subject’s normal baseline without any residual symptoms of depression, and a “2” indicating a state of continued symptoms although of no more than mild severity, and described

as the subject not being “back to usual self”. The PRS “2” vs. “1” cohorts were statistically more likely to have had no relapses in the 10-year follow-up, and relapses were more rapid among the PRS “2” group, with the median time to relapse being 68 vs. 231 weeks. In terms of relapse to a minor depressive episode these subjects relapsed 5.5 times faster than the asymptomatic patients [34].

In a further analysis of the CDS prospective database described above, Judd et al. reported that those with an incomplete recovery had more subthreshold depressive symptoms over the follow-up period, a higher rate of relapse into a syndromic MDE, and overall had a more severe and chronic illness course. These patients had overall a median of 70.1% of follow-up weeks with subthreshold symptoms, minor depression, dysthymia or an MDE compared to 21.4% in the asymptomatic group. The symptomatic group were much more likely to have highly recurrent minor depressive episodes, with 23.1% having three or more episodes, versus 2.9% for the asymptomatic individuals [18]. These data would appear to support the heuristic of neural networks becoming more triable with highly recurrent MDD, by the greater prevalence of symptoms in those most likely to relapse.

8.3.1

Time to Recurrence of a Major Depressive Episode after Remission

The cardinal feature of unipolar depression is recurrence. Naturalistic as well as longitudinal treatment studies have demonstrated the highly recurrent nature of this illness [14, 35]. While discussion of the effects of the number of prior episodes will be considered below, it will be briefly stated here that number of prior episodes has been repeatedly demonstrated to predict the relative duration of the well-interval [28, 36–38]. In a study by Solomon et al., 258 patients were followed for 10 years in a prospective naturalistic study. Of the two-thirds that relapsed, relapse was predicted by the number of prior episodes, with the risk of relapse in the follow-up period increasing by 16% with each additional prior episode of depression [28].

While not as clearly established, an early age of onset of major depression has been associated in some studies with more rapid recurrences [39]. Coryell’s study of 396 relatives, age- and sex-matched comparison subjects and spouses of affectively ill individuals were followed for 6 years. Minor symptoms of depression at intake, the number of symptoms recalled in the worst MDE, a non-affective comorbid psychiatric diagnosis and early age of onset were all associated with recurrence [40].

A 15-year prospective trial examining recurrence after remission of a depressive episode examined 380 subjects. Thirty-three of these remained well and were followed for the entire 15 years, while 66 did not experience a relapse up until the time they were lost to follow-up. Multiple demographic and clinical characteristics at intake were examined for their association with the subsequent course of their major affective disorder [41]. In this cohort, the median number of weeks to recurrence was 132, with the mean time to recurrence 145 weeks. The percentage recurrence over the 15 years was 85% overall. Of some interest, a total of 19% either had mania or hypomania during the follow-up period, although it was not noted whether this was while on antidepressant treatment or not.

Gender has been associated in some studies with relapse risk. Consistent with this women in this cohort were 43% more likely to experience a recurrence, and women that never married 55% more likely than those divorced or married. Women are more likely to have a higher prevalence rate, up to 2 : 1 in some studies, and most studies have reported an earlier age of onset and higher risk of recurrence [42–45]. However, some well-designed retrospective studies did not find a gender effect [45]. It required reanalysis of this data with follow-up for more than 5 years before a gender effect was identified [44] suggesting that gender effects may not be apparent after a first MDE [27] but become apparent within 5 years of an index MDE, e.g. over the longitudinal cause of illness.

Chronicity of the current major depressive episode has also consistently been identified as a marker for recurrence. In the CDS study a longer duration of the current MDE before entry into the study was associated with a higher risk of relapse, amounting to an 11% increased risk for every year of being depressed. In a similar fashion, each additional major depressive episode prior to the index episode resulted in an 18% increase in the risk of recurrence [41]. This is consistent with findings from the Pittsburgh imipramine/interpersonal psychotherapy maintenance studies suggesting that early aggressive treatment in a prospectively-observed MDE was associated with a decrease in the duration of the observed MDE to 11–12 weeks. Thus early treatment resulted in a shortening of the MDE compared to the prior prospectively-observed MDE by 4–5 months [46]. More recently, a small prospective study of 25 inpatients with major depressive disorder, were followed for up to 12 months. Despite the fact that all subjects received adequate pharmacotherapy, 42% were still ill after 52 weeks. The best predictor of chronicity in this short and relatively small study was the length of the index depressive episode [47].

Compliant use of antidepressant treatment and maintenance of euthymia has been demonstrated in one long-term follow-up study. Kupfer and Frank blindly assigned remitted subjects with recurrent major depressive disorder (RMDD) to imipramine, interpersonal psychotherapy or combinations of these treatments or placebo for 3 years. This landmark study was followed by randomization of subjects that had remained well into continued active imipramine (average of 200 mg/day) or placebo groups for the next 2 years. They found a highly significant effect of reduced relapse rates in the imipramine-treated group [14]. The subjects that remained well were once again randomized to imipramine or placebo and again followed for another 5 years with similar results [48]. Thus, a consistent benefit of continued maintenance pharmacotherapy was associated with a reduced rate of relapse. In the NCS study following recurrence over 15 years, antidepressant treatment between the remitted and relapsed groups was not significantly different using scores on the composite antidepressant scale, either during the index episode or during the well-interval. We will discuss the significance of findings related to antidepressant treatment received and outcomes during prospective longitudinal studies in Section 8.4 which reviews the effect of treatment on disease course.

Some have suggested that antidepressant use may increase the risk of relapse or severity of illness [49]. In the long NCS follow-up study, there was no significant difference between the number of those subjects receiving antidepressant treatment

during the index episode (89% in the recurrent group, and 84% in the non-recurrent group) [41]. Given the results of Kupfer and Frank, this suggests that acute treatment, even when successful, may not by itself affect the course of illness or risk of relapse. However, continued maintenance treatment can profoundly affect relapse rates, and grew our model of illness course progressing with each MDE, it would imply successful maintenance treatment may affect the illness course. Unfortunately in all long-term naturalistic prospective studies the degree of medication treatment is not striking [28], and given the lack of major differences between outcomes among “treated” versus “untreated”, the adequacy of treatment is questioned. For example, in the Solomon et al. study, they rated the highest level of treatment received for at least four consecutive weeks during a MDE. Across the five prospectively followed MDE recoveries 54 to 78% received 100 mg of imipramine or its equivalent, 33% received 200 mg or its equivalent for the first three recurrences. By the fifth recurrence, 51% received 200 mg or more [28].

The question of the effect of prolonged remission on relapse risk and course of illness is interesting from the standpoint of what the underlying neurobiologic process may be, and what the clinical effect may be of prolonged remission such as in the Frank and Kupfer studies. In the NCS cohort, 105 subjects were remitted for 5 years or more. About half of the 105 relapsed within the next 5 years, while 42% remained well to 15 years. No demographic or clinical variables predicted time to recurrence among the subjects with 5 years of euthymia [41]. However, antidepressant treatment was followed naturalistically and among the subjects that relapsed in this group antidepressant treatment was received for 66 for those who relapsed vs. 91 weeks in those who remained remitted ($p < 0.02$, though the significance level set for this study was 0.01). Another long-term prospective trial of 258 subjects followed over 10 years likewise showed that the risk of relapse decreased as the time spent in remission increased [28].

8.3.2

The Effect of Residual Symptoms of Depression on Recurrence Risk

The studies reviewed above consider various courses and demographic risk factors for recurrence of a MDE, however longitudinal prospective studies over periods as long as 12 years clearly demonstrate that the majority of time with symptom and disability burden is not spent during a syndromal episode of depression [34]. Even within a MDE, it has been estimated that for only 32% of the time will a patient meet requirements for a syndromal diagnosis of depression [9]. At recovery from an index MDE, about one-third will have residual symptoms [33, 34]

Residual symptoms, minor depression and dysthymia all represent subsyndromal active illness states for those who have “recovered” from a major depressive episode. This view of depression as existing on a continuum of symptom expression was also supported by a 26-year prospective study by Angst et al., recently reanalyzed by Angst and Merikangas, which clearly demonstrated that many patients met diagnostic criteria for multiple depressive subtypes over the course of follow-up [50, 51]. Conceptually, we might think of subsyndromal symptom expression as

continued dysregulation of connected networks modulating mood. Ongoing subsyndromal symptoms could represent a friability of this system: perhaps due to inadequacy of compensatory re-regulatory mechanisms, changes in the underlying neurophysiology or structural change in these areas, or all three. Such a friable network would most likely be reflected in a course of illness characterized by more syndromal illness, more time spent symptomatic in a sub-syndromal state, and more disability than seen with a more stable network that maintains euthymia despite the challenge of the stress and strain of daily life.

One of the most important studies to date characterizing the symptomatic course of unipolar depression examined weekly depressive symptoms in 431 subjects in a multi-site trial. The symptom burden was stratified into four tiers: no depressive symptoms, symptoms below the threshold for minor depression (mD) referred to as subsyndromal symptoms of depression (SSD), depressive symptoms at the threshold for mD or dysthymic disorder, and syndromic MDE. Using the psychiatric rating scale, patients were assessed over 12 years prospectively. It was found that these subjects were symptomatically ill for 59% of the weeks of follow-up, with 17% of time spent with SSD, 27% spent with mD and 15% of time with a syndromal MDE. In this cohort, subjects with double depression (72% of weeks ill) and recurrent depression (65% of weeks ill) were more likely than those with a single MDE (46% of weeks ill) to be symptomatic [17]. Of the patients with MDD 23% were not free of depressive symptoms over a 2-year period for even 1 week. Thus, chronicity and recurrence were correlated to the overall non-syndromic burden of illness, just as has been true of syndromic illness. With reference to the hypothesis stated at the start of this chapter, syndromic and non-syndromic MDE exist on a continuum, and both reflect a friable network that cannot stably maintain euthymia. Thus a friable network is more likely to relapse into mD, dysthymic as well as MDE episodes.

Supporting this interpretation, 70 completely asymptomatic subjects that had completely recovered from a first MDE were compared with 26 with subsyndromal symptoms. A survival analysis over 5 years reflecting assessments every 6 months showed that subthreshold depressive symptoms were associated with a greater than three-fold higher rate of relapse to a syndromic MDE. If relapse was defined as an MDE, mD or dysthymia, the rate of relapse was 12-fold higher. Of the asymptomatic patients 34% remained in remission for the entire follow-up period while only 8% of subjects with subthreshold symptoms on recovery were well at the end of the 5-year period. These subjects with subsyndromal symptoms also had more chronic MDEs but not more chronic mD episodes (dysthymia). As might be expected, the well-interval was seven times shorter for the recovery group with subsyndromal symptoms (22 weeks) versus the asymptomatic group (154 weeks) [34].

In contrast to patients with MDD, patients with dysthymia have less severe symptoms, though the level of disability approaches that seen in severe MDD. In a naturalistic prospective study, 86 subjects with early-onset MDD with dysthymia, were compared to 39 subjects with episodic MDD, and had symptoms assessed at 30 and 60 months using the Longitudinal Interval Follow-Up Evaluation and the 24-item Hamilton Depression Rating Scale (HDRS). Patients with dysthymia and

a history of MDE were more likely to relapse into a new MDE than those with episodic MDD with a euthymic well-interval, again supporting the hypothesis that chronically dysregulated circuits are more likely to cause relapse into an MDE. Data from this study also supported the suggestion that a diagnosis of dysthymia increased the risk of onset of an MDE. Among 19 subjects who had reported no history of an MDE, 74% suffered such an episode during the 5 years of follow-up whilst among those subjects with a history of dysthymia, and recovered from an MDE, 78% had relapsed by the second assessment at 60 months. Finally, 93% of these patients subsequently relapsed into a third MDE. These rates were significantly higher than those seen for the episodically depressed subjects, 60% of whom relapsed in the same time-frame ($p < 0.01$) [52]. These data highlight the interaction between chronicity and risk of relapse.

Another study designed to examine whether the level of symptomatic recovery from an MDE was predictive of the duration of the well-period and risk of relapse [34] followed 82 subjects. These subjects had continued residual symptoms based on the Psychiatric Status Rating scale (PSR), and were compared to 155 completely asymptomatic subjects, and then assessed every 6 months for 5 years. The risk of development of residual symptoms was in part based on the duration of the MDE. Subjects with intake MDEs of more than 2 years were twice as likely to have residual symptoms as those individuals who had suffered the MDE for less than 6 months.

The asymptomatic subjects were less likely than the symptomatic subjects to relapse in the 10 years of follow-up; 34% of asymptomatic patients were without a recurrence, versus 13% in the symptomatic group. Those with residual symptoms relapsed to an MDE at a rate three times that seen in asymptomatic patients. Overall survival showed the median time to relapse to an MDE to be 68 weeks in the residual symptom group, versus 231 weeks in the asymptomatic group. Survival to any relapse (MDE, dysthymia, mD) was 184 weeks in the asymptomatic group versus 33 weeks in those with residual symptoms, nearly a six-fold difference. In an analysis of the risk associated with residual symptoms and the number of recurrent episodes (< 3 or > 4 episodes), more than four episodes was significantly associated with early relapse only within the group with an asymptomatic recovery from their MDE. The survival curve for multiple episodes was found to be nearly identical to that for the residual symptom group [34]. This suggests that current evidence of dysregulated networks regulating mood, as demonstrated by ongoing residual symptoms, is as potent a marker for future susceptibility to relapse as is the number of prior recurrent MDEs.

8.3.3

Comorbidity

There is ample literature supporting the hypothesis that comorbidity with an anxiety disorder or substance abuse increases the overall severity of illness. In the study of residual symptoms mentioned above [34], residual symptoms after recovery were more likely for those with comorbid non-affective psychiatric illness or substance abuse at intake (34 vs. 12% without comorbidity).

Anxiety disorders and depression share a high rate of comorbidity. A recent 15-year prospective study of the Zurich Cohort examined the development and course of illness of anxiety and depression, with an analysis of the development of comorbidity [53]. As was the case in MDD, anxiety disorders and combined anxiety and depression was found to occur in females at 1.5–2 times the rate found in males. Overall, 21% of subjects with depression and 24% with anxiety developed anxiety and depression over the follow-up period. Of those with anxiety 50% or more developed depression or mixed anxiety/depression during the same period, with women being more likely to transition to another diagnosis or to develop comorbidity. This study also confirmed that anxiety is more likely to predict the subsequent onset of depression, than depression the onset of anxiety.

These data suggest that comorbid anxiety may in fact be a prognostic factor for recurrence in MDD though this was not assessed in this data set. As commented on by Merikangas et al. [53], comorbidity may be a misnomer. They suggested that “anxiety and depression may be manifestations of the same underlying diathesis”. This is consistent with the functional imaging literature which suggests that dysregulation of limbic, paralimbic, and prefrontal structures in anxiety significantly overlap with those regulating mood. The implication of comorbid anxiety would be that more widespread dysregulation would be prognostic of a more chronic and unstable neural network, and more severe illness course. Multiple studies have reported that comorbid anxiety and depression leads to a more severe, chronic and persistent illness than pure depression alone [54].

8.3.4

Effect of Recurrence on Sensitivity to Stressful Precipitants

The above-mentioned studies clearly demonstrate that multiple factors appear to modify the risk for relapse into a subsyndromic or syndromic MDE. This is fortified by related consequences: increased risk of chronicity, decreased well-interval, and increased psychosocial disability. From these data we begin to see the outlines of a “course of illness” for MDD. Below we will review studies which support the idea that progressive changes in the neurobiologic substrate occur with each recurrence (or the presence of disabling residual symptoms), and that this has consequences for the likelihood of recurrence, and possibly other factors such as treatment responsiveness.

In a pair of landmark studies examining the effect of the number of recurrent episodes on the presence of precipitating stressors before relapse into the next MDE, and the interplay of genetic risk in this model [32], Kendler has tried to demonstrate “kindling” in a clinical context [31].

As discussed earlier, kindling is a model for the development of spontaneous seizures following repetitive exposure to an initially sub-convulsive stimulus. Some have considered the progression of this experimental pathology from induced seizures to spontaneous seizures as representative of the disease course of affective disorders. The change from sensitivity to environmental stressors early in the illness course, to being relatively independent of stressors, with relapse occurring

apparently “out of the blue” [55], is consistent with the pattern seen in these studies described in detail below.

The first study examined members of 2395 female twin-pairs followed over a period of 9 years in four assessments. This study clearly demonstrated that the odds ratio for the presence of a stressful life event in the 4 weeks preceding the onset of a MDE decreased dramatically between the first and sixth MDE. It also showed that the risk of onset of the next MDE increased linearly over the first eight MDEs. Combining these two risk variables, the study showed a nearly linear increase in the odds ratio for risk of onset up to over 30 recurrences in subjects who had experienced at least one stressful life event in the preceding month [56].

The next study looked at the same cohort using a discrete-time interval survival analysis examining the interaction between stressful life events, genetic risk and the number of recurrent episodes. Kendler et al. demonstrated that genetic risk interacted with the effect of stressful life events and the number of depressive episodes [32]. Stratifying genetic risk in the twin-pairs by zygosity, they defined the lowest genetic risk to be the twin with a monozygotic twin with no history of an MDE, low risk to be as the above in a dizygotic twin-pair, high risk to be as the dizygotic twin with a history of an MDE, and highest risk associated with monozygosity with a history of an MDE in the other twin. They noted that across all genetic risk groups both stressful life events and previous depressive episodes predicted the risk for the onset of an MDE. Comparing those with the lowest and highest risk, it became apparent that the association between stressful life events and onset of an MDE was more robust in the low genetic risk groups, and the increase in risk seen with multiple recurrences was more elevated in this group as well. Of interest was that the incidence of stressful life events were consistently greater in the high-risk group.

Examining these risk factors in more detail, a first MDE in the lowest genetic risk group was associated with a stressful life event 60% of the time. In a parallel circumstance at the highest genetic risk, there was a stressful life event preceding the onset of the first MDE 38% of the time. In the lowest genetic risk group the effect of the number of prior episodes was to increase the risk of onset of the next MDE, while in the highest genetic risk group, the increase was much less robust [32]. These data give shape to the hypothesis that recurrence, genetic risk, and stressful life events can modulate the course of illness in recurrent major depression.

8.3.5

Effect of Recurrence on Subsyndromic Symptoms

Compared to patients experiencing recurrent episodes of depression, patients with a single MDE in a 12-year prospective study of subsyndromal depressive symptoms, had a significantly more benign course of illness, fewer of these subjects had an age of onset before 21 years, and they were overall asymptomatic over half the time at follow-up. Those with a recurrent illness had a significantly earlier onset of illness. Those with double depression had more time ill, and more than 50% of these

individuals were ill before the age of 21 years. Once chronicity was established, it tended to persist and recur [17].

In another prospective trial with follow-up over 5 years at 6-month intervals, risk of relapse was again correlated to the presence of subsyndromal symptoms. Of interest with regard to possible interaction between the number of recurrent episodes and residual symptoms of depression, was the finding that in the group with more than four depressive episodes, early relapse was predicted on the basis of the number of prior episodes only in the asymptomatic recovered group. This suggests that subsyndromal symptoms may be a more powerful predictor of relapse than a history of multiple recurrences in symptomatic patients [17]. At the same time, the development of residual symptoms has also been associated with the number of prior recurrences [8], suggesting these two parameters, residual symptoms and number of prior recurrences, are markers for a friable network, susceptible to dysregulation to non-syndromal as well as syndromal depressive illness. Supporting this are two findings: that subsyndromal symptoms predicted a higher likelihood of having a family history of depression [57], and that residual symptoms predicted a course of illness characterized by more severe and chronic symptom expression, more MDEs, more chronic MDEs, shorter well intervals, and fewer weeks spent asymptomatic [8].

8.3.6

Effect of Recurrence on Psychosocial and Neurocognitive Function

One aspect of the hypothesis that mood is regulated through a network of connected neural structures is directly related to the subcortical processing of prefrontal cortical domains. Output from the anterior cingulate and orbitofrontal cortex is processed through the striatum. Topographical organization of these prefrontal efferents is consistently found in the striatum. Multisynaptic relays process prefrontal output through the direct and indirect pathways, involving the globus pallidus interior (direct) and exterior (indirect), the subthalami nucleus (indirect), a final output back to the prefrontal cortex from the mediodorsal thalamus. In addition, working memory subserved by the dorsolateral prefrontal cortex, and motor output from the premotor planning area and motor strip are also processed through the dorsal striatum and overlap to a certain extent with those connected to prefrontal structures implicated in mood regulation. One of the predicted consequences from the hypothesis that there is some progressive plastic change in the underlying neurobiologic substrate is that in areas where frontal outputs converge, such as the subcortical structures mentioned above, there will be dysfunction found in adjacent or overlapping functional domains. In this case, we would expect dysfunction in a number of prefrontal domains underlying cognitive function, motor function, and psychosocial functioning.

In particular, poor psychosocial functioning may be an excellent integrated measure of prefrontal output. For example, normal psychosocial functioning clearly requires intact function in areas such as the dorsolateral prefrontal cortex with its role in working memory and planning, the anterior cingulate and the part of its

function mediating motivated behaviors, and the orbitofrontal cortex with its role in awareness of appropriate social behaviors, and the ability to inhibit behaviors that are negatively reinforced. With this in mind we review the consequence of recurrent or chronic MDD on cognition, motor function and psychosocial functioning.

The CDS followed measures of psychosocial function prospectively at monthly periods for an average of 10 years. A total of 371 patients with unipolar disorder were assessed using the Longitudinal Interval Follow-up Evaluation (LIFE) over nine domains of psychosocial function. This study confirmed that psychosocial disability is pervasive and chronic and affects nearly all areas of functioning. There was evidence that the level of disability was correlated to symptom severity, and that the presence of psychosocial dysfunction was absent when symptoms were in complete remission [58]. It was speculated that residual dysfunction between episodes in the absence of even residual symptomatology persists after enough recurrent episodes have been experienced. Others have suggested that the time course for symptomatic improvement and improvement in functioning at work and interpersonally may occur at a slower rate, even after remission of symptoms [59]. As reviewed earlier in this chapter, residual symptoms are present to a higher degree after more recurrent episodes, or longer duration of time spent in an MDE. Thus the time spent with residual symptoms and the associated disability noted in the CDS study [58] even with a few symptoms would be more prevalent later in the illness course (after a high number of prior MDEs).

Several authors have suggested that subtle cognitive deficits are present in syndromic depression. These include encoding deficits, retrieval inefficiency [60], and other memory deficits, such as “false alarms” with regard to “good” words [61], and visuospatial memory [62]. Some have argued that frontal “executive” functioning such as dealing with novelty, selecting strategies, inhibiting incorrect responses, monitoring performance and using feedback to adjust future responding are primary to dysfunction in encoding and retrieval [62, 63]. Relevant to the model outlined at the beginning of this chapter, these deficits, including prefrontal and memory storage and retrieval strategies, have been suggested to be due to subcortical dysfunction [64]. Only limited data are available on psychomotor skills. It has been suggested that effortful perceptual-motor tasks are impaired in depressives, while non-effortful tasks are not different from controls [61]. These data are provocative, but not replicated in every study [62].

Two additional studies have examined the effect of the number of recurrent episodes on memory retrieval. In a study of 32 inpatients with an ongoing MDE, half of whom had had at least three recurrent MDEs (the others were in their first MDE). The mean HDRS was 25.5 among the recurrent group, and 26.6 in the single episode group. This study demonstrated difficulty with autobiographical memory retrieval in the form of “general responses” to queries characteristic of poor recall of detailed memory while in the depressed state. Of note was the nature of this deficit, i.e. it was only associated with positive memories. When the symptoms of depression remitted, the memory deficit was absent in the subjects with a single MDE. In contrast, memory deficits which were present in the subjects

with recurrent illness persisted into the well-state, and general responses were also found now in association with negative memories. While the recurrent episode group was slightly older than the first episode group (44.9 vs. 34.4 years) this was not significant; the average age of the control group was 41.7 years. This suggested that some change in the mechanism for retrieval of memories had degraded with multiple recurrences [65].

Another study examined memory in 20 patients with a single MDE, and compared their performance to 46 patients with recurrent MDD. A battery of neuropsychological tests was administered including the California Verbal Learning Test (CVLT). This study showed that patients with recurrent episodes had memory deficits not found in people with a single MDE, or when compared to published normative scores [66]. The recurrent group was specifically impaired for delayed recall, short-delayed cue recall, and long-delay free and cued recall. The authors argued that these deficits were not due to encoding effort, or proactive or retroactive inhibition, and that there was no relative retrieval deficit between the groups. Overall, the CVLT results for the recurrent group fell in the mildly impaired range, while the single episode group was within normal limits, and the deficits appeared to be in the acquisition of new memory. Of interest, non-psychotically depressed subjects that were not stratified single MDE versus multiple recurrences, performed far better than psychotically depressed individuals in a similar study. These non-psychotically depressed subjects performed within normal limits in a similar battery of neuropsychological testing suggesting that the effects of recurrent episodes on neurocognitive function can be obscured when subjects have not been stratified for the number of prior recurrences [67].

These results are broadly consonant with other literature demonstrating that geriatric patients with a history of multiple recurrent episodes show pronounced cognitive deficits, including memory difficulties [68]. The study by Beats et al. [68] also showed a correlation between increasing cognitive impairment and the number of hospitalizations due to a severe MDE; a marker for recurrence and severity. The mechanism of dysfunction may not be the same as that seen in younger subjects with multiple recurrences. Vascular insults in geriatric depression may interrupt connected networks affecting mood regulation as well as higher cognitive function thus affecting the same networks, but may dysregulate the circuitry via a different mechanism [69].

8.4

Effect of Treatment on Disease Course

Many of the naturalistic studies, some following patients over 10 years, included some indication of how much antidepressant treatment subjects had received during their illness course. For the most part, the degree of treatment in these populations had not been robust, and in most studies there were no striking effect of medication treatment or outcome. This is in contrast to the imipramine maintenance studies which clearly demonstrated the ability of continued antidepressant treatment to

maintain euthymia in an at-risk population [70]. From this, one might wonder whether the difference in outcome from studies that are naturalistic and do not define treatment strategies or closely follow compliance is due to inadequate treatment. Alternatively, there may be a higher risk of relapse associated with withdrawal from an antidepressant on entry to the placebo maintenance phase of the trial, or there may be a meaningful stratification of subjects in controlled studies biasing the results by only studying those who benefit from acute and some degree of continuation antidepressant treatment prior to randomization. In contrast to most naturalistic studies, one 20-year prospective trial undertaken as part of the CDS, examined the effectiveness of antidepressant treatments in the community in a group of 285 subjects. These findings indicated that those with a more recurrent or severe illness were more likely to have been treated with antidepressants, during both prior episodes, prospectively-observed episodes, and during well-intervals. Further, those who received higher intensity antidepressant treatment were more likely to recover from an MDE than those who did not [71].

While the data on maintenance antidepressant treatment in unipolar depression is not as developed as that relating to acute treatment, there have been a number of studies with remarkably similar findings: consistent treatment with the agent and dose that resulted in remission of the current MDE results in both statistically significant and clinically meaningful reductions in the risk of relapse. Table 8.3 is a thorough, though not exhaustive, list of prospective trials that have examined the benefits of continued antidepressant treatment in populations with recurrent major depression.

These studies generally follow a design of selecting subjects from a pool of individuals who have remitted after acute treatment with the study drug and have then been given continuation treatment on the study drug for 4 to 16 weeks before randomization to placebo or medication. Table 8.3 demonstrates that across follow-up periods, there is a consistent benefit of continued antidepressant treatment for up to 5 years [14] in terms of relapse prevention in subjects with a relatively high propensity to have recurrent illness. This suggests that a number of different antidepressant and dosing strategies may provide longitudinal benefit if the treatment dose is maintained or increased [72] during maintenance treatment following complete recovery with monotherapy. The outcome for those who require more complicated medication strategies or who show less robust clinical improvement is less clear.

When analyzed by drug treatment, that is SSRI versus TCA/MAOI, and examining those studies where subjects were followed for 1 year or more, there is some suggestion that the risk of relapse may not be as high in the TCA/MAOI studies. If we look at the outcomes in Table 8.3 among the prospective trials with durations of 1 year or more (see Table 8.4) the TCA placebo relapse rate is 66% (range 31–87%) while the SSRI studies reported an average of 53% subjects on placebo relapsing (range 23–84%). This issue arose following the publication of the sertraline maintenance study in chronically depressed individuals. This study reported a placebo relapse rate over 76 weeks of 23 vs. 6% in the group receiving sertraline [73].

Table 8.3 Long-term antidepressant maintenance studies

<i>Drug</i>	<i>Reference</i>	<i>Weeks of treatment</i>	<i>Relapse rates (%) Drug</i>	<i>Placebo</i>
Less than 6 months of medication treatment				
Amitriptyline/imipramine	92	8	12	50
Amitriptyline	93	8	12	29
Fluoxetine	94	12	26	49
Paroxetine	95	16	24	52
Milnacipran	96	16	16	24
Fluoxetine	94	23	9	23
Mean (range)			12 (9–26)	37 (23–50)
More than 6 months continued medication treatment				
Citalopram	97	24	11	31
Citalopram	98	24	13	24
Phenelzine	99	28	14	100
Nefazadone	100	44	13	46
Sertraline	101	48	20	40
Fluoxetine	102	48	20	40
Fluoxetine	94	50	11	16
Mean (range)			14 (11–20)	41 (16–100)
1 year or more continued medication treatment				
Amitriptyline	103	52	0	31
Phenelzine	104	52	13	65
Fluoxetine	105	52	26	57
Paroxetine	106	52	16	43
Fluvoxamine	107	52	12	35
Zimeldine	108	76	32	84
Sertraline	73	76	6	23
Imipramine	109	< 104	11	52
Phenelzine	110	104	20	81
Citalopram	111	104	22	76
Phenelzine	112	> 104	23	87
Imipramine	70	156	22	78
Imipramine	14	260	9	67
Mean (range)			16 (6–32)	60 (23–87)

Table 8.4 Long-term antidepressant studies: summary of the results of TCA/MAOI versus SSRI

	<i>Relapse rates (%) Medication</i>	<i>Placebo</i>
TCA/MAOI		
> 1 year continued medication treatment (seven studies)		
Mean (range)	14 (9–23)	66 (31–87)
SSRI		
> 1 year continued medication treatment (six studies)		
Mean (range)	19 (6–32)	53 (23–84)

A letter to the editor challenged the conclusion that maintenance pharmacotherapy was not indicated based on that single, albeit large, long-term prospective study, and may have been due to drug withdrawal effects [74]. Keller et al. responded to these concerns in a second letter [75], and argued that as the drug was tapered, and Kaplan–Meier relapse estimates immediately after discontinuation and from 9 to 24 weeks post-sertraline were not different, therefore this relapse rate was an actual estimate of relapse of illness in this cohort. While the relapse rate among those randomized to placebo was lower than in some other studies (see the review of the SSRI studies in Table 8.3 and the mean and range for these studies in Table 8.4), there is at this time no compelling argument to suggest that these rates of relapse across drug class in maintenance treatment are different. However, it may also be that there is a moderate cohort effect, with older TCA and MAOI studies enrolling more severely ill and more highly recurrent subjects than more recent outpatient SSRI studies which is obscured by this cursory analysis.

Cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT) have both been investigated for their ability to reduce relapse risk either with medications or alone. The study by Frank and Kupfer [70] treated recurrent depressives with imipramine and IPT in combination. Recurrence rates at 3 years were 90% on placebo alone, and 20% on imipramine. There was no significant benefit to IPT and imipramine in combination, and IPT by itself was only modestly helpful compared to placebo. A reanalysis of the IPT data showed that those therapist/client pairs that maintained a high consistency of focus on interpersonal issues had a significantly better outcome (median time to relapse 2 years) in the 3-year study than those with a low consistency (median time to relapse 5 months). These data supported the concept that IPT may be efficacious in reducing recurrences in subjects with highly recurrent MDD if therapists adhere to the manualized treatment protocol [76].

Although the focus of this chapter has not been on geriatric populations, an IPT trial in a cohort of recurrent depressives over the age of 59 years bears mention. Following acute treatment and a 16-week continuation phase, subjects were randomized.

The recurrence rate for placebo with medication clinic was 90%, placebo plus IPT 64%, nortriptyline alone 43%, and nortriptyline plus IPT 20%. These results are quite comparable to the Kupfer and Frank study, and again suggest that combined IPT and medication may provide some benefit in maintenance of euthymia.

CBT may also provide some benefit in patients with highly recurrent MDD. A large controlled trial of patients with residual symptoms after acute treatment with an antidepressant at adequate dosages was conducted to assess whether CBT provided additional benefit in these high-risk subjects. Patients were randomized to receive clinical management only, or clinical management with 5 months of CBT. Relapse rates were reduced by CBT from 47 to 29%. Additionally, more subjects achieved complete remission and social adjustment with CBT than with clinical management alone [77, 78].

Table 8.5 Prognosis can be stratified by response to aggressive treatment: maintenance on a treatment that results in complete remission improves prognosis

<i>Symptom state</i>	<i>Risk of relapse</i>	<i>Prognosis</i>
Complete recovery	Low	Good
Continued residual symptoms	Moderate	Fair
Subsyndromal symptoms	High	Poor
Chronic syndromal illness	Never remitted	Poorest

While only representative of the extant literature on psychological therapies, these studies suggest that empirically defined therapies such as CBT and IPT may reduce relapse risk, residual symptoms, and improve psychosocial outcomes. The impact these treatments may have on the long-term course of illness is yet to be defined, yet most would argue for combined treatments of medication and psychotherapy for those at highest risk of relapse. This is supported by the meta analysis by Thase et al. [13] of outcomes with combined psychotherapy and medication. Again, the major import of these data is not only the degree of effect, but that they fundamentally demonstrate that the course of illness may be modified using psychotherapeutic strategies (Table 8.5).

8.5 Summary

We have reviewed the course and prognosis of recurrent major depression. It is an illness course that is highly recurrent, frequently chronic, but also dominated by the presence of disabling residual symptoms between syndromic MDEs. We have proposed an hypothesis which outlines a course of illness based on prospective studies correlating the risk of chronicity and recurrence with clinical parameters such as dependence on external precipitants, cyclicity (duration of well-interval), severity, psychosocial disability, genetic vulnerability, age at onset, and severity (Table 8.6). However, the most clearly demonstrated and perhaps the two most important predictors for the course of illness are the number of prior episodes, and chronicity in the form of residual symptoms, syndromal illness, or mD/dysthymia.

We propose that symptoms are the result of a dysregulated network made up of multiple interconnected nodes that regulate mood. We have suggested that there may be modulation or modification of the neurobiologic substrate with multiple recurrent episodes increasing the risk of chronicity and recurrence, and negatively affecting function in a number of domains (Figure 8.1). This would suggest that the regulating circuits and the neurons that are contained within these areas are neurophysiologically and structurally indistinguishable between normal individuals and those early in a single MDE, but altered in those with highly recurrent illness. The point at which multiple recurrences have distinguishable neurophysiologic or structural effects may be linked to severity, duration, comorbidity, or genetic loading

Table 8.6 Prognosis can be stratified by risk factors for recurrence: the more risk factors for relapse, the greater the likelihood for recurrence and the poorer the long-term outcome

Risk factor
Early age of onset
Genetic vulnerability
Number of prior episodes
Severity
Chronicity of the current episode
Presence of subsyndromal symptoms at remission
Psychosocial disability

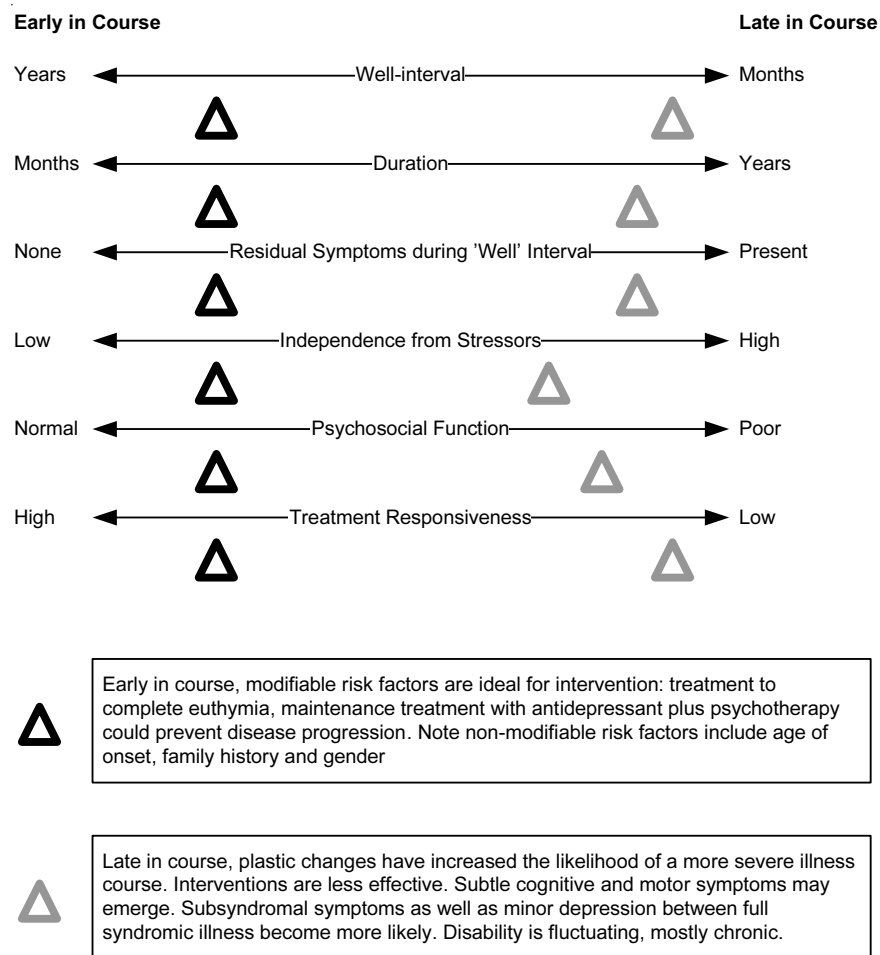


Figure 8.1 Variables affecting the course of early versus late illness.

Note: high genetic risk may overshadow the effect of recurrence

in different individuals, but the transition may be postulated to occur in most individuals after three to six recurrent MDEs. After a certain critical number of recurrences there is an increasing likelihood of network dysfunction and either syndromic or subsyndromic symptom expression.

There are multiple broad possibilities leading to the phenotype of highly recurrent depressive illness. We could postulate plastic change leading to apparently unmodifiable alterations, to possibly-modifiable effects, to highly-modifiable dysregulation. Unmodifiable change would be characterized by some persistent structural change, either cytoarchitectural or gross anatomic, as mirrored by animal models of epilepsy such as kindling. While hippocampal change has been postulated to be the consequence of multiple recurrent MDE [79, 80], it cannot as yet be conclusively said to be a result of highly recurrent illness as opposed to part of the etiology of such an illness course [81].

Possibly-modifiable change would be more like sensitization, e.g. some persistent neurophysiologic change that may potentially be re-modified back to the initial condition. Sensitization studies have shown that persistent changes in NMDA function and dopaminergic systems from the ventral tegmental area and nucleus accumbens to the dorsal striatum may be affected by re-challenge with stimulants [82, 83]. Dopamine antagonists may prevent the sensitization process [84], and recent work suggests that NMDA antagonists and nitric oxide inhibitors may restore normal reactivity to stimulants in sensitized animals [85]. While highly recurrent depression may have the hallmarks of a progressive irreversible illness, it may be that we have yet to find the proper “key” to unlock the apparent persistent plastic change. Evidence for reversing the apparent progressive plastic changes in chronic or recurrent illness may be the apparent low relapse rate in placebo-randomized subjects in the sertraline chronic depression study over the 76 months of follow-up. While the significance of this apparent low relapse rate is still debated, it is possible to entertain the idea that some deleterious effect of chronicity on the risk of future relapse was reversed by treatment with an SSRI.

A highly-modifiable change would be more characteristic of illnesses affected by the usual function of a system under duress, such as the hypothalamic–pituitary axis. This type of plastic change would be completely reversed if HPA function were normalized, e.g. the risk of future relapse would be equivalent to that among those individuals suffering only a single MDE [86]. There is a large database suggesting that dexamethasone non-suppression is a risk factor for relapse after medication treatment [87]. Animal models of early adverse experience have demonstrated persistent HPA hyper-reactivity to stress that is normalized with paroxetine [88, 89]. In humans, paroxetine has also been shown to normalize cortisol levels in an outpatient setting [90]. This SSRI has also been shown to normalize prefrontal metabolic abnormalities following a treatment response [91]. An hypothesis of a highly-modifiable plastic change with chronicity or recurrence would not predict the need for long-term pharmacotherapy, as the elastic nature of the change would allow the brain to reset after an MDE, if it was successfully treated. To date, longitudinal maintenance studies with antidepressants do not support this type of mechanism.

Stratifying patients by number of recurrences, or chronicity, or neurobiologic evidence of advanced illness may mobilize clinicians to consider the longitudinal course in their treatments, both somatic and psychotherapeutic. The next challenge in treating major depression will be clearly defining outcomes to patients with recurrent illness so that patient and physician choices concerning somatic treatments will be better weighed by clinical outcomes that include a greater likelihood of chronicity, and recurrence with each relapse. The possibility that these downstream effects of recurrence will include cognitive dysfunction and significant psychosocial disability may be one more aspect of the burden of the longitudinal course of major depression. Integrating the long-term course of depression into standard care will require the use of life charts and prospective identification of residual symptoms, and may require the use of standardized scales to quantify these symptoms, allowing more careful monitoring of residual symptoms for the targeted treatment.

Major depression appears to be a progressive illness. There is ample evidence to date that there may be progressive atrophy in some structures associated with recurrence, and some evidence that neurophysiologic changes modeled by kindling and sensitization contribute to the progression of illness. Ultimately, our understanding of the neurobiology of depression may show that all three possible mechanisms, irreversible structural change, partly reversible or modifiable plastic change, and completely reversible dysfunction such as in the case of the HPA, are implicated in the pathophysiology of recurrent depressive illness.

As we better understand the neurobiologic basis for major mood disorders, we begin to truly appreciate the aspects of the illness which parallel those seen in other neurodegenerative illnesses. The longitudinal antidepressant maintenance studies are the best evidence to date that the course of this illness may be modified and its progression arrested.

References

- 1 ANGST, J., PREISIG, M., Course of a clinical cohort of unipolar, bipolar, and schizoaffective patients: results of a prospective study from 1959 to 1985. *Schweiz. Archiv. Neurol. Psychiatr.* **1995**, *146*, 1–16.
- 2 ANGST, J., PREIZIG, M., Outcome of a clinical cohort of unipolar, bipolar, and schizoaffective patients: results of a prospective study from 1959 to 1985. *Schweiz. Archiv. Neurol. Psychiatr.* **1995**, *146*, 17–23.
- 3 ANGST, J., Clinical course of affective disorders. In *Depressive Illness: Prediction of Course and Outcome*, HELGASON, T., DALY, R. J. (Eds.). **1988**, Springer-Verlag: Berlin, 1–44.
- 4 ANGST, J., The course of affective disorders. *Psychopathology* **1985**, *19* (Suppl. 2), 47–52.
- 5 ANGST, J., BASSTRUP, P., GROF, H., HIPPIUS, W., POLDINGER, W., WEISS, P., The course of monopolar depression and bipolar psychoses. *Psychiatr. Neurol. Neurochir. (Amst.)* **1973**, *76*, 489–500.
- 6 LEHMANN, H. E., et al., An 11-year follow-up study of 110 depressed patients. *Acta Psychiatr. Scand.* **1988**, *78*, 57–65.
- 7 KILOH, L. G., ANDREWS, G., NEILSON, M., The long-term outcome of depressive illness. *Br. J. Psychiatry* **1988**, *153*, 752–757.
- 8 JUDD, L. L., AKISKAL, H. S., PAULUS, M. P., The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive

- disorder. *J. Affect Disord.* **1997**, *45*, 5–17; discussion 17–18.
- 9 KELLER, M. B., et al., Relapse in major depressive disorder: analysis with the life table. *Arch. Gen. Psychiatry* **1982**, *39*, 911–915.
 - 10 KELLER, M. B., et al., Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch. Gen. Psychiatry* **1992**, *49*, 809–816.
 - 11 KELLER, M. B., BOLAND, R. J., Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biol. Psychiatry* **1998**, *44*, 348–360.
 - 12 MUELLER, T. I., et al., Recovery after 5 years of unremitting major depressive disorder. *Arch. Gen. Psychiatry* **1996**, *53*, 794–799.
 - 13 THASE, M. E., The clinical, psychosocial, and pharmacoeconomic ramifications of remission. *Am. J. Manag. Care* **2001**, *7* (11 Suppl.), S377–S385.
 - 14 KUPFER, D. J., et al., Five-year outcome for maintenance therapies in recurrent depression. *Arch. Gen. Psychiatry* **1992**, *49*, 769–773.
 - 15 NIERENBERG, A. A., PETERSON, T. J., ALPERT, J. E., Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *J. Clin. Psychiatry* **2003**, *64* (Suppl. 15), 13–17.
 - 16 GELENBERG, A. J., et al., Randomized, placebo-controlled trial of nefazodone maintenance treatment in preventing recurrence in chronic depression. *Biol. Psychiatry* **2003**, *54*, 806–817.
 - 17 JUDD, L. L., et al., A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch. Gen. Psychiatry* **1998**, *55*, p. 694–700.
 - 18 JUDD, L. L., et al., Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am. J. Psychiatry* **2000**, *157*, 1501–1504.
 - 19 CUFFEL, B. J., et al., Remission, residual symptoms, and nonresponse in the usual treatment of major depression in managed clinical practice. *J. Clin. Psychiatry* **2003**, *64*, 397–402.
 - 20 WEISS, S. R., POST, R. M., Kindling: separate vs. shared mechanisms in affective disorders and epilepsy. *Neuropsychobiology* **1998**, *38*, 167–180.
 - 21 POST, R. M., WEISS, S. R., Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders: the role of serotonergic mechanisms in illness progression. *Biol. Psychiatry* **1998**, *44*, 193–206.
 - 22 NESTLER, E. J., et al., Neurobiology of depression. *Neuron* **2002**, *34*, 13–25.
 - 23 MANJI, H. K., et al., Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol. Psychiatry* **2003**, *53*, 707–742.
 - 24 KESSLER, R. C., et al., Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J. Affect Disord.* **1997**, *45*, 19–30.
 - 25 JUDD, L. L., Pleomorphic expressions of unipolar depressive disease: summary of the 1996 CINP President's Workshop. *J. Affect Disord.* **1997**, *45*, 109–116.
 - 26 SOLOMON, D. A., et al., Recovery from major depression. A 10-year prospective follow-up across multiple episodes. *Arch. Gen. Psychiatry* **1997**, *54*, 1001–1006.
 - 27 SIMPSON, H. B., NEE, J. C., ENDICOTT, J., First-episode major depression. Few sex differences in course. *Arch. Gen. Psychiatry* **1997**, *54*, 633–639.
 - 28 SOLOMON, D. A., et al., Multiple recurrences of major depressive disorder. *Am. J. Psychiatry* **2000**, *157*, 229–233.
 - 29 HOENCAMP, E., et al., A 3.5-year naturalistic follow-up study of depressed out-patients. *J. Affect Disord.* **2001**, *66*, 267–271.
 - 30 KENDLER, K. S., KARKOWSKI, L. M., PRESCOTT, C. A., Stressful life events and major depression: risk period, long-term contextual threat, and diagnostic specificity. *J. Nerv. Ment. Dis.* **1998**, *186*, 661–669.
 - 31 KENDLER, K. S., KARKOWSKI, L. M., PRESCOTT, C. A., Causal relationship between stressful life events and the onset of major depression. *Am. J. Psychiatry* **1999**, *156*, 837–841.
 - 32 KENDLER, K. S., THORNTON, L. M., GARDNER, C. O., Genetic risk, number of previous depressive episodes, and

- stressful life events in predicting onset of major depression. *Am. J. Psychiatry* **2001**, *158*, 582–586.
- 33 PAYKEL, E. S., et al., Residual symptoms after partial remission: an important outcome in depression. *Psychol. Med.* **1995**, *25*, 1171–1180.
 - 34 JUDD, L. L., et al., Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J. Affect Disord.* **1998**, *50*, 97–108.
 - 35 ROY-BYRNE, P., et al., The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. *Acta Psychiatr. Scand. Suppl.* **1985**, *317*, 1–34.
 - 36 KELLER, M. B., et al., Predictors of relapse in major depressive disorder. *JAMA* **1983**, *250*, 3299–3304.
 - 37 GONZALES, L. R., LEWINSOHN, P. M., CLARKE, G. N., Longitudinal follow-up of unipolar depressives: an investigation of predictors of relapse. *J. Consult. Clin. Psychol.* **1985**, *53*, 461–469.
 - 38 MAJ, M., et al., Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. *Am. J. Psychiatry* **1992**, *149*, 795–800.
 - 39 GILES, D. E., et al., Clinical predictors of recurrence in depression. *Am. J. Psychiatry* **1989**, *146*, 764–767.
 - 40 CORYELL, W., J., ENDICOTT, KELLER, M. B., Predictors of relapse into major depressive disorder in a nonclinical population. *Am. J. Psychiatry* **1991**, *148*, 1353–1358.
 - 41 MUELLER, T. I., et al., Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am. J. Psychiatry* **1999**, *156*, 1000–1006.
 - 42 EATON, W. W., et al., Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. *Arch. Gen. Psychiatry* **1997**, *54*, 993–999.
 - 43 PAJER, K., New strategies in the treatment of depression in women. *J. Clin. Psychiatry* **1995**, *56* (Suppl. 2), 30–37.
 - 44 WINOKUR, G., et al., A prospective follow-up of patients with bipolar and primary unipolar affective disorder. *Arch. Gen. Psychiatry* **1993**, *50*, 457–465.
 - 45 KESSLER, R. C., et al., Sex and depression in the National Comorbidity Survey.
 - I: Lifetime prevalence, chronicity and recurrence. *J. Affect Disord.* **1993**, *29*, 85–96.
 - 46 KUPFER, D. J., FRANK, E., PEREL, J. M., The advantage of early treatment intervention in recurrent depression. *Arch. Gen. Psychiatry* **1989**, *46*, 771–775.
 - 47 KRAVITZ, H. M., BLOOM, R. W., FAWCETT, J., Recovery from a recurrent major depressive episode. *Depress. Anxiety* **2000**, *12*, 40–43.
 - 48 KUPFER, D. J., Management of recurrent depression. *J. Clin. Psychiatry* **1993**, *54* (Suppl.), 29–33; discussion 34–35.
 - 49 FAVA, G. A., Can long-term treatment with antidepressant drugs worsen the course of depression? *J. Clin. Psychiatry* **2003**, *64*, 123–133.
 - 50 ANGST, J., SELLARO, R., MERIKANGAS, K. R., Depressive spectrum diagnoses. *Compr. Psychiatry* **2000**, *41* (2 Suppl. 1), 39–47.
 - 51 ANGST, J., MERIKANGAS, K., The depressive spectrum: diagnostic classification and course. *J. Affect Disord.* **1997**, *45*, 31–39; discussion 39–40.
 - 52 KLEIN, D. N., et al., Five-year course and outcome of dysthymic disorder: A prospective, naturalistic follow-up study. *Am. J. Psychiatry* **2000**, *157*, 931–939.
 - 53 MERIKANGAS, K. R., et al., Longitudinal trajectories of depression and anxiety in a prospective community study: the Zurich Cohort Study. *Arch. Gen. Psychiatry* **2003**, *60*, 993–1000.
 - 54 CORYELL, W., et al., Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. *Am. J. Psychiatry* **1988**, *145*, 293–300.
 - 55 POST, R. M., Sensitization and kindling perspectives for the course of affective illness: toward a new treatment with the anticonvulsant carbamazepine. *Pharmacopsychiatry* **1990**, *23*, 3–17.
 - 56 KENDLER, K. S., THORNTON, L. M., GARDNER, C. O., Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the “kindling” hypothesis. *Am. J. Psychiatry* **2000**, *157*, 1243–1251.
 - 57 SHERBOURNE, C. D., et al., Subthreshold depression and depressive disorder: clinical characteristics of general medical

- and mental health specialty outpatients. *Am. J. Psychiatry* **1994**, *151*, 1777–1784.
- 58 JUDD, L. L., et al., Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch. Gen. Psychiatry* **2000**, *57*, 375–380.
 - 59 MINTZ, J., MINTZ, L. I., ARUDA, M. J., HWANG, S. S., Treatments of depression and the functional capacity to work. *Arch. Gen. Psychiatry* **1993**, *50*, 761–768.
 - 60 ZAKZANIS, K. K., LEACH, L., KAPLAN, E., On the nature and pattern of neuro-cognitive function in major depressive disorder. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **1998**, *11*, 111–119.
 - 61 DEIJEN, J. B., ORLEBEKE, J. F., RIJSDIJK, F. V., Effect of depression on psychomotor skills, eye movements and recognition-memory. *J. Affect Disord.* **1993**, *29*, 33–40.
 - 62 PORTER, R. J., et al., Neurocognitive impairment in drug-free patients with major depressive disorder. *Br. J. Psychiatry* **2003**, *182*, 214–220.
 - 63 FOSSATI, P., ERGIS, A. M., ALLILAIRE, J. F. [Executive functioning in unipolar depression: a review]. *Encephale* **2002**, *28*, 97–107.
 - 64 FOSSATI, P., et al., [Deficits in memory retrieval: an argument in favor of frontal subcortical dysfunction in depression]. *Encephale* **1995**, *21*, 295–305.
 - 65 NANDRINO, J. L., et al., Autobiographical memory in major depression: a comparison between first-episode and recurrent patients. *Psychopathology* **2002**, *35*, 335–340.
 - 66 BASSO, M. R., BORNSTEIN, R. A., Relative memory deficits in recurrent versus first-episode major depression on a word-list learning task. *Neuropsychology* **1999**, *13*, 557–563.
 - 67 BASSO, M. R., BORNSTEIN, R. A., Neuropsychological deficits in psychotic versus nonpsychotic unipolar depression. *Neuropsychology* **1999**, *13*, 69–75.
 - 68 BEATS, B. C., SAHAKIAN, B. J., LEVY, R., Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol. Med.* **1996**, *26*, 591–603.
 - 69 ALEXOPOULOS, G. S., Role of executive function in late-life depression. *J. Clin. Psychiatry* **2003**, *64* (Suppl. 14), 18–23.
 - 70 FRANK, E., et al., Three-year outcomes for maintenance therapies in recurrent depression. *Arch. Gen. Psychiatry* **1990**, *47*, 1093–1099.
 - 71 LEON, A. C., et al., A 20-year longitudinal observational study of somatic antidepressant treatment effectiveness. *Am. J. Psychiatry* **2003**, *160*, 727–733.
 - 72 PERLIS, R. H., et al., Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder. *J. Clin. Psychopharmacol.* **2002**, *22*, 474–480.
 - 73 KELLER, M. B., et al., Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. *JAMA* **1998**, *280*, 1665–1672.
 - 74 BALDESSARINI, R. J., VIGUERA, A. C., Relapse of depressive symptoms after discontinuing sertraline. *JAMA* **1999**, *282*, 323–324.
 - 75 KELLER, M., et al., Relapse of depressive symptoms after discontinuing sertraline. *JAMA* **1999**, *282*, 323–324.
 - 76 FRANK, E., et al., Efficacy of interpersonal psychotherapy as a maintenance treatment of recurrent depression. Contributing factors. *Arch. Gen. Psychiatry* **1991**, *48*, 1053–1059.
 - 77 SCOTT, J., et al., Effects of cognitive therapy on psychological symptoms and social functioning in residual depression. *Br. J. Psychiatry* **2000**, *177*, 440–446.
 - 78 PAYKEL, E. S., et al., Prevention of relapse in residual depression by cognitive therapy: a controlled trial. *Arch. Gen. Psychiatry* **1999**, *56*, 829–835.
 - 79 SHELINE, Y. I., et al., Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J. Neurosci.* **1999**, *19*, 5034–5043.
 - 80 MACQUEEN, G. M., et al., Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 1387–1392.
 - 81 FRODL, T., et al., Hippocampal changes in patients with a first episode of major depression. *Am. J. Psychiatry* **2002**, *159*, 1112–1118.
 - 82 VANDERSCHUREN, L. J., KALIVAS, P. W., Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical

- studies. *Psychopharmacology (Berl.)* **2000**, *151*, 99–120.
- 83 CADOR, M., et al., D-amphetamine-induced behavioral sensitization: implication of a glutamatergic medial prefrontal cortex-ventral tegmental area innervation. *Neuroscience* **1999**, *94*, 705–721.
 - 84 VOIKAR, V., et al., Apomorphine-induced behavioural sensitization in rats: individual differences, role of dopamine and NMDA receptors. *Eur. Neuropsychopharmacol.* **1999**, *9*, 507–514.
 - 85 BATTISTI, J. J., et al., NMDA antagonists block expression of sensitization of amphetamine- and apomorphine-induced stereotypy. *Pharmacol. Biochem. Behav.* **2000**, *67*, 241–246.
 - 86 PARKER, K. J., SCHATZBERG, A. F., LYONS, D. M., Neuroendocrine aspects of hypercortisolism in major depression. *Horm. Behav.* **2003**, *43*, 60–66.
 - 87 RIBEIRO, S. C., et al., The DST as a predictor of outcome in depression: a meta-analysis. *Am. J. Psychiatry* **1993**, *150*, 1618–1629.
 - 88 KECK, M. E., et al., Reduction of hypothalamic vasopressinergic hyperdrive contributes to clinically relevant behavioral and neuroendocrine effects of chronic paroxetine treatment in a psychopathological rat model. *Neuropsychopharmacology* **2003**, *28*, 235–243.
 - 89 LEHMANN, J., et al., Effect of a single maternal separation at different pup ages on the corticosterone stress response in adult and aged rats. *Pharmacol. Biochem. Behav.* **2002**, *73*, 141–145.
 - 90 DEUSCHLE, M., et al., Antidepressive treatment with amitriptyline and paroxetine: effects on saliva cortisol concentrations. *J. Clin. Psychopharmacol.* **2003**, *23*, 201–205.
 - 91 BRODY, A. L., et al., Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Res.* **1999**, *91*, 127–139.
 - 92 MINDHAM, R. H., HOWLAND, C., SHEPHERD, M., An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. *Psychol. Med.* **1973**, *3*, 5–17.
 - 93 PAYKEL, E. S., et al., Effects of maintenance amitriptyline and psychotherapy on symptoms of depression. *Psychol. Med.* **1975**, *5*, 67–77.
 - 94 REIMHERR, F. W., et al., Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. *Am. J. Psychiatry* **1998**, *155*, 1247–1253.
 - 95 FRANCHINI, L., et al., Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. *J. Clin. Psychiatry* **1998**, *59*, 229–232.
 - 96 ROUILLON, F., et al., Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. Milnacipran recurrence prevention study group. *Int. Clin. Psychopharmacol.* **2000**, *15*, 133–140.
 - 97 MONTGOMERY, S. A., RASMUSSEN, J. G., TANGHOJ, P., A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. *Int. Clin. Psychopharmacol.* **1993**, *8*, 181–188.
 - 98 ROBERT, P., MONTGOMERY, S. A., Citalopram in doses of 20–60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. *Int. Clin. Psychopharmacol.* **1995**, *10* (Suppl. 1), 29–35.
 - 99 DAVIDSON, J., RAFT, D., Use of phenelzine in continuation therapy. *Neuropsychobiology* **1984**, *11*, 191–194.
 - 100 FEIGER, A. D., et al., Double-blind, placebo-substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. *Int. Clin. Psychopharmacol.* **1999**, *14*, 19–28.
 - 101 DOOGAN, D. P., CAILLARD, V., Sertraline in the prevention of depression. *Br. J. Psychiatry* **1992**, *160*, 217–222.
 - 102 GILABERTE, I., et al., Fluoxetine in the prevention of depressive recurrences: a double-blind study. *J. Clin. Psychopharmacol.* **2001**, *21*, 417–424.
 - 103 COPPEN, A., et al., Continuation therapy with amitriptyline in depression. *Br. J. Psychiatry* **1978**, *133*, 28–33.
 - 104 GEORGOTAS, A., McCUE, R. E., COOPER, T. B., A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of

- elderly depressed patients. *Arch. Gen. Psychiatry* **1989**, 46, 783–786.
- 105** MONTGOMERY, S. A., et al., The prophylactic efficacy of fluoxetine in unipolar depression. *Br. J. Psychiatry Suppl.* **1988**, 247 (3), 69–76.
- 106** MONTGOMERY, S. A., DUNBAR, G., Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. *Int. Clin. Psychopharmacol.* **1993**, 8, 189–195.
- 107** TERRA, J. L., MONTGOMERY, S. A., Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. *Int. Clin. Psychopharmacol.* **1998**, 13, 55–62.
- 108** BJORK, K., The efficacy of zimeldine in preventing depressive episodes in recurrent major depressive disorders – a double-blind placebo-controlled study. *Acta Psychiatr. Scand. Suppl.* **1983**, 308, 182–189.
- 109** KOC SIS, J. H., et al., Maintenance therapy for chronic depression. A controlled clinical trial of desipramine. *Arch. Gen. Psychiatry* **1996**, 53, 769–774; discussion 775–776.
- 110** ROBINSON, D. S., et al., Continuation and maintenance treatment of major depression with the monoamine oxidase inhibitor phenelzine: a double-blind placebo-controlled discontinuation study. *Psychopharmacol. Bull.* **1991**, 27, 31–39.
- 111** HOCHSTRASSER, B., et al., Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. *Br. J. Psychiatry* **2001**, 178, 304–310.
- 112** STEWART, J. W., et al., Prophylactic efficacy of phenelzine and imipramine in chronic atypical depression: likelihood of recurrence on discontinuation after 6 months' remission. *Am. J. Psychiatry* **1997**, 154, 31–36.

9

Treatment of Depression in Medical Illness

Charles L. Raison, David C. Porselle, Lucile Capuron and Andrew H. Miller

Abstract

Depression is a common and potentially deadly concomitant of many medical illnesses. While the multiple psychological stressors associated with being sick have long been recognized as a risk factor for depression, increasing data indicate that activation of the pro-inflammatory cytokine network also directly contributes to mood disturbance in the medically ill. Moreover, recent studies using treatment with the cytokine interferon-alpha-2b (IFN-alpha) as a model system for immune-based depression indicate that depression in the medically ill may represent an amalgam of mood-specific and neurovegetative symptom clusters that are mediated by different neuroendocrine/neurotransmitter pathways. These findings provide novel insights into ongoing diagnostic controversies created by the striking symptom overlap between major depression and sickness and have clear implications for the pharmacological treatment of depressive syndromes in patients with medical illnesses.

9.1

Introduction

Depression is a common and debilitating illness among otherwise healthy individuals, with an estimated 30-day prevalence rate of 5% among the general population of the United States [1]. Among patients suffering from medical illness, however, the prevalence of depression is far higher, often exceeding 50% in disorders such as cancer, Parkinson's disease, and multiple sclerosis. [2] In addition to markedly exacerbating the suffering that accompanies serious illness, depression has been shown to increase morbidity and mortality across a wide range of medical conditions. [2] Depression in the medically ill also represents a significant financial burden upon society, given the increased economic cost associated with providing health care to patients with major depression compared to those without depression [3].

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While explanations for the strikingly elevated prevalence of depression in the medically ill have traditionally focused on the multiple psychological stressors attendant upon being sick, increasing data demonstrate that physiological processes inherent to illness – especially activation of the cytokine network – may directly contribute to the pathophysiology of depression in medically-ill patients. These data have encouraged a paradigm shift, such that depression is increasingly recognized as a potential symptom of illness itself, with the corollary that treating depression represents an integral, rather than ancillary, component of good medical care. Concomitant with this changing perspective is a growing recognition that agents known to effectively treat depression also modulate immunological and neuroendocrine pathways that are altered in the context of immune system activation, such as occurs regularly in the context of medical illness.

This chapter will review our knowledge of treating depression in medically-ill patients. However, a full discussion of all relevant treatment modalities, including psychotherapy and related psychosocial interventions, is beyond the scope of this chapter. Here we limit our discussion to the rapidly expanding database substantiating the usefulness of antidepressant medications in treating depression in the medically ill, focusing on recent advances in our understanding of the pathways by which cytokines contribute to depression and the relevant effects of antidepressant therapies upon these pathways.

9.2

Diagnosing Depression in Medical Illness: Inclusive versus Exclusive Approaches

Depression must be identified before it can be treated. This identification, in turn, has much to do with how depression is defined – a matter of no small consequence for medically-ill patients, in whom the diagnosis of depression has long been recognized to be highly problematic as a result of the striking symptom overlap between sickness and depression; that is, from the fact that non-depressed sick individuals demonstrate many symptoms that are also experienced by medically healthy patients with major depression (see Table 9.1). Especially relevant in this regard are neurovegetative symptoms of depression that are often directly caused by pathophysiological processes inherent to illness itself or by concurrent treatment modalities, such as chemotherapy. These symptoms include fatigue, anorexia, weight loss, loss of libido, sleep alterations and psychomotor slowing. Thus, the question facing the clinician boils down to this: when, if ever, should neurovegetative symptoms be counted toward a diagnosis of depression in medically-ill patients, who may have these symptoms simply because they are sick?

Various methods for addressing this issue have been proposed. An oft-cited compromise was proposed by Cohen-Cole and colleagues who recommended that two systems of diagnosis be employed in medically-ill patients [5]. The first, an exclusive approach, removes fatigue and anorexia and requires only four (instead of five) of the remaining DSM-IV criteria for major depression. This approach improves specificity by privileging symptoms that are more common in the context

Table 9.1 Comparison of symptoms in sickness behavior and major depression (adapted from Raison and Miller [4])

<i>Sickness behavior</i>	<i>Major depression</i>
Anhedonia*	Anhedonia*
Anorexia*	Anorexia*
Cognitive disturbance*	Cognitive disturbance*
Decreased libido*	Decreased libido*
Fatigue*	Fatigue*
Psychomotor retardation*	Psychomotor retardation*
Sleep disturbance*	Sleep disturbance*
Social isolation*	Social isolation*
Weight loss*	Weight loss*
Hyperalgesia*	Increased pain complaints*
	Sad mood [†]
	Suicidal ideation [†]
	Worthlessness/guilt [†]

* Common to both depression and sickness behavior.

[†] More frequent in depression than sickness behavior.

of depression than illness. The second approach proposed by Cohen-Cole et al. is inclusive in nature and counts all DSM-IV symptoms of depression, without making a determination of whether they result from depression or illness [5]. The authors suggest that an exclusive approach is most appropriate for obtaining the specificity required for research, whereas the inclusive approach is more appropriate for the clinical management of medically-ill patients.

Recent data on the behavioral effects of chronic cytokine exposure cast intriguing light on the first suggestion (see below) and provide strong support for the second suggestion: namely that antidepressant treatment benefits depressive symptoms regardless of putative etiology in medically-ill patients and may improve clinical outcome. Given the highly favorable risk/benefit profile of newer antidepressants and the devastating effects of depression in medically-ill patients, all depressive symptoms should be addressed and treated, although recent research suggests that symptoms privileged in exclusive diagnostic approaches may be more responsive to antidepressant intervention (see below). Significant data indicate that antidepressants may also be of value even for sick patients who do not meet criteria for “clinical depression”, given that these agents ameliorate physical and neurovegetative symptoms, such as pain, insomnia, nausea and hot flashes, even if these symptoms occur outside the context of a diagnosable mood disorder [6–11]. The importance of addressing these symptoms in their own right is highlighted by data demonstrating that sickness symptoms such as insomnia and pain represent significant risk factors for the later development of major depression [12, 13].

9.3

Prevalence and Predictors of Depression in the Medically Ill

9.3.1

Issues of Depression Prevalence

Given the multiple confounds that complicate the diagnosis of mood disorders in medically-ill patients, it should not be surprising, perhaps, that prevalence rates of depression vary tremendously between studies. For example, studies in patients with cancer have reported depression prevalence rates that range between 0 and approximately 50% [14, 15]. And while affective disturbances appear to be two to three times higher on average in the medically ill than in the general population, [16] rates vary widely between studies and between illnesses. Table 9.2 summarizes reported prevalence rates of depression in a number of medical conditions.

A number of factors affect prevalence. The most obvious include (1) differences in depression between disease states and their attendant treatments, (2) differences in disease severity, and (3) variations in the criteria used to define depression. For example, among patients with cancer, those with tumors of the brain, pancreas or head/neck appear to be at increased risk of depression compared to patients with other tumor types [34]. Other medical conditions that have been repeatedly associated with elevated rates of depression include coronary heart disease, stroke, neurodegenerative diseases and autoimmune disorders [2, 15]. Similarly, certain forms of chemotherapy are especially notorious for inducing depressive syndromes, including the use of interferon-alpha, interleukin-2, corticosteroids, cyproterone, vincristine, tamoxifen, vinblastine, asparaginase and procarbazine [35].

Almost universally, studies observe that rates of mood disturbance increase as disease severity worsens, with prevalence rates of depression increasing from between 4.8 and 9.2% in ambulatory outpatients to between 22 and 33% in hospitalized patients [36–40]. That severity independently affects prevalence is suggested by a recent study that found similar rates of depressive symptoms in patients near the end of life, whether they had cancer or other terminal conditions [41]. While the effect of severity has often been ascribed to the increased suffering

Table 9.2 Prevalence of major depression in patients diagnosed with a medical disorder

<i>Medical disease</i>	<i>Prevalence of co-morbid depression</i>	<i>Reference</i>
Cancer*	1.5–50%	17
Coronary artery disease	15–23%	18–22
Diabetes mellitus	11–15%	23
HIV infection	4–23%	24
Multiple sclerosis	16–30%	25, 26
Parkinson's disease	20–30%	27–29
Post-stroke	9–31%	30

* Prevalence varies depending on the type of cancer (e.g. 50% in pancreatic cancer [31]; 13–25% in colon cancer [31, 32]; 1.5% in acute leukemia [33]).

and psychological stress that attends worsening illness, it should also be noted that disease-related pathophysiological processes also tend to escalate as symptoms worsen and may directly contribute to increased affective disturbance via activation of inflammatory pathways (see below). In support of this, rates of depression increase with the heightened immune activation that accompanies increasing dosages of interferon-alpha [42].

Depression is a notoriously slippery word, simultaneously connoting states that range from mild, transient unhappiness to life-threatening, catatonic stupors. Compounding this problem in patients with medical illnesses is the symptom overlap between sickness and depression discussed above. In general, rates of depression decrease when “psychological” symptoms such as sadness, anxiety, hopelessness and helplessness are privileged and physical symptoms are either removed or downplayed in counting toward a diagnosis. Rates of depression also drop when the condition is assessed by stringently defined diagnostic criteria as opposed to symptomatically (i.e. as a score on a rating scale). In addition, many patients with affective disturbances do not meet full criteria for major depression, suggesting that depression becomes increasingly common in the context of medical illness when minor to moderate intensity mood disturbances are brought under the aegis of depression [43]. These observations were elegantly demonstrated by Chochinov and colleagues who found that easing severity and stringency criteria (i.e. increasing inclusiveness of neurovegetative symptoms) doubled the rate of diagnosable depression in 130 patients with cancer [44].

9.3.2

Risk Factors for Developing Depression

As with major depression in general, depression in the context of medical illness follows the old biblical adage that “To those who have more will be given”. Thus, people who have already experienced depression prior to illness onset and/or who have a family psychiatric history are at increased risk of developing depression in the context of sickness [34, 45, 46]. A patient’s mood state just prior to diagnosis and/or treatment seems to be an especially potent marker of vulnerability. Even subsyndromal levels of depression and/or anxiety have been shown to predict the later development of both depressive symptoms and full major depression during the course of illness or during treatment with depression-engendering modalities such as IFN-alpha [47, 48]. In addition to pre-morbid factors brought to the experience of illness by a patient, certain disease-related factors also seem to increase the risk of depression. Disease severity has already been discussed. Other risk factors for depression include poorly controlled and/or severe pain, physical impairment and disease-related dependency, as well as being an inpatient in a medical hospital [34, 49].

9.4

Immune System Activation and the Pathophysiology of Depression in the Medically Ill

A lesson repeatedly offered by the history of science is that complications in existing schema often point to possibilities for new discoveries and novel paradigms. Recent research suggests that this is germane to the diagnostic dilemma posed by the symptom overlap between sickness and depression: the dilemma offers clues to mechanisms by which the physiology of illness contributes to the pathophysiology of depression. Moreover, as often happens, expanding knowledge has provided support for dichotomous positions previously perceived as being exclusive, in this case giving credence to both inclusive and exclusive ways of understanding depression in the context of sickness. Indeed, accumulating data lend credence to an emerging paradigm in which immune system activation is seen to induce physical and behavioral symptoms common to both illness and depression and to induce changes in central nervous and stress system pathways that additionally predispose vulnerable individuals to the development of profound mood and hedonic alterations in the context of sickness.

9.4.1

Sickness Behavior

While psychosocial factors associated with medical illness undoubtedly contribute to the development of depression in sick individuals, recent advances in our understanding of the biological changes that occur with disease have prompted a shift in how depression in the context of medical illness is conceptualized [50]. The immune system, specifically the cytokine network, has received increasing attention as a potential contributor to the depressive symptoms often observed in the medically ill.

Most processes integral to illness, including infection, neoplasia, autoimmunity and tissue trauma activate a network of functionally-related proteins known as pro-inflammatory cytokines, the best described of which are tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Once produced, these cytokines gain access to the central nervous system (CNS) by several routes and induce behavioral changes in humans and animals that have been characterized as sickness behavior (see Table 9.1) [35, 51–53]. The symptoms of sickness behavior overlap strikingly with symptoms frequently observed in major depression and include anhedonia, cognitive dysfunction, anxiety/irritability, psychomotor slowing, anergia/fatigue, anorexia, loss of libido, sleep alterations, and increased sensitivity to pain [51]. Each of the pro-inflammatory cytokines has been shown to reliably reproduce sickness behavior when administered individually. Additionally, induction of the pro-inflammatory cascade using the bacterial cell-wall product lipopolysaccharide also produces sickness behavior [54]. It should be noted that cytokine-induced sickness behavior in animals can be ameliorated or reversed by administering specific cytokine antagonists (e.g. IL-1 receptor antagonist) or anti-inflammatory cytokines (e.g. IL-10) directly into the brain [55, 56]. Consistent with

this, when compared with placebo, the soluble TNF-alpha receptor etanercept (which attenuates TNF-alpha activity) improves mood, energy and other sickness type symptoms in patients with rheumatoid arthritis, a condition characterized by increased production of pro-inflammatory cytokines [57].

The clinical relevance of these observations is underscored by studies linking increased cytokine activity with behavioral disturbance in the context of illness. For example, significantly increased plasma concentrations of IL-6 have been found in cancer patients with depression compared with cancer patients who do not have depression [58]. Consistent with this, depression scores have been reported to correlate with increased concentrations of the soluble receptor for the cytokine IL-2 in patients with metastatic colorectal cancer [59]. In cancer patients receiving cytokine therapy (IL-2 or IL-2 plus IFN-alpha), increases in pro-inflammatory activity, as assessed by the concomitant production of the anti-inflammatory cytokine IL-10, correlated with the development of depressive symptoms early in the course of treatment [60]. Depressive symptom scores have also been correlated with increased serum levels of TNF-alpha and interferon-gamma in patients with multiple sclerosis who experience an acute exacerbation, such that acutely ill patients with higher cytokine levels also endorse increased depression [61]. Similarly, increased serum concentrations of IL-6 have been reported to correlate with decreased cognitive performance and increased depression in patients with systemic lupus erythematosus and rheumatoid arthritis [62]. Finally, correlations have been observed between increased production of pro-inflammatory cytokines, such as IL-1 and IL-6, and fatigue (a common symptom of both major depression and medical illness) in cancer patients receiving chemotherapy or radiation treatment [63, 64].

9.4.2

Effects of Antidepressants on Pro-inflammatory Cytokine Activity

Although not traditionally conceptualized as anti-inflammatory agents, antidepressants have been shown in a number of studies to modulate cytokine activity and to ameliorate or prevent cytokine-induced behavioral disturbances in animals and humans. Most *in vitro* studies indicate that acute and chronic antidepressant exposure downregulates pro-inflammatory signaling. Both tricyclic and serotonin reuptake inhibitor (SRI) antidepressants have been reported to inhibit *in vitro* pro-inflammatory cytokine production from monocytes and lymphocytes and to increase production of IL-10, a cytokine with anti-inflammatory activity [65]. Similarly, phosphodiesterase inhibitors, which increase signaling in c-AMP pathways and demonstrate antidepressant efficacy in humans, suppress *in vitro* and *in vivo* measurements of TNF-alpha production and have been shown to block the development of autoimmune encephalomyelitis, a rodent model for multiple sclerosis [66, 67]. In addition to direct suppression of pro-inflammatory cytokine production, antidepressants also appear capable of inhibiting "downstream" inflammatory pathways that are activated by cytokines, given evidence that fluoxetine and amitriptyline suppress both nitric oxide and prostaglandin release from lipopolysaccharide (LPS)-stimulated human synovial cells [68].

Consistent with these *in vitro* findings, several *in vivo* studies in rodents have demonstrated that chronic, but not acute, antidepressant administration attenuates inflammatory activity in response to an immune challenge [69–74]. Interestingly, studies more consistently demonstrate inhibition of cytokine production following an *in vivo* immune challenge for agents with norepinephrine reuptake activity when compared to serotonin reuptake inhibitors [74, 75]. Not surprisingly, agents with noradrenergic activity also appear to more reliably attenuate cytokine-induced behavioral changes in animals than do the SRIs. Shen and colleagues found that chronic treatment with desipramine inhibited TNF- α production in rats challenged with LPS and blocked behavioral changes, whereas neither paroxetine (an SRI) nor venlafaxine affected either cytokine production or behavior [74]. Of note, the dose of venlafaxine used in this study has been shown to affect CNS serotonin, but not norepinephrine activity *in vivo* in rats [76], suggesting that, in this study, venlafaxine was functioning as a serotonergic agent and not as a combined serotonin–norepinephrine inhibitor. Yirmiya et al. observed that although chronic treatment with either imipramine (a tricyclic with norepinephrine and serotonin activity) or fluoxetine (an SRI) blocked LPS-induced reductions in food consumption and body weight, only imipramine attenuated decrements in social exploration and open field behavior [75, 77]. Concomitant with this, fluoxetine had no effect on measures of peripheral cytokine activation, consistent with the results observed for paroxetine or low-dose venlafaxine [74]. However, the data are not entirely consistent: tianeptine – a serotonergic antidepressant that *increases* activity at the reuptake site – has been reported to abolish LPS-induced sickness behavior and one study found that imipramine had no effect on either IL-1b or LPS-induced reductions in sweetened milk intake [78, 79]. Moreover, a recent study, aimed at dissociating pro-inflammatory cytokine effects on gustatory hedonic drive from food intake, found that chronic fluoxetine treatment attenuated cytokine-induced decrements in motivation to obtain sucrose, without affecting overall reductions in food intake [80]. This specific effect of an SRI on hedonic tone is intriguing in light of findings by our group that paroxetine prevents the development of anhedonia, but not anorexia, in patients receiving the cytokine interferon- α -2-beta (IFN- α) for the treatment of malignant melanoma [81].

An obvious question arising from the animal literature is whether antidepressant therapy reduces pro-inflammatory cytokine production in humans undergoing the types of immune challenge that attend medical illness, and whether such a reduction would correlate with reduced depression in the medically ill. And yet, remarkably, no data directly address this question. Rather, our knowledge of the effect of antidepressants on *in vivo* cytokine production in humans derives entirely from studies of medically healthy subjects. This is not surprising, given the intense interest that has developed from the rapidly growing database demonstrating that states of emotional upheaval, especially depression and anger, are associated with increased pro-inflammatory cytokine activity, even in subjects lacking a medical reason for immune system activation [82]. In these subjects, the effects of antidepressant treatment have been somewhat contradictory, with studies reporting no effect of antidepressant treatment on cytokine levels in major depression [83–

85] and one study reporting that chronic clomipramine therapy actually increased production of IL-1b and IL-2, although it should be noted that depressed patients demonstrated suppression of pro-inflammatory cytokines prior to treatment [86]. Nonetheless, recent data are more consistent with the animal literature and with several earlier studies showing that antidepressants have anti-inflammatory actions in depressed patients with baseline evidence of immune activation [87, 88]. For example, in a recent comparison of depressed patients and normal controls, depression was associated with markedly increased concentrations of TNF-alpha and C-reactive protein (CRP). Six weeks of treatment with an SRI significantly improved the symptom scores in depressed patients and lowered TNF-alpha and CRP levels to values similar to those seen among the controls [89]. Similarly, ECT treatment significantly reduced serum TNF-alpha concentrations in a group of severely depressed patients. In contrast, depressed patients who did not receive treatment demonstrated no diminution of cytokine levels [90]. In this study, TNF-alpha levels decreased gradually with repeated ECT sessions in concert with the onset of antidepressant efficacy, suggesting that, as in animal models, the anti-inflammatory properties of antidepressant therapies are related not to immediate effects on neurotransmitters, but to longer-term physiological changes that correlate with clinical response.

9.4.3

IFN-alpha as a Model System for Cytokine-induced Depression in Humans

Given evidence that antidepressants effectively treat depression in medically-ill patients [2], and given animal data indicating that antidepressants ameliorate cytokine-induced behavioral symptoms in animals [74, 75, 77], the question arises as to whether antidepressants are effective in the medically ill, at least in part because they prevent cytokine-induced sickness symptoms by downregulating activity in pathways involved in mediating the physiological effects of pro-inflammatory cytokines. In an attempt to address this question, researchers have become increasingly interested in utilizing treatment with IFN-alpha as a model system for understanding the development and treatment of cytokine-induced depression in humans.

IFN-alpha is a cytokine released early in viral infection that has both antiviral and anti-proliferative activities [91]. Accordingly, IFN-alpha is currently used for the treatment of viral infections and cancers, including hepatitis C virus (HCV) infection and malignant melanoma [42]. Although frequently of benefit in each of these conditions, IFN-alpha has been repeatedly observed to cause a variety of neuropsychiatric side-effects that closely resemble sickness behavior in animals and that meet symptom criteria for major depression in 30–50% of patients depending on the dosage and duration of treatment [42]. Concomitant with the induction of sickness symptoms, IFN-alpha also potently stimulates the production of pro-inflammatory cytokines including IL-6 and to a lesser extent, TNF-alpha and IL-1 alpha and beta [92, 93], making it a unique model system for examining the relationship between immune activation and behavioral disturbance in humans.

To evaluate the effect of antidepressants in patients exposed to an unambiguous immune stimulus, our group examined the possibility that antidepressant pretreatment might ameliorate neurobehavioral toxicity in patients receiving high doses of IFN- α for the treatment of malignant melanoma [94]. In this study, 40 patients with non-metastatic disease were randomized in a double-blind manner to receive either the SRI paroxetine or placebo. Antidepressant (or placebo) treatment was commenced 2 weeks prior to the initiation of IFN- α and continued for an additional 10 weeks of IFN- α therapy. At the end of this period only 11% of patients receiving paroxetine had developed symptoms sufficient to meet diagnostic criteria for major depression, compared to 45% of patients receiving placebo. Moreover, rates of discontinuation from IFN- α were significantly lower in paroxetine-treated patients, 5 vs. 35% for patients receiving placebo. The generalizability of these findings to other IFN- α -based treatment regimens has been recently upheld by an open trial of pre-treatment with the SRI citalopram in patients receiving pegylated IFN- α plus ribavirin for HCV. In this study, patients with a psychiatric history who received citalopram pre-treatment developed significantly less depression during IFN- α /ribavirin therapy than did patients with a psychiatric history who did not receive pre-treatment [95]. Data on the efficacy of pre-treatment are also consistent with earlier case reports and larger recent studies demonstrating that antidepressants effectively treat depression once it has developed during IFN- α therapy [96–101].

9.4.4

Cytokine-Induced Symptom Dimensions: the Inclusive–Exclusive Debate Revisited

As mentioned above, a recent study in rodents suggested that the SRI fluoxetine might be effective in preventing cytokine-induced decrements in the hedonic domain, while having no impact on cytokine-induced anorexia [80]. Given that major depression is a syndrome consisting of both mood/hedonic and neurovegetative symptoms (like anorexia) [102], we examined whether paroxetine was equally effective in ameliorating all depressive symptoms in patients receiving IFN- α or whether its ability to prevent major depression derived from a more limited spectrum of therapeutic efficacy. A dimensional analysis revealed that symptoms more commonly seen in depression than in sickness, including depressed mood, loss of interest, suicidal thoughts, guilt, and anxiety, as well as subjective cognitive complaints, were exquisitely sensitive to SRI pre-treatment, whereas neurovegetative symptoms, including fatigue, anorexia and psychomotor retardation, were minimally responsive to the antidepressant [81]. Additionally, neurovegetative and somatic symptoms were noted to develop early during treatment (within the first 2 weeks) in the majority of patients, whereas depression-specific and cognitive symptoms developed later and tended only to occur in patients who met DSM-IV criteria for major depression.

Similar patterns have been identified in the phenomenology and treatment response of behavioral disturbances in the context of cancer, a condition typically characterized by activation of the pro-inflammatory cytokine network. In terms of

phenomenology, a factor analysis in a large group of patients found that mood, anxiety and cognitive symptoms clustered together, whereas fatigue, anorexia and physical symptoms represented separate factors [103]. Consistent with SRI response patterns during IFN- α treatment, paroxetine has been recently shown in a large double-blind, placebo-controlled trial to ameliorate depression but not fatigue, in cancer patients undergoing chemotherapy [104].

Taken together, these findings suggest that depressive conditions occurring in response to immune activation may represent an amalgam of at least two separable sub-syndromes: a mood–anxiety–cognitive syndrome and a neurovegetative–somatic syndrome, each of which demonstrate a different time course and treatment response. Intriguingly, these observations may cast important light on whether neurovegetative symptoms should count toward a diagnosis of major depression in medically-ill patients. While cytokine activation in the context of medical illness may promote the development of the full range of DSM-IV symptom criteria for major depression, lending support to the view that all symptoms should count toward a diagnosis, it appears that depression-specific symptoms represent an added dimension that occur in some, but not all patients who experience more typical sickness symptoms, providing a rationale for viewing depression in the medically ill more exclusively in terms of mood and anxiety disturbances. As will be discussed below, emerging data also suggest that depression-specific and neurovegetative symptoms are mediated, at least in part, by separate physiological systems, providing a deeper rationale for recognizing a distinction in medically-ill patients between generalized sickness/depressive symptom profiles and symptoms that more specifically reflect the presence of depression.

9.5

Symptom Dimensions and the Physiology of Cytokine-induced Depression

Although the brain has been traditionally viewed as an “immune privileged” organ, it is now abundantly clear that cytokines play an important role within the CNS, not only in terms of orchestrating sickness behavior, but also in functions as diverse as the timing of circadian cycles, sleep and the consolidation of memory [82, 105, 106]. Significant data demonstrate that in addition to direct effects via receptors on CNS cells, pro-inflammatory cytokines affect neurotransmitter and neuroendocrine activity in ways that are potentially relevant to the development of depression during conditions of immune activation. These changes include (1) CNS overproduction of corticotrophin-releasing hormone (CRH) and subsequent activation of the HPA axis and (2) alterations in the metabolism of the neurotransmitters serotonin and dopamine within the CNS [82, 92, 107–114].

The finding that IFN- α -induced depression can be meaningfully subdivided on the basis of phenomenology and treatment response into a more depression-specific syndrome of mood, anxiety and cognitive symptoms and a more generalized sickness syndrome comprised of neurovegetative and somatic symptoms, strongly suggests that separate pathophysiological mechanisms may underlie these syn-

dromes, with the corollary that different symptoms may respond to different treatment strategies in depressed, medically-ill patients [81]. Recent work aimed at delineating pathways by which immune activation produces behavioral disturbance strongly supports this notion and has led to a novel model system for cytokine-induced neurobehavioral alterations [115].

9.5.1

Pathways for the Mood/Cognitive Syndrome

9.5.1.1 Serotonin

As with other inflammatory stimuli, IFN- α exposure leads to a depletion of tryptophan (TRP) via an immune-mediated induction of the enzyme indoleamine 2,3-dioxygenase (IDO), which metabolizes TRP to kynurenine and hence reduces the amount of TRP that is available for the synthesis of serotonin [113, 116]. It has been argued that IDO induction serves several adaptive purposes, including diminishing TRP availability for bacterial pathogens (for which TRP is also an essential amino acid) and promoting maternal T-cell tolerance toward the fetus during pregnancy [117].

Despite these evolutionary benefits, however, IDO induction might also be expected to increase the risk of developing depressive symptoms during conditions of immune activation, given evidence that TRP depletion is capable of rapidly inducing depressive symptoms in non-depressed, but vulnerable individuals [118, 119]. Data from patients receiving high IFN- α suggest this is true: several studies report that treatment results in decreases in serum TRP and increases in kynurenine [113, 116, 120], consistent with activation of IDO [121]. Moreover, the amount of reduction in TRP during treatment has been correlated with depressive symptom severity scores [116, 120]. Similarly, Capuron et al. recently observed that antidepressant-free patients who met criteria for major depression during IFN- α therapy for malignant melanoma demonstrated significantly larger increases in kynurenine and the ratio of kynurenine to TRP and prolonged decreases in TRP during treatment when compared to patients who did not develop major depression [113]. In patients receiving the SRI paroxetine, no association was seen between markers of IDO activity and mood status. In keeping with this, a dimensional analysis demonstrated that the relationship between major depression and TRP depletion resulted from a significant correlation between decreases in serum TRP concentrations and the development of mood, anxiety and cognitive symptoms. No association was seen between TRP metabolism and neurovegetative symptoms or pain complaints. That alterations in TRP metabolism correlated with the same symptoms that responded to treatment with paroxetine, and did not correlate with symptoms that were not responsive to the SRI [81], strongly suggests that serotonergic mechanisms contributed significantly to the expression of mood, anxiety and cognitive complaints in these patients, a finding strengthened by the fact that no such correlation was observed in patients pre-treated with paroxetine which might be expected via effects on the serotonin reuptake pump, to compensate for IDO-induced decrements in serotonergic functioning. By the same logic, sero-

tonergic mechanisms did not appear to play a central role in the mediation of neurovegetative or pain symptoms.

9.5.1.2 CRH Pathways

Because CRH hyperactivity is a frequently reported abnormality in major depression [122], especially in melancholia – a condition characterized by profound neurovegetative abnormalities that resemble those seen in illness – and because IFN-alpha robustly stimulates the HPA axis in animals and humans via stimulation of CRH, we sought to determine if patients who responded to IFN-alpha treatment with HPA axis hyperactivity would be at increased risk of developing depression during treatment. In 14 antidepressant-free patients, those who developed major depression during IFN-alpha treatment exhibited increased CRH activity in response to the first dose of IFN-alpha (as assessed by post-injection increases in serum concentrations of ACTH and cortisol). Of note, none of the patients met criteria for depression at the time of the first injection [92]. Although the first dose of IFN-alpha also markedly increased serum concentrations of IL-6, no differences in this cytokine were observed between patients who did and did not develop major depression, suggesting that the vulnerability to depression was accounted for by pre-existing sensitivity of CRH pathways to an immune stimulus and not by an abnormality within the pro-inflammatory cytokine network itself.

Interestingly, both CRH pathway and cytokine responses to IFN-alpha rapidly attenuated with repeated treatment, such that within a week of initiating therapy no differences were observed in post-injection ACTH or cortisol responses between patients who did and did not subsequently develop major depression [92]. This finding is quite different from the temporal pattern observed between IDO-induced TRP depletion and depression, where changes in TRP levels and the development of depressive symptoms were contemporaneous [113]. However, it is intriguing that patients who demonstrated CRH hyperactivity in response to an initial dose of IFN-alpha were also more likely to later demonstrate increased TRP depletion, indicating a possible link between CRH and serotonergic systems in the mediation of depressive symptoms in the context of immune activation. Moreover, as with IDO-induced TRP depletion, CRH hyperactivity predicted the subsequent development of major depression through an effect on mood, anxiety and cognitive symptoms [92]. No correlation was observed between CRH hyperactivity and the later development of neurovegetative or somatic symptoms. Taken together these findings suggest that patients with pre-existing super-sensitivity in CRH-mediated stress pathways may be at risk of developing mood, anxiety and cognitive symptoms, not perhaps through ongoing abnormalities in stress system responses to immune stimulation, but rather through as yet unidentified functional connections between CRH and serotonergic metabolism. On the other hand, neurovegetative and physical symptoms that are frequent in the context of illness, even when more depression-specific symptoms are absent, may not be as directly related to alterations in CRH and/or serotonergic systems.

9.5.2

Potential Mechanisms Underlying Cytokine-induced Neurovegetative Symptoms

In beginning to search for neural mechanisms by which activation of the cytokine network promotes the development of neurovegetative symptoms such as fatigue or psychomotor slowing, a first clue is provided by data linking abnormalities in CNS dopamine with fatigue and psychomotor slowing in medically-ill patients. For example, human immunodeficiency virus (HIV) infection and Parkinson's disease, conditions in which fatigue and psychomotor slowing are prominent, are characterized by abnormalities in dopamine metabolism in basal ganglia and by extreme sensitivity to medications, such as antipsychotic agents, that further reduce dopaminergic signaling via post-synaptic receptor blockade [123, 124]. Similarly, medically-healthy depressed patients who demonstrate affective flattening and psychomotor retardation – symptoms prominent in HIV dementia and Parkinson's disease – show evidence of altered dopaminergic functioning in the left caudate when compared to depressed patients without these symptoms and to normal controls [125]. Finally, agents with dopaminergic activity have been repeatedly shown to effectively treat fatigue in a number of medical conditions [126–128].

Chronic immune activation appears to inhibit dopamine signaling within fronto-striatal circuits within the CNS. Rodents treated chronically with IFN- α demonstrate inhibition of dopaminergic neural activity and CNS dopamine metabolism, with concomitant decrements in motor activity [114]. In humans, IFN- α reliably slows reaction time on standardized neuropsychological tests and in extreme cases has been reported to produce frankly parkinsonian states that are responsive to treatment with levodopa [129, 130].

These findings support the possibility that psychomotor retardation and fatigue observed during states of immune activation may be related in part to cytokine-induced reductions in dopamine activity. Cytokine receptors are expressed in abundance in key areas of the basal ganglia/thalamo-cortical circuitry including the striatum and cerebral cortex [131] and therefore are uniquely poised to influence dopamine neuronal activity in these brain regions. Moreover, chronic infusion of LPS into rat brain leads to delayed and selective degeneration of dopaminergic neurons in the substantia nigra through microglial activation [132]. Finally, the targeting of basal ganglia and dopamine pathways during activation of the cytokine network is suggested by involvement of these pathways in infectious diseases associated with neuropsychiatric alterations including human immunodeficiency virus [124].

Taken together, these data suggest that alterations in basal ganglia, notably in dopamine neurotransmission, may contribute to the development of core neurovegetative symptoms of IFN- α -induced depression, including psychomotor slowing. Consistent with this, preliminary data from our group and others demonstrate altered glucose metabolism in the basal ganglia of IFN- α -treated patients [133, 134].

9.6

Treatment Implications

The recognition that pro-inflammatory cytokines likely contribute to many of the behavioral alterations that accompany illness has implications for both the diagnosis and treatment of depression in medically-ill patients. In terms of diagnosis, the fact that cytokines induce a wide range of symptoms, from classic depressive complaints such as sadness and hopelessness to symptoms typically viewed as primarily “physical” such as pain, encourages a broadening of the behavioral terrain for which treatment is deemed appropriate and supports an “inclusive” approach to diagnosing depression in the medically ill, with the implication that all sickness symptoms, even those not included in current conceptions of major depression, are worthy targets for therapeutic intervention. On the other hand, recent data from patients receiving IFN- α and from patients with cancer [81, 103, 135], suggest that cytokine-induced depression is not a unitary phenomenon, but represents an amalgam of an SRI-responsive mood–anxiety–cognitive syndrome and a neurovegetative–somatic syndrome that is minimally responsive to SRIs. When combined with recent studies demonstrating that depression-specific symptoms are responsible for the link between depression and increased morbidity/mortality, these data provide a new rationale for the wisdom inherent in “exclusive” diagnostic notions that privilege mood and cognitive symptoms in the context of medical illness.

Figure 9.1 presents an algorithm for integrating inclusive and exclusive approaches to the diagnosis and treatment of depression in the medically ill, based on a theoretical model articulated by Capuron and Miller (and discussed above) that provides a unified framework for understanding mechanisms by which cytokines induce behavioral alterations [115]. In terms of treatment, this algorithm suggests that depression in medically-ill patients may be fruitfully addressed not only by traditional antidepressants, but also by novel strategies that alter activity at different levels within pathways that mediate the effects of pro-inflammatory cytokines.

Although not currently included in the standard treatment armamentarium for depression, an obvious first place to intervene in cytokine-induced behavioral disturbance is at the level of cytokine signaling itself. And indeed, accumulating data indicate that anti-cytokine agents effectively diminish a wide range of depressive and sickness symptoms in humans and animals. For example, etanercept (a soluble receptor for TNF- α) reduced circulating TNF- α in rats with experimentally-induced heart failure and restored hedonic drive in a brain stimulation paradigm [137]. In patients with rheumatoid arthritis (RA), etanercept has been shown to significantly improve fatigue and reduce depressive and anxiety symptoms. Similar results have recently been observed in patients with Crohn’s disease receiving the anti-TNF- α antibody infliximab. When compared to placebo, treatment with infliximab significantly improved the ability to work and pursue leisure activities and decreased fatigue, depression and anger [138]. Animal studies suggest that the soluble receptor antagonist for IL-1 β (IL-1ra) may also have potential as a treatment for cytokine-induced symptoms [55, 139, 140], but little has been published with

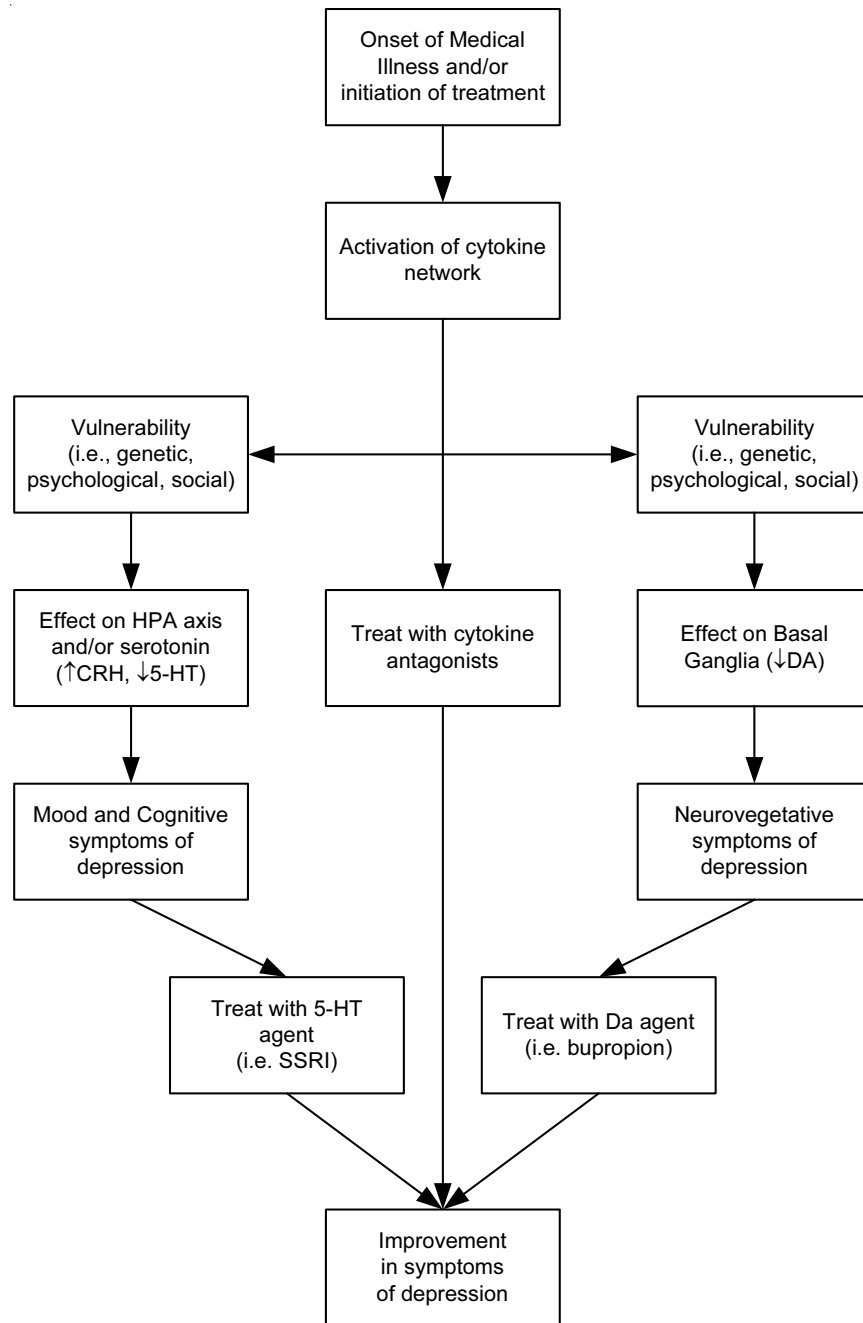


Figure 9.1 Diagram of potential pathways by which medical illness and immune activation may cause depression and sickness behavior symptoms. Treatment implications are indicated (adapted from Capuron and Miller [136])

regard to the effect of this agent on sickness/depressive symptoms in humans. Despite their potential usefulness, however, the value of anti-cytokine therapies in the treatment of cytokine-induced depressive syndromes will need to be balanced against the potential for serious side-effects posed by these agents, including an increased risk for infection and autoimmune conditions [141–143].

The physiological effects of pro-inflammatory cytokines are mediated by activation of intracellular second messenger systems, such as mitogen-activated protein kinase and nuclear factor-kappa-beta signaling pathways [82]. Studies evaluating the therapeutic potential of attenuating activity in these pathways are in their infancy. Nevertheless agents that increase signaling in intracellular pathways known to inhibit inflammatory signaling may be of benefit in the treatment of immune-related depression. These agents include phosphodiesterase type 4 inhibitors, such as rolipram and ariflo, which decrease pro-inflammatory cytokine signaling by increasing signaling in cyclic adenosine monophosphate (c-AMP) pathways and possibly through enhancement of anti-inflammatory glucocorticoid pathways [82, 144].

Overwhelming data document that conventional antidepressants are effective in the treatment of depression in medically-ill patients [2, 35]. However, when looked at more carefully in terms of symptom dimensions in patients undergoing chronic immune stimulation, patterns of treatment response become more complicated – and more interesting. Serotonin reuptake inhibitors appear to be highly effective in ameliorating mood, anxiety and subjective cognitive complaints, but far less effective in addressing neurovegetative and somatic symptoms, such as fatigue and anorexia [92]. These findings may provide an explanation for the oft repeated observation that agents with catecholaminergic activity are generally more effective than SRIs in the treatment of neurovegetative and somatic symptoms, such as pain and fatigue, especially when these symptoms occur outside the context of a diagnosable mood disorder [6, 126–128, 145, 146]. Moreover, given evidence that pro-inflammatory cytokines contribute to the development of depression even in medically-healthy individuals [82], these findings may also provide a partial explanation for the growing dataset indicating that combined serotonin–norepinephrine/dopamine treatment strategies (such as adding desipramine or bupropion to an SRI or using a serotonin–norepinephrine reuptake inhibitor, such as venlafaxine, duloxetine or milnacipran) outperform serotonergic strategies in the treatment of major depression, even in medically-healthy individuals [147]. This increased efficacy may occur because serotonergic and noradrenergic reuptake inhibition targets different symptom dimensions: by invoking both mechanisms combined strategies address both depression-specific and neurovegetative symptoms. And indeed, some evidence suggests that combined serotonin–norepinephrine agents are more effective in treating both symptom domains, even in medically-healthy individuals [148].

Two implications emerge from these data. The first is that agents with both a broad spectrum of activity (i.e. with effects on serotonin and norepinephrine/dopamine) should be more often considered as first-line treatment in medically-ill patients with depression, especially when symptoms such as sadness and loss of

interest are combined with prominent fatigue and/or psychomotor slowing. A second implication is that medically-ill patients with neurovegetative symptoms, but without prominent mood or anxiety symptoms, might be more parsimoniously treated with noradrenergic/dopaminergic agents, such as psychostimulants or modafinil that will target symptoms such as fatigue and psychomotor slowing, without the added side-effect burden (especially sexual dysfunction) imposed by agents that block the reuptake of serotonin. Although less data are available, dopaminergic agonists may also hold promise for the treatment of cytokine-mediated fatigue. Nonetheless, these considerations need to be tempered by data which indicate that serotonergic reuptake blockade may provide other benefits through mechanisms not discussed in this chapter, such as anti-platelet effects that may be of special relevance for patients with coronary artery and cerebrovascular disease [149].

9.7

Conclusion

Recent advances in our understanding of how pro-inflammatory cytokines contribute to the development of depression highlight a recurring theme in the history of medicine: treatment advances often come in the wake of new discoveries in the realm of disease pathophysiology.

The discovery that activation of the pro-inflammatory network reliably produces a syndrome resembling major depression provides a new synthetic explanation for the old conundrum of why depression and sickness share so many symptoms: the shared symptoms likely reflect shared pathophysiological mechanisms. Recent findings suggesting that immune-based depression is an amalgam of at least two separable subsyndromes cast new light on the recurrent observation that agents with catecholaminergic activity are more effective in eradicating certain neurovegetative symptoms, especially fatigue and pain. Mood, anxiety and cognitive symptoms are associated with changes in serotonergic functioning and respond to serotonergic antidepressants. On the other hand, preliminary data suggest that in the context of immune activation, neurovegetative symptoms such as fatigue and psychomotor slowing may be more related to changes in CNS dopaminergic activity. Finally, the recognition that pro-inflammatory cytokines likely contribute to depression in the medically ill opens up new therapeutic vistas, including the use of anti-cytokine agents and agents that modulate activity in the intracellular second messenger systems by which cytokines exert their physiological effects.

References

- 1 BLAZER, D. G., KESSLER, R. C., MCGONAGLE, K. A., SWARTZ, M. S., The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am. J. Psychiatry* **1994**, *151* (7), 979–986.
- 2 EVANS, D. L., STAAB, J. P., PETITTO, J. M., MORRISON, M. F., SZUBA, M. P., WARD, H. E., WINGATE, B., LUBER, M. P., O'REARDON, J. P., Depression in the medical setting: biopsychological interactions and treatment considerations. *J. Clin. Psychiatry* **1999**, *60* (Suppl. 4), 40–55; discussion 56.
- 3 SIMON, G. E., VONKORFF, M., BARLOW, W., Health care costs of primary care patients with recognized depression. *Arch. Gen. Psychiatry* **1995**, *52* (10), 850–856.
- 4 RAISON, C. L., MILLER, A. H., Depression in cancer: new developments regarding diagnosis and treatment. *Biol. Psychiatry* **2003**, *54* (3), 283–294.
- 5 COHEN-COLE, S. A., BROWN, F. W., MCDANIEL, J. S., Diagnostic assessment of depression in the medically ill. In: STOUDEMIRE, A., FOGEL, B. (Eds.), *Psychiatric Care of the Medical Patient*. New York: Oxford University Press, **1993**, 53–70.
- 6 MAX, M. B., LYNCH, S. A., MUIR, J., SHOAF, S. E., SMOLLER, B., DUBNER, R., Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N. Engl. J. Med.* **1992**, *326* (19), 1250–1256.
- 7 SEMENCHUK, M. R., SHERMAN, S., DAVIS, B., Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. *Neurology* **2001**, *57* (9), 1583–1588.
- 8 SUMPTON, J. E., MOULIN, D. E., Treatment of neuropathic pain with venlafaxine. *Ann. Pharmacother.* **2001**, *35* (5), 557–559.
- 9 KAST, R. E., Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy. *Support Care Cancer* **2001**, *9* (6), 469–470.
- 10 LOPRINZI, C. L., KUGLER, J. W., SLOAN, J. A., MAILLIARD, J. A., LAVASSEUR, B. I., BARTON, D. L., NOVOTNY, P. J., DAKHIL, S. R., RODGER, K., RUMMANS, T. A., CHRISTENSEN, B. J., Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* **2000**, *356* (9247), 2059–2063.
- 11 STEARNS, V., ISAACS, C., ROWLAND, J., CRAWFORD, J., ELLIS, M. J., KRAMER, R., LAWRENCE, W., HANFELT, J. J., HAYES, D. F. A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. *Ann. Oncol.* **2000**, *11* (1), 17–22.
- 12 BRESLAU, N., ROTH, T., ROSENTHAL, L., ANDRESKI, P., Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol. Psychiatry* **1996**, *39* (6), 411–418.
- 13 GUREJE, O., SIMON, G. E., VON KORFF, M., A cross-national study of the course of persistent pain in primary care. *Pain* **2001**, *92* (1–2), 195–200.
- 14 VAN'T SPIJKER, A., TRIJSBURG, R. W., DUIVENVOORDEN, H. J., Psychological sequelae of cancer diagnosis: a meta-analytical review of 58 studies after 1980. *Psychosom. Med.* **1997**, *59* (3), 280–293.
- 15 KRISHNAN, K. R., DELONG, M., KRAEMER, H., CARNEY, R., SPIEGEL, D., GORDON, C., MCDONALD, W., DEW, M., ALEXOPOULOS, G., BUCKWALTER, K., COHEN, P. D., EVANS, D., KAUFMANN, P. G., OLIN, J., OTEY, E., WAINSCOTT, C., Comorbidity of depression with other medical diseases in the elderly. *Biol. Psychiatry* **2002**, *52* (6), 559–588.
- 16 PATTEN, S. B., Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *J. Affect Disord.* **2001**, *63* (1–3), 35–41.
- 17 MCDANIEL, J. S., MUSSELMAN, D. L., PORTER, M. R., REED, D. A., NEMEROFF, C. B., Depression in patients with cancer. Diagnosis, biology, and treatment. *Arch. Gen. Psychiatry* **1995**, *52* (2), 89–99.
- 18 CARNEY, R. M., RICH, M. W., TEVELDE, A., SAINI, J., CLARK, K., JAFFE, A. S., Major depressive disorder in coronary artery disease. *Am. J. Cardiol.* **1987**, *60* (16), 1273–1275.
- 19 FRASURE-SMITH, N., LESPERANCE, F., TALAJIC, M., Depression following myocardial infarction. Impact on 6-month survival. *JAMA* **1993**, *270* (15), 1819–1825.

- 20 GONZALEZ, M. B., SNYDERMAN, T. B., COLKET, J. T., ARIAS, R. M., JIANG, J. W., O'CONNOR, C. M., KRISHNAN, K. R., Depression in patients with coronary artery disease. *Depression* **1996**, 4 (2), 57–62.
- 21 MAYOU, R. A., GILL, D., THOMPSON, D. R., DAY, A., HICKS, N., VOLMINK, J., NEIL, A., Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom. Med.* **2000**, 62 (2), 212–219.
- 22 SCHLEIFER, S. J., MACARI-HINSON, M. M., COYLE, D. A., SLATER, W. R., KAHN, M., GORLIN, R., ZUCKER, H. D., The nature and course of depression following myocardial infarction. *Archiv Intern. Med.* **1989**, 149 (8), 1785–1789.
- 23 ANDERSON, R. J., FREEDLAND, K. E., CLOUSE, R. E., LUSTMAN, P. J., The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* **2001**, 24 (6), 1069–1078.
- 24 CIESLA, J. A., ROBERTS, J. E., Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *Am. J. Psychiatry* **2001**, 158 (5), 725–730.
- 25 HAKIM, E. A., BAKHEIT, A. M., BRYANT, T. N., ROBERTS, M. W., MCINTOSH-MICHAELIS, S. A., SPACKMAN, A. J., MARTIN, J. P., MCLELLAN, D. L., The social impact of multiple sclerosis – a study of 305 patients and their relatives. *Disability Rehab.* **2000**, 22 (6), 288–293.
- 26 PATTEN, S. B., METZ, L. M., REIMER, M. A., Biopsychosocial correlates of lifetime major depression in a multiple sclerosis population. *Multiple Sclerosis* **2000**, 6 (2), 115–120.
- 27 MAYEUX, R., WILLIAMS, J. B., STERN, Y., COTE, L., Depression and Parkinson's disease. *Adv. Neurol.* **1984**, 40, 241–250.
- 28 SCHRAG, A., JAHANSHAH, M., QUINN, N. P., What contributes to depression in Parkinson's disease? *Psychol. Med.* **2001**, 31 (1), 65–73.
- 29 STARKSTEIN, S. E., PREZIOSI, T. J., BOLDUC, P. L., ROBINSON, R. G., Depression in Parkinson's disease. *J. Nerv. Mental Dis.* **1990**, 178 (1), 27–31.
- 30 WHYTE, E. M., MULSANT, B. H., Post stroke depression: epidemiology, pathophysiology, and biological treatment. *Biol. Psychiatry* **2002**, 52 (3), 253–264.
- 31 FRAS, I., LITIN, E. M., PEARSON, J. S., Comparison of psychiatric symptoms in carcinoma of the pancreas with those in some other intra-abdominal neoplasms. *Am. J. Psychiatry* **1967**, 123 (12), 1553–1562.
- 32 KOENIG, R., LEVIN, S. M., BRENNAN, M. J., The emotional status of cancer patients as measured by a psychological test. *J. Chron. Dis.* **1967**, 20 (11), 923–930.
- 33 COLON, E. A., CALLIES, A. L., POPKIN, M. K., MCGLAIVE, P. B., Depressed mood and other variables related to bone marrow transplantation survival in acute leukemia. *Psychosomatics* **1991**, 32 (4), 420–425.
- 34 CHOCHINOV, H. M., Depression in cancer patients. *Lancet Oncol.* **2001**, 2 (8), 499–505.
- 35 RAISON, C. L., MILLER, A. H., Depression in cancer: new developments regarding diagnosis and treatment. *Biol. Psychiatry* **2003**, 54 (3), 283–294.
- 36 SCHWAB, J., BIALOW, M., CLEMMONS, R., MARTIN, P., HOLZER, C., The Beck Depression Inventory with medical inpatients. *Acta Psychiatr. Scand.* **1967**, 43 (3), 255–266.
- 37 KNIGHTS, E. B., FOLSTEIN, M. F., Unsuspected emotional and cognitive disturbance in medical patients. *Ann. Intern. Med.* **1977**, 87 (6), 723–724.
- 38 MOFFIC, H. S., PAYKEL, E. S., Depression in medical in-patients. *Br. J. Psychiatry* **1975**, 126, 346–353.
- 39 VONAMMON CAVANAUGH, S., The prevalence of emotional and cognitive dysfunction in a general medical population: using the MMSE, GHQ, and BDI. *Gen. Hosp. Psychiatry* **1983**, 5 (1), 15–24.
- 40 KATON, W., SULLIVAN, M. D., Depression and chronic medical illness. *J. Clin. Psychiatry*, **1990**, 51 (Suppl.), 3–11; discussion 12–14.
- 41 TRANMER, J. E., HEYLAND, D., DUDGEON, D., GROLL, D., SQUIRES-GRAHAM, M., COULSON, K., Measuring the symptom experience of seriously ill cancer and noncancer hospitalized patients near the end of life with the memorial symptom assessment scale. *J. Pain Symptom Manag.* **2003**, 25 (5), 420–429.
- 42 SCHAEFER, M., ENGELBRECHT, M. A., GUT, O., FIEBICH, B. L., BAUER, J., SCHMIDT, F., GRUNZE, H., LIEB, K.,

- Interferon alpha (IFN α) and psychiatric syndromes: a review. *Prog. Neuro-Psychopharmacol Biol. Psychiatry* **2002**, *26*, 731–746.
- 43 AKECHI, T., NAKANO, T., OKAMURA, H., UEDA, S., AKIZUKI, N., NAKANISHI, T., YOSHIKAWA, E., MATSUKI, H., HIRABAYASHI, E., UCHITOMI, Y., Psychiatric disorders in cancer patients: descriptive analysis of 1721 psychiatric referrals at two Japanese cancer center hospitals. *Japanese J. Clin. Oncol.* **2001**, *31* (5), 188–194.
 - 44 CHOCHINOV, H. M., WILSON, K. G., ENNS, M., LANDER, S., Prevalence of depression in the terminally ill: effects of diagnostic criteria and symptom threshold judgments. *Am. J. Psychiatry* **1994**, *151* (4), 537–540.
 - 45 BURGESS, C. C., RAMIREZ, A. J., RICHARDS, M. A., POTTS, H. W., Does the method of detection of breast cancer affect subsequent psychiatric morbidity? *Eur. J. Cancer* **2002**, *38* (12), 1622–1625.
 - 46 WELLISCH, D. K., KALEITA, T. A., FREEMAN, D., CLOUGHESY, T., GOLDMAN, J., Predicting major depression in brain tumor patients. *Psycho-Oncology* **2002**, *11* (3), 230–238.
 - 47 AKECHI, T., OKAMURA, H., NISHIWAKI, Y., UCHITOMI, Y., Psychiatric disorders and associated and predictive factors in patients with unresectable nonsmall cell lung carcinoma: a longitudinal study. *Cancer* **2001**, *92* (10), 2609–2622.
 - 48 RAISSON, C. L., DEMETRASHVILI, M., CAPURON, L., MILLER, A. H., Neuro-psychiatric side effects of interferon-alpha: recognition and management. *CNS Drugs* **2004** (in press).
 - 49 HARTER, M., REUTER, K., ASCHENBRENNER, A., SCHRETZMANN, B., MARSCHNER, N., HASENBURG, A., WEIS, J., Psychiatric disorders and associated factors in cancer: results of an interview study with patients in inpatient, rehabilitation and outpatient treatment. *Eur. J. Cancer* **2001**, *37* (11), 1385–1393.
 - 50 MAIER, S. F., WATKINS, L. R., Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol. Rev.* **1998**, *105* (1), 83–107.
 - 51 KENT, S., BLUTHE, R. M., KELLEY, K. W., DANTZER, R., Sickness behavior as a new target for drug development. *TIPS* **1992**, *13* (1), 24–28.
 - 52 DANTZER, R., Cytokine-induced sickness behavior: mechanisms and implications. *Ann. NY Acad. Sci.* **2001**, *933*, 222–234.
 - 53 DUNN, A. J., WANG, J., ANDO, T., Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Adv. Exp. Med. Biol.* **1999**, *461*, 117–127.
 - 54 YIRMIYA, R., WEIDENFELD, J., POLIAK, Y., MORAG, M., MORAG, A., AVITSUR, R., BARAK, O., REICHENBERG, A., COHEN, E., SHAVIT, Y., OVADIA, H., Cytokines, “depression due to a general medical condition”, and antidepressant drugs. *Adv. Exp. Med. Biol.* **1999**, *461*, 283–316.
 - 55 MAIER, S. F., WATKINS, L. R., Intra-cerebroventricular interleukin-1 receptor antagonist blocks the enhancement of fear conditioning and interference with escape produced by inescapable shock. *Brain Res.* **1995**, *695* (2), 279–282.
 - 56 PUGH, C. R., NGUYEN, K. T., GONYEA, J. L., FLESHNER, M., WAKINS, L. R., MAIER, S. F., RUDY, J. W., Role of interleukin-1 beta in impairment of contextual fear conditioning caused by social isolation. *Behav. Brain Res.* **1999**, *106* (1–2), 109–118.
 - 57 MATHIAS, S. D., COIWELL, H. H., MILLER, D. P., MORELAND, L. W., BUATTI, M., WANKE, L., Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. *Clin. Ther.* **2000**, *22* (1), 128–139.
 - 58 MUSSELMAN, D. L., Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *Am. J. Psychiatry* **2001**, *158* (8), 1252–1257.
 - 59 ALLEN-MERSH, T. G., GLOVER, C., FORDY, C., HENDERSON, D. C., DAVIES, M., Relation between depression and circulating immune products in patients with advanced colorectal cancer. *J. Roy. Soc. Med.* **1998**, *91* (8), 408–413.
 - 60 CAPURON, L., RAVAUD, A., GUALDE, N., BOSMANS, E., DANTZER, R., MAES, M., NEVEU, P. J., Association between immune activation and early depressive symptoms in cancer patients treated with

- interleukin-2-based therapy. *Psychoneuroendocrinology* **2001**, 26 (8), 797–808.
- 61 KAHL, K. G., KRUSE, N., FALLER, H., WEISS, H., RIECKMANN, P., Expression of tumor necrosis factor-alpha and interferon-gamma mRNA in blood cells correlates with depression scores during an acute attack in patients with multiple sclerosis. *Psychoneuroendocrinology* **2002**, 27 (6), 671–681.
 - 62 KOZORA, E., LAUDENSLAGER, M., LEMIEUX, A., WEST, S. G., Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. *J. Int. Neuropsychol. Soc.* **2001**, 7 (6), 745–754.
 - 63 BOWER, J. E., GANZ, P. A., AZIZ, N., FAHEY, J. L., Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom. Med.* **2002**, 64 (4), 604–611.
 - 64 GREENBERG, D. B., GRAY, J. L., MANNIX, C. M., EISENTHAL, S., CAREY, M., Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. *J. Pain Symptom Manag.* **1993**, 8 (4), 196–200.
 - 65 MAES, M., Major depression and activation of the inflammatory response system. *Adv. Exp. Med. Biol.* **1999**, 461, 25–46.
 - 66 SOMMER, N., LOSCHMANN, P. A., NORTHOFF, G. H., WELLER, M., STEINBRECHER, A., STEINBACH, J. P., LICHTENFELS, R., MEYERMANN, R., RIETHMULLER, A., FONTANA, A., The antidepressant rolipram suppresses cytokine production and prevents autoimmune encephalomyelitis. *Nature Med.* **1995**, 1 (3), 244–248.
 - 67 GRISWOLD, D. E., WEBB, E. F., BADGER, A. M., GORYCKI, P. D., LEVANDOSKI, P. A., BARNETTE, M. A., GROUS, M., CHRISTENSEN, S., Torphy, T. J. SB 207499 (Ariflo), a second generation phosphodiesterase 4 inhibitor, reduces tumor necrosis factor alpha and interleukin-4 production *in vivo*. *J. Pharmacol. Exp. Ther.* **1998**, 287 (2), 705–711.
 - 68 YARON, I., SHIRAZI, I., JUDOVICH, R., LEVARTOVSKY, D., CASPI, D., YARON, M., Fluoxetine and amitriptyline inhibit nitric oxide, prostaglandin E2, and hyaluronic acid production in human synovial cells and synovial tissue cultures. *Arthritis Rheum.* **1999**, 42 (12), 2561–2568.
 - 69 SONG, C., LEONARD, B. E., An acute phase protein response in the olfactory bulb-ectomized rat: effect of sertraline treatment. *Med. Sci. Res.* **1994**, 22, 313–314.
 - 70 KUBERA, M., SYMBIRTSEV, A., BASTA-KAIM, A., BORYCZ, J., ROMAN, A., PAPP, M., CLAESSEON, M., Effect of chronic treatment with imipramine on interleukin 1 and interleukin 2 production by splenocytes obtained from rats subjected to a chronic mild stress model of depression. *Pol. J. Pharmacol.* **1996**, 48 (5), 503–506.
 - 71 ZHU, J., BENGTSSON, B. O., MIX, E., THORELL, L. H., OLSSON, T., LINK, H., Effect of monoamine reuptake inhibiting antidepressants on major histocompatibility complex expression on macrophages in normal rats and rats with experimental allergic neuritis (EAN). *Immunopharmacology* **1994**, 27 (3), 225–244.
 - 72 BIANCHI, M., ROSSONI, G., SACERDOTE, P., PANERAI, A. E., BERTI, F., Effects of clomipramine and fluoxetine on subcutaneous carrageenin-induced inflammation in the rat. *Inflammation Res.* **1995**, 44 (11), 466–469.
 - 73 MICHELSON, D., MISIEWICZ-POLTORAK, B., RAYBOURNE, R. B., GOLD, P. W., STERNBERG, E. M., Imipramine reduces the local inflammatory response to carrageenin. *Agents Actions* **1994**, 42 (1–2), 25–28.
 - 74 SHEN, Y., CONNOR, T. J., NOLAN, Y., KELLY, J. P., LEONARD, B. E., Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat. *Life Sci.* **1999**, 65 (17), 1773–1786.
 - 75 YIRMIYA, R., POLLAK, Y., BARAK, O., AVITSUR, R., OVADIA, H., BETTE, M., WEIHE, E., WEIDENFELD, J., Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacology* **2001**, 24 (5), 531–544.
 - 76 DAWSON, L. A., NGUYEN, H. Q., GEIGER, A., Effects of venlafaxine on extracellular concentrations of 5-HT and noradrenaline in the rat frontal cortex: augmentation via 5-HT1A receptor antagonism. *Neuropharmacology* **1999**, 38 (8), 1153–1163.

- 77 YIRMIYA, R., Endotoxin produces a depressive-like episode in rats. *Brain Res.* **1996**, 711 (1–2), 163–174.
- 78 CASTANON, N., BLUTHE, R. M., DANTZER, R., Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1beta in the rat. *Psychopharmacology (Berl.)* **2001**, 154 (1), 50–60.
- 79 DUNN, A. J., SWIERGIEL, A. H., The reductions in sweetened milk intake induced by interleukin-1 and endotoxin are not prevented by chronic antidepressant treatment. *Neuroimmunomodulation* **2001**, 9 (3), 163–169.
- 80 MERALI, Z., BRENNAN, K., BRAU, P., ANISMAN, H., Dissociating anorexia and anhedonia elicited by interleukin-1beta: antidepressant and gender effects on responding for “free chow” and “earned” sucrose intake. *Psychopharmacology (Berl.)* **2003**, 165 (4), 413–418.
- 81 CAPURON, L., GUMNICK, J. F., MUSSELMAN, D. L., LAWSON, D. H., REEMSnyder, A., NEMEROFF, C. B., MILLER, A. H., Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* **2002**, 26 (5), 643–652.
- 82 RAISON, C. L., MILLER, A. H., When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am. J. Psychiatry* **2003**, 160 (9), 1554–1565.
- 83 BRAMBILLA, F., MAGGIONI, M., Blood levels of cytokines in elderly patients with major depressive disorder. *Acta Psychiatr. Scand.* **1998**, 97 (4), 309–313.
- 84 MAES, M., MELTZER, H. Y., BOSMANS, E., BERGMANS, R., VANDOOOLAEGHE, E., RANJAN, R., DESNYDER, R., Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J. Affect Disord.* **1995**, 34 (4), 301–309.
- 85 LANDMANN, R., SCHAUB, B., LINK, S., WACKER, H. R., Unaltered monocyte function in patients with major depression before and after three months of antidepressive therapy. *Biol. Psychiatry* **1997**, 41 (6), 675–681.
- 86 WEIZMAN, R., LAOR, N., PODLISZEWSKI, E., NOTTI, I., DJALDETTI, M., BESSLER, H., Cytokine production in major depressed patients before and after clomipramine treatment. *Biol. Psychiatry* **1994**, 35 (1), 42–47.
- 87 SLUZEWSKA, A., RYBAKOWSKI, J., LACIAK, M., MACKIEWICZ, A., SOBIESKA, M., WIKTOROWICZ, K., Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Ann. NY Acad. Sci.* **1995**, 762, 474–476.
- 88 SEIDEL, A., AROLT, V., HUNSTIGER, M., RINK, L., BEHNISCH, A., KIRCHNER, H., Major depressive disorder is associated with elevated monocyte counts. *Acta Psychiatr. Scand.* **1996**, 94 (3), 198–204.
- 89 TUĞLU, C., KARA, S. H., CALIYURT, O., VARDAR, E., ABAY, E., Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl.)* **2003**, 170, 429–433.
- 90 HESTAD, K. A., TONSETH, S., STOEN, C. D., UELAND, T., AUKRUST, P., Raised plasma levels of tumor necrosis factor alpha in patients with depression. *J. ECT* **2003**, 19 (4), 183–188.
- 91 ROITT, I., BOSTOFF, J., MALE, D., *Immunology* 5th ed. New York: Mosby, **1998**.
- 92 CAPURON, L., RAISON, C. L., MUSSELMAN, D. L., LAWSON, D. H., NEMEROFF, C. B., MILLER, A. H., Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am. J. Psychiatry* **2003**, 160 (7), 1342–1345.
- 93 TAYLOR, J. L., GROSSBERG, S. E., The effects of interferon-alpha on the production and action of other cytokines. *Semin. Oncol.* **1998**, 25 (1 Suppl. 1), 23–29.
- 94 MUSSELMAN, D. L., LAWSON, D. H., GUMNICK, J. F., MANATUNGA, A. K., PENNA, S., GOODKIN, R. S., GREINER, K., NEMEROFF, C. B., MILLER, A. H., Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med.* **2001**, 344 (13), 961–966.
- 95 SCHAEFER, M., SCHWAIGER, M., BERG, T., Citalopram for the prevention of interferon-alpha associated depression in

- psychiatric risk patients. *Hepatology* **2003**, 38 (4, Suppl. 1), 320A.
- 96 MOHR, D. C., GOODKIN, D. E., LIKOSKY, W., GATTO, N., BAUMANN, K. A., RUDICK, R. A., Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch. Neurol.* **1997**, 54 (5), 531–533.
 - 97 SCHRAMM, T. M., LAWFOR, B. R., MACDONALD, G. A., COOKSLEY, W. G., Sertraline treatment of interferon-alfa-induced depressive disorder. *Med. J. Aust.* **2000**, 173 (7), 359–361.
 - 98 GLEASON, O. C., YATES, W. R., Five cases of interferon-alpha-induced depression treated with antidepressant therapy. *Psychosomatics* **1999**, 40 (6), 510–512.
 - 99 LEVENSON, J. L., FALLON, H. J., Fluoxetine treatment of depression caused by interferon-alpha. *Am. J. Gastroenterol.* **1993**, 88 (5), 760–761.
 - 100 HAUSER, P., KHOSLA, J., AURORA, H., LAURIN, J., KLING, M. A., HILL, J., GULATI, M., THORNTON, A. J., SCHULTZ, R. L., VALENTINE, A. D., MEYERS, C. A., HOWELL, C. D. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Mol. Psychiatry* **2002**, 7 (9), 942–947.
 - 101 KRAUS, M. R., SCHAFER, A., FALLER, H., CSEF, H., SCHEURLEN, M., Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. *Alim. Pharmacol. Ther.* **2002**, 16 (6), 1091–1099.
 - 102 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV–4th ed.* **1994**, Washington, DC: American Psychiatric Association.
 - 103 CLEELAND, C. S., MENDOZA, T. R., WANG, X. S., CHOU, C., HARLE, M. T., MORRISSEY, M., ENGSTROM, M. C., Assessing symptom distress in cancer patients: the M. D. Anderson Symptom Inventory. *Cancer* **2000**, 89 (7), 1634–1646.
 - 104 MORROW, G. R., HICKOK, J. T., ROSCOE, J. A., RAUBERTAS, R. F., ANDREWS, P. L. R., FLYNN, P. J., HYNES, H. E., BANERJEE, T. K., KIRSHNER, J. J., KING, D. K., Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J. Clin. Oncol.* **2003**, 21 (24), 4635–4641.
 - 105 KRUEGER, J. M., OBAL, F. J., FANG, J., KUBOTA, T., TAISHI, P., The role of cytokines in physiological sleep regulation. *Ann. NY Acad. Sci.* **2001**, 933, 211–221.
 - 106 RACHAL PUGH, C., FLESHNER, M., WATKINS, L. R., MAIER, S. F., RUDY, J. W., The immune system and memory consolidation: a role for the cytokine IL-1beta. *Neurosci. Biobehav. Rev.* **2001**, 25 (1), 29–41.
 - 107 OWENS, M. J., NEMEROFF, C. B., Physiology and pharmacology of corticotropin-releasing factor. *Pharmacol. Rev.* **1991**, 43 (4), 425–473.
 - 108 DELGADO, P. L., MILLER, H. L., SALOMON, R. M., LICINIO, J., KRISTAL, J. H., MORENO, F. A., HENINGER, G. R., CHARNEY, D. S., Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. *Biol. Psychiatry* **1999**, 46 (2), 212–220.
 - 109 NARANJO, C. A., TREMBLAY, L. K., BUSTO, U. E., The role of the brain reward system in depression. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2001**, 25 (4), 781–823.
 - 110 BESEDOVSKY, H., DEL REY, A., SORKIN, E., DINARELLO, C. A., Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* **1986**, 233 (4764), 652–654.
 - 111 RIVIER, C., Influence of immune signals on the hypothalamic–pituitary axis of the rodent. *Frontiers Neuroendocrinol.* **1995**, 16 (2), 151–182.
 - 112 RABER, J., KOOB, G. F., BLOOM, F. E., Interferon-alpha and transforming growth factor-beta 1 regulate corticotropin-releasing factor release from the amygdala: comparison with the hypothalamic response. *Neurochem. Int.* **1997**, 30 (4–5), 455–463.
 - 113 CAPURON, L., NEURAUER, G., MUSSELMAN, D. L., LAWSON, D., NEMEROFF, C. B., Interferon-alpha-induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. *Biol. Psychiatry* **2003** (in press).
 - 114 SHUTO, H., KATAOKA, Y., HORIKAWA, T., FUJIHARA, N., OISHI, R., Repeated

- interferon-alpha administration inhibits dopaminergic neural activity in the mouse brain. *Brain Res.* **1997**, 747 (2), 348–351.
- 115 CAPURON, L., MILLER, A. H., Cytokines and psychopathology: lessons from interferon-alpha. *Biol. Psychiatry* **2004** (in press).
 - 116 CAPURON, L., RAVAUD, A., NEVEU, P. J., MILLER, A. H., MAES, M., DANTZER, R., Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol. Psychiatry* **2002**, 7 (5), 468–473.
 - 117 MELLOR, A. L., MUNN, D. H., Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? *Immunol. Today* **1999**, 20 (10), 469–473.
 - 118 MORENO, F. A., GELENBERG, A. J., HENINGER, G. R., POTTER, R. L., MCKNIGHT, K. M., ALLEN, J., PHILLIPS, A. P., DELGADO, P. L., Tryptophan depletion and depressive vulnerability. *Biol. Psychiatry* **1999**, 46 (4), 498–505.
 - 119 MORENO, F. A., HENINGER, G. R., MCGAHUEY, C. A., DELGADO, P. L., Tryptophan depletion and risk of depression relapse: a prospective study of tryptophan depletion as a potential predictor of depressive episodes. *Biol. Psychiatry* **2000**, 48 (4), 327–329.
 - 120 BONACCORSO, S., MARINO, V., PUZELLA, A., PASQUINI, M., BIONDI, M., ARTINI, M., ALMERIGHI, C., VERKERK, R., MELTZER, H., MAES, M., Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J. Clin. Psychopharmacol.* **2002**, 22 (1), 86–90.
 - 121 WIDNER, B., LEDOCHOWSKI, M., FUCHS, D., Interferon-gamma-induced tryptophan degradation: neuropsychiatric and immunological consequences. *Curr. Drug Metab.* **2000**, 1 (2), 193–204.
 - 122 HOLSBOER, F., The corticosteroid hypothesis of depression. *Neuropsychopharmacology* **2000**, 23, 477–501.
 - 123 CUMMINGS, J. L., Depression and Parkinson's disease: a review. *Am. J. Psychiatry* **1992**, 149 (4), 443–454.
 - 124 BERGER, J. R., ARENDT, G., HIV dementia: the role of the basal ganglia and dopaminergic systems. *J. Psychopharmacol.* **2000**, 14 (3), 214–221.
 - 125 MARTINOT, M., BRAGULAT, V., ARTIGES, E., DOLLE, F., HINNEN, F., JOUVENT, R., MARTINOT, J., Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. *Am. J. Psychiatry* **2001**, 158 (2), 314–316.
 - 126 SUGAWARA, Y., AKECHI, T., SHIMA, Y., OKUYAMA, T., AKIZUKI, N., NAKANO, T., UCHITOMI, Y., Efficacy of methylphenidate for fatigue in advanced cancer patients: a preliminary study. *Palliative Med.* **2002**, 16 (3), 261–263.
 - 127 SARHILL, N., WALSH, D., NELSON, K. A., HOMSI, J., LEGRAND, S., DAVIS, M. P., Methylphenidate for fatigue in advanced cancer: a prospective open-label pilot study. *Am. J. Hospice Palliative Care* **2001**, 18 (3), 187–192.
 - 128 ZIFKO, U. A., RUPP, M., SCHWARZ, S., ZIPKO, H. T., MAIDA, E. M., Modafinil in treatment of fatigue in multiple sclerosis. Results of an open-label study. *J. Neurol.* **2002**, 249 (8), 983–987.
 - 129 CAPURON, L., RAVAUD, A., DANTZER, R., Timing and specificity of the cognitive changes induced by interleukin-2 and interferon-alpha treatments in cancer patients. *Psychosom. Med.* **2001**, 63 (3), 376–386.
 - 130 SUNAMI, M., NISHIKAWA, T., YOROGI, A., SHIMODA, M., Intravenous administration of levodopa ameliorated a refractory akathisia case induced by interferon-alpha. *Clin. Neuropharmacol.* **2000**, 23 (1), 59–61.
 - 131 HAAS, H. S., SCHAUENSTEIN, K., Neuroimmunomodulation via limbic structures – the neuroanatomy of psychoimmunology. *Prog. Neurobiol.* **1997**, 51 (2), 195–222.
 - 132 GAO, H. M., JIANG, J., WILSON, B., ZHANG, W., HONG, J. S., LIU, B., Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. *J. Neurochem.* **2002**, 81 (6), 1285–1297.
 - 133 CAPURON, L., PAGNONI, G., LAWSON, D., DEMETRASHVILI, M., WOOLWINE, B. J., KILTS, C. D., BREMNER, J. D., NEMEROFF, C. B., MILLER, A. H., Altered fronto-

- pallidal activity during high-dose interferon-alpha treatment as determined by positron emission tomography. *Soc. Neurosci. Abstr.* **2002**, 498.5.
- 134 JUENGLING, F. D., EBERT, D., GUT, O., ENGELBRECHT, M. A., RASENACK, J., NITZSCHE, E. U., BAUER, J., LIEB, K., Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology (Berl.)* **2000**, 152 (4), 383–389.
 - 135 MORROW, G. R., HICKOK, J. T., ROSCOE, J. A., RAUBERTAS, R. F., ANDREWS, P. L., FLYNN, P. J., HYNES, H. E., BANERJEE, T. K., KIRSHNER, J. J., KING, D. K., Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the university of Rochester cancer center community clinical oncology program. *J. Clin. Oncol.* **2003**, 21 (24), 4635–4641.
 - 136 CAPURON, L., MILLER, A. H., Cytokines and psychopathology: lessons from interferon-alpha. *Biol. Psychiatry* **2004** (in press).
 - 137 GRIPPO, A. J., FRANCIS, J., WEISS, R. M., FELDER, R. B., JOHNSON, A. K., Cytokine mediation of experimental heart failure-induced anhedonia. *Am. J. Physiol. – Reg. Integ. Comp. Physiol.* **2003**, 284 (3), R666–R673.
 - 138 LICHTENSTEIN, G. R., BALA, M., HAN, C., DEWOODY, K., SCHAIBLE, T., Infliximab improves quality of life in patients with Crohn's disease. *Inflammatory Bowel Dis.* **2002**, 8 (4), 237–243.
 - 139 LUHESI, G., MILLER, A. J., BROUWER, S., DASCOMBE, M. J., ROTHWELL, N. J., HOPKINS, S. J., Interleukin-1 receptor antagonist inhibits endotoxin fever and systemic interleukin-6 induction in the rat. *Am. J. Physiol.* **1996**, 270 (1 Pt 1), E91–E95.
 - 140 OPP, M. R., KRUEGER, J. M., Interleukin 1-receptor antagonist blocks interleukin 1-induced sleep and fever. *Am. J. Physiol.* **1991**, 260 (2 Pt 2), R453–R457.
 - 141 GOMEZ-REINO, J. J., CARMONA, L., VALVERDE, V. R., MOLA, E. M., MONTERO, M. D., GROUP, B., Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum.* **2003**, 48 (8), 2122–2127.
 - 142 KWON, H. J., COTE, T. R., CUFFE, M. S., KRAMER, J. M., BRAUN, M. M., Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann. Intern. Med.* **2003**, 138 (10), 807–811.
 - 143 KROESEN, S., WIDMER, A. F., TYNDALL, A., HASLER, P., Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. *Rheumatology* **2003**, 42 (5), 617–621.
 - 144 MILLER, A. H., VOGT, G., PEARCE, B. D., The phosphodiesterase type 4 inhibitor, rolipram, enhances glucocorticoid receptor function. *Neuropsychopharmacology* **2002**, 27 (6), 939–948.
 - 145 GOODNICK, P. J., Treatment of chronic fatigue syndrome with venlafaxine. *Am. J. Psychiatry* **1996**, 153 (2), 294.
 - 146 GOODNICK, P. J., Bupropion in chronic fatigue syndrome. *Am. J. Psychiatry* **1990**, 147 (8), 1091.
 - 147 TRAN, P. V., BYMASTER, F. P., MCNAMARA, R. K., POTTER, W. Z., Dual monoamine modulation for improved treatment of major depressive disorder. *J. Clin. Psychopharmacol.* **2003**, 23 (1), 78–86.
 - 148 ENTSUAH, A. R., HUANG, H., THASE, M. E., Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J. Clin. Psychiatry* **2001**, 62 (11), 869–877.
 - 149 SAUER, W. H., BERLIN, J. A., KIMMEL, S. E., Effect of antidepressants and their relative affinity for the serotonin transporter on the risk of myocardial infarction. *Circulation* **2003**, 108 (1), 32–36.

10

Depression and Suicidality in Children and Adolescents

Cynthia R. Pfeffer

Abstract

Suicidal behavior is a complex phenomenon for which risk is elevated by multiple and distinct factors. This chapter will focus on the role of depression as principle risk for youth suicidal behavior. It will outline the epidemiology of depression and suicidal behavior in children and adolescents to point out the significance of these morbidities for youth. It will describe how certain environmental factors, especially stressful events, effect vulnerability to depression and suicidal behavior. Such environmental factors involving family suicidal behavior, violence, and family conflict, in addition to genetic propensity, may affect neurophysiological regulation and lead to depression and suicidal behavior. This chapter will point out that risk in children and adolescents for suicidal behavior is affected by the relations between biological characteristics related to depression and suicidal behavior. It will emphasize that identification of children and adolescents who are at risk for depression and suicidal behavior is essential in preventing suicidal acts. Treatments will be described that have potential to reduce risk for suicidal behavior in children and adolescents.

10.1

Epidemiology of Depression and Suicidal Behavior

The significance of depression and suicidal behavior in children and adolescents is highlighted in epidemiological trends for these psychopathological entities. Notably, depression is among the most under-recognized psychopathologies in children and adolescents. A conference sponsored by the National Depression and Manic-Depressive Association aimed to address the unmet needs of children and adolescents at risk for or suffering from mood disorders [1]. Some of the conclusions emphasized the need to have better methods for identifying children and adolescents with bipolar disorder, more effective methods to educate primary care clinicians about adequate identification of youth who suffer mood disorders, greater

understanding of the different psychopharmacologic responses of children and adolescents compared to adults, and more effective prevention interventions to reduce the likelihood of children and adolescents being afflicted with mood disorders [1].

Community samples provide the most generalizable information about rates of youth depression and suicidal behavior. The prevalence of major depressive disorder has been estimated from several studies. Among children it is 0.4 to 2.5% and among adolescents 0.4 to 8.3% [2, 3]. Episodes of major depression are recurrent with a cumulative probability of recurrence of 40% by 2 years and 70% by 5 years after the first episode in childhood or adolescence [4–6]. Furthermore, episodes of major depression with onset in adolescence appear to continue into adulthood as inferred by similar lifetime prevalence rates of 15 to 20% for adolescents and adults [7]. There is no difference in gender rates among children but in adolescents, the rates for girls are twice that for boys [2, 3]. Other mood disorders, such as dysthymic disorder, have rates of 0.6 to 1.7% for children and 1.6 to 8.0% for adolescents [3]. Major depressive disorder is highly comorbid with other psychiatric disorders including dysthymic (30 to 80%), anxiety (30 to 80%), disruptive (10 to 80%), and substance abuse (20 to 30%) disorders [8, 9]. Approximately 20 to 40% of adolescents with major depressive disorder develop bipolar disorder within 5 years of onset of their first episode of major depression [10, 11]. The early onset, comorbidity, and recurrences of major depressive disorder increase the vulnerability of children and adolescents to suicidal states from childhood into adulthood.

National data from 1998 onward indicate that the youth suicide rates have decreased [12]. In the year 2000, National Vital Statistics indicated that the age-adjusted rate of suicide for youth, aged 15 to 24 years, was 10.1 per 100 000 population [13]. Suicide was the third leading cause of death in this youth group. Approximately 60% of youth in this age group died by suicide inflicted with the use of firearms [12]. Among the youngest categorical group involving children and young adolescents, aged 5 to 14 years, the age-adjusted suicide rate was 0.7 per 100 000 population [13]. Suicide was the fifth leading cause of death in this age group. Approximately, 42% of children and young adolescents committed suicide as a result of firearm use [12]. In general for children and adolescents, males commit suicide more frequently than females and males use firearms to commit suicide at greater rates than females [12]. This gender trend for firearm use in suicide rates is similar to that for all ages. Similar to suicide rates for all ages, whites commit suicide more frequently than non-whites.

The Youth Risk Behavior Surveillance System Survey, evaluating health behaviors among 1270 high school students, reported that approximately 20% of high school students seriously thought of attempting suicide [14]. Females were significantly more likely to report suicidal ideation than males (24 and 14%, respectively) [14]. Females (11%), compared to males (6%), attempted suicide at higher rates [14]. Other epidemiological reports suggest that non-fatal suicide attempts among children and high school students are predicted by presence of current mood, anxiety, and disruptive disorders [15, 16]. These data indicate that mood disorders impart greatest risk for suicidal acts in children and adolescents.

10.2

Depression as a Main Risk Factor for Youth Suicidal Behavior

Many studies have utilized the psychological autopsy methodology to evaluate risk factors for youth suicide. This method uses standard strategies to interview those who knew the deceased as a means of informing about psychiatric status and life events of the deceased. Validation that youth who committed suicide suffered psychiatric disorders in approximately 90% of the cases has been revealed in most of the psychological autopsy studies [17, 18]. These studies indicated that major depressive disorder was the strongest psychopathological risk factor for youth suicide. Youth who suffered from major depressive disorder were approximately 27 times more likely to commit suicide than those who were not afflicted with this psychiatric disorder [17]. The risk was additionally elevated over that for major depression when this disorder was comorbid with such psychiatric disorders as anxiety, conduct, and substance abuse disorders [19].

Psychological autopsy studies of youth suicide victims pointed out that approximately 26 to 33% of youths who committed suicide made prior suicide attempts [17, 18]. This rate of suicide attempts among youth suicide victims was significantly higher than the rate of approximately 1.5% of adolescents in the community who attempted suicide but did not commit suicide [17]. These studies highlighted that recurrent suicidal acts was a significant risk factor for youth suicide.

Cross-sectional and longitudinal studies also validated the significance of major depressive disorder in childhood and adolescence as the strongest psychopathological risk factor for non-fatal suicidal acts [20–22]. However, it is important to understand that all youth who suffer from major depressive disorder do not experience suicidal tendencies. For example, the National Comorbidity Survey indicated that approximately 30% of adolescents or adults who suffered from major depressive disorder reported a lifetime episode of a suicide attempt [23].

10.3

The Role of Life Event Stresses on Risk for Youth Suicidal Behavior

Growing up in a family atmosphere with stresses from parental or sibling psychiatric disability involving suicidal behavior, violence, physical or sexual abuse, substance abuse, and alcoholism imparts significant risk for youth suicidal behavior [24]. Adolescents who grow up in families in which a parent is depressed and has attempted suicide are at significantly higher risk for a suicide attempt than adolescents whose depressed parent has not attempted suicide [25]. Additional risk from other family or environmental stresses involves school problems including poor grades, school suspension, and school dropout, disciplinary situations involving police or court issues, and family conflict involving poor communication [26]. Research is needed to evaluate the relationships among severe life event stresses and biological factors associated with depression and suicidal behavior in children and adolescents.

10.4

Biological Correlates of Depression and Youth Suicidal Behavior

Additional research is needed to identify biological factors that are involved in the strong association between depression and suicidal behavior among children and adolescents. Knowledge of these results may enhance the development of novel interventions to reduce risk for youth suicidal behavior. However, interpretation of results of neurobiological studies of children and adolescents rests on the complexities of developmental effects. Thus, results of studies of adults may not reflect the same biological status regarding the role of depression as a risk factor for suicide in children and adolescents.

Genetic factors, considered to underlie risk for depression and suicidal behavior, are yet to be understood. The complexity of phenotypic identification of depression and suicidal behavior among children and adolescents limits genetic studies. Among the strongest hypotheses for genetic factors that are associated with suicidal behavior are those related to the serotonergic neurotransmitter system [27]. Candidate genes for study include the 5-hydroxytryptamine type 1B gene, the tryptophan hydroxylase gene, the serotonin transporter gene, the serotonin type 2A gene, the serotonin type 1A gene and the monoamine oxidase A gene [27].

Few studies exist regarding evaluation of these genetic issues in children and adolescents. Among such studies, no significant relations were found between adolescent suicidal behavior and the serotonin transporter-linked promoter region polymorphism [28] or the polymorphism A218C in intron 7 of the tryptophan hydroxylase gene [29].

Studies of neurobiological correlates of childhood and adolescent suicidal behavior that focused on serotonergic indices highlighted that pre-pubertal suicidal psychiatric inpatients had significantly lower whole blood tryptophan content [30]. This study also reported that pre-pubertal psychiatric inpatients with a mood disorder had higher platelet serotonin content than pre-pubertal inpatients without a mood disorder [30]. This study also supported efforts to understand serotonergic regulation associated with mood disorders and suicidal behavior in children and adolescents.

Studies among depressed adolescents suggested that they have blunted growth hormone secretion after various challenge tests including insulin-induced hypoglycemia, oral clonidine, L-dopa, desmethylinipramine, and growth hormone-releasing hormone. Some of these trends persist after remission of the episode of major depressive disorder [31]. One study noted that nocturnal secretion of growth hormone was decreased in a group of depressed, suicidal inpatient adolescents [32]. However, studies of children with major depression regarding cortisol secretion have been inconsistent in finding dysregulation of this hormone system [33–35]. The complex relationships between these neurohormonal systems and the serotonergic system require further study regarding risk for depression and suicidal behavior among youth.

10.5

Clinical and Research Implications

Identification of children and adolescents at risk for or who suffer from major depressive disorder is a key feature for preventing youth suicidal behavior. Identifying youth who report suicidal ideation or have made suicide attempts are other key factors in preventing suicidal behavior. Despite the recent decrease in youth suicide, there appears to be an increase in youth suicide attempts as identified in the Youth Risk Behavior Survey during the years 1991 through 1997 [36]. All professionals, such as psychiatrists, pediatricians and school personnel should be skilled in speaking with children and adolescents about their feelings and behavior, especially feelings of depression and suicidal ideation or behavior.

Recent strategies considered use of screening measures to identify youth at risk [37]. Many self-report questionnaires have been developed to identify features of risk. However, their predictive validity has not been conclusively demonstrated and they often have high sensitivity with less specificity. This yields identification of many false positive results and may over identify risk. Methods that incorporate follow-up interviews may be a more specific way of identifying those at risk.

Interventions should be offered to those at risk. Methods should be utilized to improve adherence to interventions, especially for adolescents who attempted suicide [38]. Interventions to reduce risk for suicidal behavior among children and adolescents may include psychotherapeutic approaches often combined with medication. Recent studies to evaluate efficacy of psychotherapy have been undertaken. Such studies suggest efficacy for acute phases of moderate to severe depression in adolescents for such psychosocial interventions as interpersonal psychotherapy [39–41], dialectical behavior therapy [42], cognitive behavioral therapy [43, 44], and cognitive behavioral therapy for depressed suicidal adolescents [45, 46]. However, long-term effects of such interventions have not been evaluated for all of these treatment types. Cognitive behavioral therapy for depressed suicidal adolescents appears not to have long-term beneficial effects when compared to supportive or family interventions [47].

Medication should be specific to psychiatric disorders or symptoms. Use of the selective serotonin reuptake inhibitor (SSRI) fluoxetine has been reported to be effective in reducing symptoms of major depressive disorder in children and adolescents [48]. There are no studies that were designed to determine whether intervention with medication reduces suicidal behavior in children and adolescents [49]. Caution should be exercised when using medication with suicidal children and adolescents since side-effects may include increased risk for impulsive behavior and/or suicidal ideation.

10.6

Conclusion

This chapter indicated that childhood and adolescent major depressive disorder is a recurrent psychopathology and is among the greatest risk factors for child and adolescent suicide. However, depressed and suicidal children and adolescents are often not identified. Identification of children and adolescents who express suicidal ideation or suicidal acts is crucial since such symptoms are recurrent and strong predictors of youth suicide. Other risk factors for youth suicidal behavior were described including family, other environmental and biological factors. Notably, family history of suicidal behavior increases risk for youth suicide. This chapter highlighted the fact that despite the significant incidence and prevalence of childhood and adolescent mood disorders and suicidal behavior, there has been a paucity of research on the effectiveness of treatments for these morbidities in children and adolescents. Additional research is needed to increase understanding of the relations between biological risk factors and treatment of suicide risk in children and adolescents.

References

- 1 COYLE, J. T., Childhood mood disorders: Unmet needs but important opportunities. *Biological Psychiatry* **2001**, *49*, 9959.
- 2 FLEMING, J. E., OFFORD, D. R., Epidemiology of childhood depressive disorders: A critical review. *Journal of the American Academy of Child and Adolescent Psychiatry* **1990**, *29*, 571–580.
- 3 LEWINSOHN, P. M., HOPE, H., ROBERTS, R. E., SEELEY, J. R., ANDREWS, J. A., Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology* **1993**, *102*, 133–144.
- 4 KOVACS, M., FEINBERG, T. L., CROUSE-NOVAK, M., PAULAUSKAS, S. I., POLLOCK, M., FINKELSTEIN, R., Depressive disorders in childhood: II A longitudinal study of the risk for a subsequent major depression. *Archives of General Psychiatry* **1984**, *41*, 643–649.
- 5 LEWINSOHN, P. M., ROHDE, P., SEELEY, J. R., et al., Gender differences in suicide attempts from adolescence to young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry* **2001**, *34*, 454–463.
- 6 RAO, U., RYAN, N. D., BIRMAHER, B., et al., Unipolar depression in adolescents: Clinical outcome in adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry* **1995**, *34*, 566–578.
- 7 KESSLER, R. C., MCGONAGLE, K. A., ZHAO, S., et al., Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Archives of General Psychiatry* **1994**, *51*, 8–19.
- 8 ANGOLD, A., COSTELLO, E. J., Depressive comorbidity in children and adolescents. Empirical, theoretical, and methodological issues. *American Journal of Psychiatry* **1993**, *150*, 1779–1791.
- 9 RYAN, N. D., PUIG-ANTICH, J., AMBROSINI, P., et al., The clinical picture of major depression in children and adolescents. *Archives of General Psychiatry* **1987**, *44*, 854–861.
- 10 GELLER, B., FOX, I. W., CLARK, K. A., Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. *Journal of the American Academy of Child and Adolescent Psychiatry* **1994**, *33*, 461–468.
- 11 STROBER, M., LAMPERT, C., SCHMIDT, S., MORREL, W., The course of major

- depressive disorder in adolescents:
I. Recovery and risk of manic switching
in a follow-up of psychotic and
nonpsychotic subtypes. *Journal of the
American Academy of Child and Adolescent
Psychiatry* **1993**, 32, 34–42.
- 12 HOYERT, D. L., ARIAS, E., SMITH, B. L.,
et al., Deaths: Final data for 1999. *National
Vital Statistics Report* **2001**, 49 (8), 1–113.
 - 13 MINIMO, A. M., SMITH, B. L., Deaths:
Preliminary data for 2000. *National Vital
Statistics Report* **2001**, 49 (12), 1–40.
 - 14 KANN, L., KINCHEN, S. A., WILLIAMS,
B. I., et al., Youth Risk Behavior Sur-
veillance – United States, 1999. *Journal
of School Health* **2000**, 70, 271–285.
 - 15 KING, R. A., SCHWAB-STONE, M.,
FLISHER, A. J., et al., Psychosocial and
risk behavior: Correlates of youth suicide
attempts and suicidal ideation. *Journal
of the American Academy of Child and
Adolescent Psychiatry* **2001**, 40, 837–846.
 - 16 LEWINSOHN, P. M., ROHDE, P., SEELEY,
J. R., et al., Gender differences in suicide
attempts from adolescence to young
adulthood. *Journal of the American
Academy of Child and Adolescent Psychiatry*
2001, 34, 454–463.
 - 17 BRENT, D. A., PERPER, J. A., MORITZ, G.,
et al., Psychiatric risk factors for adolescent
suicide: A case-control study. *Journal of
the American Academy of Child and
Adolescent Psychiatry* **1993**, 32, 521–529.
 - 18 SHAFFER, D., GOULD, M. S., FISHER, P.,
et al., Psychiatric diagnosis in child and
adolescent suicide. *Archives of General
Psychiatry* **1996**, 53, 339–348.
 - 19 BEAUTRAIS, A. L., Risk factors for suicide
and attempted suicide among young
people. *Australian and New Zealand
Journal of Psychiatry* **2000**, 34, 420–436.
 - 20 BRENT, D. A., PERPER, J. A., GOLDSTEIN,
C. E., et al., Risk factors for adolescent
suicide: A comparison of adolescent suicide
victims with suicidal inpatients. *Archives
of General Psychiatry* **1988**, 45, 581–588.
 - 21 BRINKMAN-SULL, D. C., OVERHOLSER, J. C.,
SILVERMAN, E., Risk of future suicide
attempts in adolescent psychiatric in-
patients at 18-month follow-up. *Suicide and
Life-Threatening Behavior* **2000**, 30, 327–340.
 - 22 PFEFFER, C. R., KLERMAN, G. L., HURT,
S. W., et al., Suicidal children grow up:
Rates and psychosocial risk factors for
suicide attempts during follow-up.
*Journal of the American Academy of Child
and Adolescent Psychiatry* **1993**, 32, 106–113.
 - 23 KESSLER, R. C., WALTERS, E. E.,
Epidemiology of DSM-III-R major
depression and minor depression among
adolescents and young adults in the
National Comorbidity Survey. *Depression
and Anxiety* **1998**, 7, 3–13.
 - 24 PFEFFER, C. R., NORMANDIN, L., KAKUMA,
T., Suicidal children grow up: Suicidal
behavior and psychiatric disorders among
relatives. *Journal of the American Academy
of Child and Adolescent Psychiatry* **1994**,
33, 1087–1097.
 - 25 BRENT, D. A., OQUENDO, M., BIRMAHER,
B., et al., Familial pathways to early-onset
suicide attempt: Risk for suicidal
behavior in offspring of mood-disordered
suicide attempters. *Archives of General
Psychiatry* **2002**, 59, 801–807.
 - 26 GOULD, M. S., FISHER, P., PARIDES, M.,
et al., Psychosocial risk factors of child and
adolescent completed suicide. *Archives of
General Psychiatry* **1996**, 53, 1155–1162.
 - 27 MANN, J. J., BRENT, D. A., ARANGO, V.,
The neurobiology and genetics of suicide
and attempted suicide: A focus on the
serotonergic system. *Neuropsychophar-
macology* **2001**, 24, 467–477.
 - 28 ZALSMAN, G., FRISCH, A., BROMBERG, M.,
et al., Family-based association study of
serotonin transporter promoter in
suicidal adolescents: No association with
suicidality but possible role in violence
traits. *American Journal of Medical
Genetics* **2001**, 105, 239–245.
 - 29 ZALSMAN, G., FRISCH, A., KING, R. A.,
et al., Case control and family-based
studies of tryptophan hydroxylase gene
A218C polymorphism and suicidality in
adolescents. *American Journal of Medical
Genetics* **2001**, 105, 451–457.
 - 30 PFEFFER, C. R., MCBRIDE, A., ANDERSON,
G. M., et al., Peripheral serotonin measures
in prepubertal psychiatric inpatients and
normal children: Associations with
suicidal behavior and its risk factors.
Biological Psychiatry **1998**, 44, 568–577.
 - 31 RYAN, N. D., DAHL, R. E., BIRMAHER, B.,
et al., Stimulatory tests of growth
hormone secretion in prepubertal major
depression: Depressed versus normal
children. *Journal of the American Academy*

- of Child and Adolescent Psychiatry 1994, 33, 824–833.
- 32 DAHL, R. E., RYAN, N. D., WILLIAMSON, D. E., et al., The regulation of sleep and growth hormone in adolescent depression. *Journal of the American Academy of Child and Adolescent Psychiatry* 1992, 31, 615–621.
 - 33 BIRMAHER, B., DAHL, R. E., RYAN, N. D., et al., Dexamethasone suppression test in adolescents with major depressive disorder. *American Journal of Psychiatry* 1992, 149, 1040–1045.
 - 34 BIRMAHER, B., RYAN, N., DAHL, R., et al., Corticotropin releasing hormone challenge test in prepubertal major depression. *Biological Psychiatry* 1996, 39, 267–277.
 - 35 KUTCHER, S., MALKIN, D., SILVERBERG, J., et al., Nocturnal cortisol, thyroid stimulating hormone, and growth hormone secretory profiles in depressed adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* 1991, 30, 407–414.
 - 36 BRENER, N. D., KRUG, E. G., SIMON, T., Trends in suicide ideation and suicide behavior among high school students in the United States, 1991–1997. *Suicide and Life-Threatening Behavior* 2000, 30, 304–312.
 - 37 PFEFFER, C. R., JIANG, H., KAKUMA, T., Child-Adolescent Suicidal Potential Index (CASPI), A screen for risk for early onset suicidal behavior. *Psychological Assessment* 2000, 12, 304–318.
 - 38 SPIRITO, A., BOEGERS, J., DONALDSON, D., BISHOP, D., LEWANDER, W., An intervention trial to improve adherence to community treatment by adolescents after a suicide attempt. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002, 41, 435–442.
 - 39 MUFSON, L., MOREAU, D., WEISSMAN, M. M., WICKRAMARATNE, P., MARTIN, J., SAMOILOV, A., Modification of interpersonal psychotherapy with depressed adolescents (IPT-A), Phase I and II studies. *Journal of the American Academy of Child and Adolescent Psychiatry* 1994, 33, 695–705.
 - 40 MUFSON, L., FAIRBANKS, J., Interpersonal psychotherapy for depressed adolescents: A one-year naturalistic follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry* 1996, 35, 1145–1155.
 - 41 SANTOR, D. A., KUSUMAKAR, V., Open trial of interpersonal therapy in adolescents with moderate to severe major depression: Effectiveness of novice IPT therapists. *Journal of the American Academy of Child and Adolescent Psychiatry* 2001, 40, 236–240.
 - 42 RATHUS, J. H., MILLER, A. L., Dialectical behavior therapy adapted for suicidal adolescents. *Suicide and Life-Threatening Behavior* 2002, 32, 146–157.
 - 43 CLARKE, G. N., HAWKINS, W., MURPHY, M., SHEEBER, I. B., LEWINSOHN, P. M., SEELEY, J. R., Targeted prevention of unipolar depressive disorder in an at-risk sample of high school adolescents: A randomized trial of group cognitive intervention. *Journal of the American Academy of Child and Adolescent Psychiatry* 1995, 34, 312–321.
 - 44 LEWINSOHN, P. M., CLARKE, G. N., HOPS, H., ANDREWS, J., Cognitive-behavioral group treatment of depression in adolescents. *Behavioral Therapy* 1990, 21, 385–401.
 - 45 BRENT, D. A., Practitioner review: The aftercare of adolescents with deliberate self-harm. *Journal of Child Psychology and Psychiatry* 1997, 38, 277–286.
 - 46 ROTHERAM-BORUS, M. J., PIACENTINI, J., MILLER, S., GRAAE, F., CASTRO-BLANCO, D., Brief cognitive-behavioral treatment of adolescent suicidal attempters and their families. *Journal of the American Academy of Child and Adolescent Psychiatry* 1994, 33, 508–517.
 - 47 BRENT, D. A., KOLKO, D. J., BIRMAHER, B., BAUGHER, M., BRIDGE, J., A clinical trial for adolescent depression: Predictors of additional treatment in the acute and follow-up phases of the trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 1999, 38, 263–270.
 - 48 EMSLIE, G., RUSH, J. A., WEINBERG, W. A., et al., A double-blind randomized placebo-controlled trial of fluoxetine in depressed children and adolescents. *Archives of General Psychiatry* 1997, 54, 1031–1037.
 - 49 ZAMETKIN, A. J., ALTER, M. R., YEMINI, T., Suicide in teenagers: Assessment, management, and prevention. *Journal of the American Medical Association* 2001, 286, 3120–3125.

11

The Biology and Genetics of Suicidality

Gustavo Turecki and Aleksandra Lalovic

Abstract

The tragic outcome of a depressive patient is far too often suicide. There are numerous factors that make some people more likely to commit suicide, yet these factors remain poorly understood. Important insights have emerged from research studies focused on the biology of suicidal behavior. Studies have consistently provided evidence that genes and other biological factors play central roles in an individual's risk of suicide. The serotonergic system has been the most extensively investigated system in the biological background for suicide. Evidence from cerebrospinal fluid, postmortem binding, and neuroendocrine challenge studies implicates a reduced function of the serotonergic system in suicidal behavior. Recently, studies have demonstrated an association between low levels of serum cholesterol and suicidality. A common underlying feature of the relationship among low cholesterol, serotonergic system abnormalities, and suicidal behavior may be due to a disorder of the inhibition of aggressive impulses. Genetic factors are likely to be involved in mediating the neurotransmitter systems and endogenous substances related to suicidal behavior. A large body of evidence from family, twin, and adoption studies has been collected and it supports a strong genetic component to suicidal behavior. Furthermore, the familial transmission of suicidal risk appears to be distinct from the genetic predisposition to psychiatric disorders. Additional evidence supporting this hypothesis comes from molecular studies involving candidate genes. As the search for specific genetic markers of suicide risk continues, it will certainly advance our understanding of the complex interactions of biological factors underlying suicidal behavior.

11.1

Introduction

Suicide is the primary cause for the increased mortality among depressed patients [1], but it is not a phenomenon confined to these individuals. The World Health

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Organization (WHO) estimates that approximately one million deaths occurred due to suicide around the globe in 2000, or one suicide every 40 s [2]. This disheartening statistic does not include suicide attempts, which occur at an estimated frequency of up to 25 times that of completed suicide [3]. The astounding financial and societal costs of suicide extend beyond the suicidal individual and make suicidal behavior one of the most important public health problems around the world [2]. In most instances, suicide is a complication of a psychiatric illness, commonly a depressive disorder [4]. Although suicide is an important concomitant of depressive illness, most depressed people never die of suicide. What makes some depressed people commit suicide while others with the same condition do not is a question that has puzzled researchers. Data accumulated over recent decades suggest that people who commit suicide do so because they have a biological predisposition.

In this chapter we review the most important factors associated with the predisposition to suicide. We focus on neurobiological and genetic factors and discuss the role of the serotonergic system, which has been extensively investigated in this condition. The role of other endogenous substances, such as cholesterol, will also be considered. Finally, we review data that support the role of genetic factors in the predisposition to suicide; we also discuss the most important molecular genetics findings.

11.2

Insights from Clinical Practice

11.2.1

What is suicidality?

The term ‘suicidality’ covers a wide spectrum of self-harming behaviors, including completed suicide, suicide attempts, and suicidal ideation [5]. A commonly cited definition for completed suicide is “death from injury, poisoning or suffocation where there is evidence (either explicit or implicit) that the injury was self-inflicted and that the decedent intended to kill himself/herself” [6]. The definition for suicide attempt, however, is not as straightforward as that for completed suicide, as it is an umbrella term that encompasses a range of diverse behaviors. One definition of a suicide attempt is “a potentially self-injurious behavior with a non-fatal outcome for which there is some evidence that the person intended to kill himself/herself” [7]. It is clear that a number of distinct behaviors can be classified as attempts according to this definition, and thus there is a need to further categorize attempts into various subtypes to more definitively characterize this form of suicidal behavior.

Attempted suicide can be considered to have two dimensions: lethality and intent [8]. The lethality aspect involves the extent of medical damage resulting from the suicidal act and can range from the level of damage in individuals who barely survive an attempt to that in individuals who suffer little or no injury. The intent behind the suicidal act can be determined by assessing the extent of preparation, the desire

to live or die, and the likelihood of being discovered [8]. Suicide attempts can also be classified as violent or nonviolent, typically based on the method used, although the validity of applying this criteria in characterizing the seriousness of an attempt remains uncertain [9]. Drug overdose and superficial wrist-cutting are generally classified as nonviolent, but all other methods, such as hanging or drowning, are considered violent.

Suicidal ideation represents a more diffuse and mild aspect of suicidality, which includes thinking about suicide. This can be of varying degrees of intensity and severity. Suicidal ideation is considerably more difficult to characterize precisely. In addition, the relationship between suicidal ideation and neurobiological factors associated with suicide completion remains unclear. Therefore, suicidal ideation has not been examined as extensively in biological studies as other suicidal behaviors.

11.2.2

Attempters and Completers

Attempted suicide is regarded as one of the most important risk factors for suicide completion; however, attempted suicide occurs far more frequently than completed suicide, and most suicide completers die at their first attempt [10]. Furthermore, in the United States more than four times as many men than women die of suicide [11], although women attempt suicide two to three times more frequently than men [12]. These differences suggest that attempted and completed suicides may represent distinct, although overlapping, behaviors that may be associated with different risk factors and hence may have different neurobiological bases.

Most of the neurobiological and molecular studies on suicidal behavior have focused on attempted and completed suicides as discrete groups. Suicide completers are believed to represent the most homogenous form of suicidal behavior. Suicide attempters are a more accessible group, and they have been studied extensively. They are often grouped according to the intensity of behavioral dimensions, such as the level of intent behind the attempt, the degree of impulsiveness, and level of aggression or violence associated with the attempt.

11.2.3

Clinical Aspects

Psychological autopsy is the accepted method of retrieving clinical information from suicide completers. The method involves gathering retrospective information on the deceased through structured proxy-based interviews, which are coupled with available health-care records and forensic examination, with the aim of gaining an understanding of the life situation, personality, and mental health of the individual prior to the suicide [13]. Psychological autopsy studies have consistently shown that the vast majority of suicide completers suffered from a psychiatric disorder – with overall estimates suggesting that 90% of suicides met criteria for a psychiatric disorder before their death [4, 14, 15].

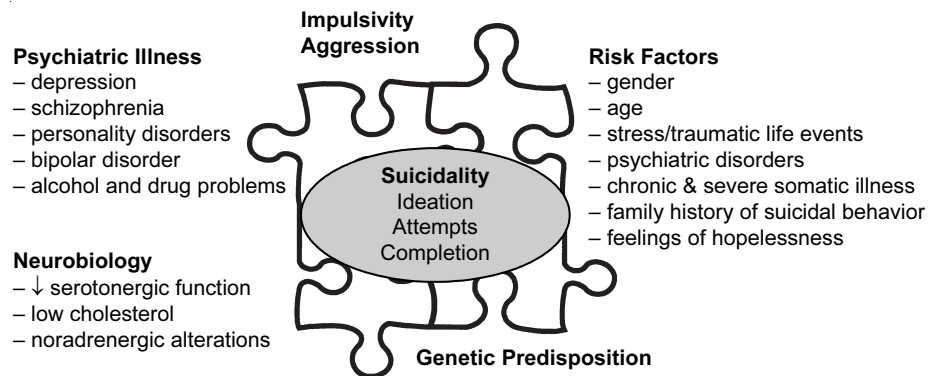


Figure 11.1 Schematic illustration summarizing the major interacting factors believed to be associated with suicidality

Affective disorders are the most commonly reported among suicides, accounting for about half of all instances, although estimates vary from 30% to 90% [16]. It has been suggested that every sixth death among psychiatric patients diagnosed with an affective disorder is the result of suicide. This represents a lifetime risk for suicide of 15% [17], although more recent estimates suggest a revised lifetime risk of 7% for all affective disorders [18]. However, most patients with affective disorders do not commit suicide, suggesting that there must be a particular vulnerability or predisposition to suicide that goes beyond the psychiatric illness. It is apparent that complex interactions of numerous variables influence suicide risk. Some of the major factors thought to be associated with suicidal behavior are summarized in Figure 11.1, and a number of these are described in greater detail below.

11.2.4

Behavioral Correlates

A number of behavioral dimensions have been shown to be associated with suicidal behavior, and these may also be of biological relevance in terms of establishing a possible common mechanism. Impulsive behavior and high levels of aggression have been frequently associated with suicidal behavior [19–21]. Brent et al. [22] found significantly higher measures of lifetime aggression and a tendency to increased impulsive violence in a group of adolescent suicide completers compared with non-suicidal controls and also noted the higher prevalence of personality disorders, particularly Cluster B (impulsive–dramatic) type. Mann et al. [23] showed that psychiatric patients with a history of attempted suicide had significantly higher lifetime aggression and impulsivity scores than did non-attempters, irrespective of psychiatric diagnosis.

Disturbances in impulse and aggression control are thought to play an important role in suicidal behavior and may be related to disturbances at the biological level.

It has been hypothesized that impulsivity, aggression, and suicidal behavior all may be related to dysregulation of the serotonergic system. This may be an underlying biological factor unifying these behavioral dimensions [24].

11.3

The Serotonergic System

The neurotransmitter serotonin (5-HT) has long been investigated for its role in major depression and suicidal behavior. Serotonergic abnormalities have been extensively investigated in relation to suicidal behavior. Although suicide often occurs in the context of a depressive illness, the abnormalities in serotonergic function found to be related to major depression appear to be distinct from those related to suicidal behavior. Alterations in serotonergic function related to suicidal behavior have been uncovered using techniques aimed at assessing various markers of serotonin in living humans and in postmortem brain tissue. The predominant evidence implicating serotonin dysfunction in suicidal behavior and the different types of investigational approaches used in each study are summarized in Table 11.1. The findings from these studies point to a net reduction in serotonergic neurotransmission as the neurobiological alteration associated with suicidality.

Table 11.1 Summary of the main lines of evidence implicating reduced serotonergic function in suicidal behavior

<i>Study Approach and Evidence</i>	<i>Selected References</i>
Cerebrospinal fluid studies	
• ↓ CSF concentration of 5-HIAA (demonstrated in suicide attempters among psychiatric patients and impulsive violent offenders)	19, 26, 28, 29, 33, 34, 36, 151
Neuroendocrine challenge tests	
• ↓ prolactin response to fenfluramine (demonstrated in suicide attempters)	39–44
Platelet studies (radiolabeled ligand binding)	
• ↑ 5-HT _{2A} receptors (in currently suicidal patients)	47–50
• Mixed findings with 5-HT: some show ↓ 5-HTT binding, others do not	51–54
Postmortem binding studies	
• Mixed findings in different brain regions of suicide completers, but overall: ↓ 5-HTT, ↑ 5-HT _{1A} and ↑ 5-HT _{2A} binding	58–61, 152–154 <i>opposite/no difs:</i> 62–67

Abbreviations:

CSF = cerebrospinal fluid; 5-HIAA = 5-hydroxyindoleacetic acid; 5-HTT = serotonin transporter

11.3.1

Cerebrospinal Fluid Studies

The most commonly used marker of serotonin in the living human brain is the cerebrospinal fluid (CSF) concentration of 5-hydroxyindoleacetic acid (5-HIAA), a major serotonin metabolite. Low CSF levels of 5-HIAA are thought to reflect decreased serotonin turnover in the brain. Studies show a strong correlation between brain and CSF levels of serotonin metabolites, which confirms that 5-HIAA is a valid marker of serotonin [25].

One of the first observations of an association between CSF 5-HIAA levels and suicidal behavior emerged unexpectedly from a study by Asberg et al. [26], while they were investigating the role of serotonin in major depression. The CSF 5-HIAA concentration appeared to be bimodally distributed in their depressed patients, suggesting the presence of some clinical or biochemical differences between the patients. Upon closer examination, they found that the depressed patients who fell into the low CSF 5-HIAA subgroup had a significantly higher incidence of suicide attempts than the high 5-HIAA subgroup (40% of the low 5-HIAA subgroup patients compared with 15% of the high 5-HIAA subgroup). Furthermore, high levels of intent and the use of more violent methods characterized suicide attempts in the low 5-HIAA subgroup, while the use nonviolent means such as drug overdose tended to occur in the high 5-HIAA subgroup. Another notable observation was that 2 of the 20 patients in the low 5-HIAA subgroup committed suicide during the study period, while there were no completed suicides among the 48 patients in the high 5-HIAA subgroup.

The major finding from this study supports an association between low CSF levels of 5-HIAA and suicidal behavior, which has since been replicated in more than 20 studies [27]. These studies have not been confined to subjects suffering from depression, but have been performed in patients in different diagnostic categories, such as schizophrenia [28], alcoholism [29], and personality disorders [30], indicating that the association is independent of psychiatric diagnosis. The relationship between low CSF 5-HIAA and suicidal behavior has been demonstrated in most studies, with few exceptions [31, 32], and thus constitutes one of the most consistently replicated biological findings in psychiatric research to date.

A follow-up study by Traskman et al. [33] found that the one-year mortality rate from suicide was 20% in psychiatric inpatients who had low CSF levels of 5-HIAA and who had made a previous suicide attempt. Roy et al. [34] similarly found that patients who were repeat attempters had lower CSF 5-HIAA levels than those who had made only a single attempt. These findings imply that low CSF 5-HIAA is an important risk factor in patients with a suicide attempt history. Furthermore, CSF 5-HIAA is likely to be a relatively stable trait over time [27] and may be under partial genetic control [35].

CSF levels of 5-HIAA have also been studied in relation to impulsive and aggressive behaviors, with similar findings irrespective of psychiatric diagnosis. Brown et al. [30] assessed aggression levels in individuals with personality disorders and found a significant inverse correlation between a history of aggressive behavior

and low CSF 5-HIAA levels. In a subsequent study, Brown et al. [19] showed that aggressive behavior was significantly associated with suicide attempts and that both aggression and suicide attempts were associated with low CSF 5-HIAA in subjects with borderline personality disorder.

Linnoila et al. [36] investigated the relationship between impulsivity and CSF 5-HIAA levels in a group of violent offenders. The impulsive violent offenders (i.e., those who killed or attempted to kill without provocation or premeditation) had significantly lower CSF 5-HIAA levels than the non-impulsive violent offenders, implying that low CSF 5-HIAA is a marker of an impulsive trait. Moreover, the impulsive offenders with suicide attempts had significantly lower CSF 5-HIAA levels than those found in the violent offenders without suicide attempts. This finding tied together the relationship among impulsivity, suicidal behavior, and low CSF 5-HIAA.

11.3.2

Neuroendocrine Challenge Tests

Neuroendocrine factors such as prolactin, growth hormone, adrenocorticotrophic hormone (ACTH), and cortisol have been widely used as markers of serotonergic activity. 5-HT receptor agonists are typically used as probes for these markers in challenge tests. Fenfluramine, the most commonly used serotonin challenge agent, causes the release of serotonin from presynaptic storage granules and inhibits its reuptake; it may also stimulate postsynaptic serotonin receptors [37]. The serotonergic activation leads to a dose-dependent increase in prolactin [38]. Decreased prolactin responses are believed to reflect reduced serotonergic activity. Blunted prolactin responses to fenfluramine challenges have been observed in patients with major depression and a history of suicidal behavior [39].

Correa et al. [40] found significantly lower prolactin responses to fenfluramine challenge in psychiatric patients with a history of suicide attempts than in healthy controls or patients without attempted suicides. They proposed that the blunted serotonergic response may represent a marker specific for suicidality, rather than for depression. Furthermore, reduced prolactin responses to fenfluramine challenge have also been seen in psychiatric patients with diagnoses other than depression, such as personality disorders [41, 42]. An inverse relationship between prolactin response to fenfluramine and impulsive aggression has been shown in patients with personality disorders [43].

Malone et al. [44] found a significantly lower prolactin response to fenfluramine in patients with a history of high-lethality suicide attempts. This suggests that high-lethality suicide attempters are more closely related to completed suicides, not only behaviorally but also at a biochemical level.

Other challenge agents such as *meta*-chlorophenylpiperazine (*m*-CPP), flesinoxan, and buspirone have also been used; however, not enough studies have been conducted with these to reach strong conclusions.

11.3.3

Platelet Studies

Serotonin receptor and transporter binding studies in platelets offer another means by which to examine serotonergic function in living subjects with a history of suicidal behavior. Human blood platelets serve as an appropriate peripheral model for study of central serotonergic mechanisms, since they share basic characteristics with serotonergic neurons, such as the presence of 5-HT_{2A} receptors and 5-HT transporter (5-HTT) recognition sites [45, 46]. 5-HT_{2A} receptors have been investigated by using radiolabeled ligand binding, typically with [¹²⁵I]lysergic acid diethylamide (LSD) or [³H]ketanserin as the ligand. The overall finding from these studies is a significant increase in platelet 5-HT_{2A} receptors in suicidal patients compared with nonsuicidal patients and normal controls. These conclusions are independent of psychiatric diagnosis [47–49]. Additionally, platelet 5-HT_{2A} receptor binding has been shown to be higher in patients with a current history of attempted suicide than in patients with a past history of attempted suicide (6 months or more), with no significant difference between the past-history patients and controls, suggesting that the 5-HT_{2A} receptor up-regulation may be a state-related phenomenon [50]. Although the significance and mechanisms behind the observed up-regulation are unclear, increased platelet 5-HT_{2A} receptors may be a useful biological marker of suicide risk.

Studies of platelet 5-HTT binding using [³H]imipramine or [³H]paroxetine have been far less conclusive. Some studies show decreased binding in psychiatric patients who had attempted suicide than in healthy controls [51, 52], and other studies show no differences [53, 54]. In any event, the relevance of platelets and their ability to reflect CNS processes remains to be determined. With recent technological advances and the emerging ability to study brain processes *in vivo* by means of imaging techniques, platelet studies have been used less frequently.

11.3.4

Postmortem Binding Studies

Several studies on postmortem brain tissue of suicide completers have examined the binding of 5-HT receptors (mainly 5-HT_{1A} and 5-HT_{2A}) and the 5-HT transporter in different brain regions using various ligands and have reported widely varying results [55–57]. The findings from these studies are summarized in Figure 11.2 and, overall, seem to point to a decrease in 5-HT transporter binding, along with an increase in 5-HT_{1A} receptor binding in brain tissue of suicide completers (both phenomena seem to be more pronounced in the ventral prefrontal cortex (PFC) [58]), and an increase in 5-HT_{2A} receptor density in certain regions of the PFC [59–61]. However, these findings are not considered conclusive, as some studies have found opposite changes or no differences at all, depending on the brain region examined [62–67]. An explanation for the apparent increase in the postsynaptic receptors could be up-regulation as a compensatory response to decreased serotonergic neuron activity [56].

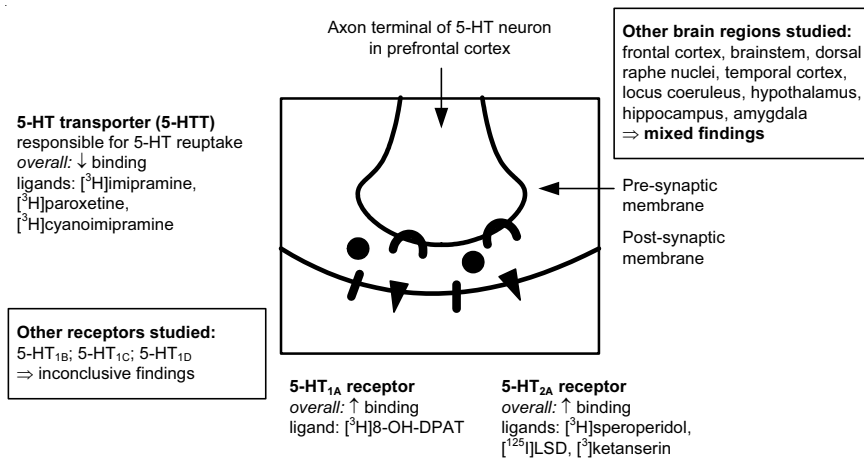


Figure 11.2 Representation of a serotonergic neuron at a synapse in the prefrontal cortex with a summary of the main findings from post-mortem binding studies of suicide completers

Taken together, the findings of a decrease in presynaptic 5-HT transporter binding and the up-regulation of postsynaptic 5-HT receptors, which are more prominent in the ventral PFC, imply reduced serotonergic input to the ventral PFC. This brain region is believed to be involved in behavioral inhibition and expression of emotion [68]. Reduced serotonergic input to this brain region might result in impaired inhibition of behaviors such as impulsive aggression and suicide [69].

11.4 Cholesterol

The interest in cholesterol as a possible biological correlate of suicide and related behaviors dates to 1979, when Virkkunen demonstrated that male subjects with antisocial personality disorder, who are a high-risk group prone to violence and suicide, had lower levels of serum cholesterol than a control group of male patients with other personality disorders [70]. It was only after concerns were raised over the safety of cholesterol-lowering medications that particular attention was paid to the seeming relationship between cholesterol and violent behavior. In particular, two large randomized double-blind lipid-lowering trials [71, 72] revealed that, although decreasing serum cholesterol with lipid-lowering medications was effective in reducing mortality from coronary heart disease, the overall mortality rate was not significantly different. The reduction in cardiac-related deaths appeared to be offset by an increase in violence-related deaths including suicide, accidents, and homicide. To examine the issue more globally, Muldoon et al. [73] combined the results of primary prevention trials using meta-analytic techniques and concluded that there was a significant increase in non-illness-related mortality (i.e. deaths

from accidents, suicide, or violence) in groups receiving treatment to lower cholesterol concentrations compared with controls.

They suggested that low cholesterol after dietary or drug intervention might be related to an increased propensity for impulsive and aggressive behaviors, resulting in the violent deaths and suicides seen in these studies [74]. Much concern and some controversy arose following these reports, resulting in a surge of studies investigating this issue over the last decade.

Substantial evidence has accumulated from large epidemiological cohort studies that demonstrates a correlation between low, or lowered, serum cholesterol and violence or suicide [75–80]. Mortality and cholesterol data from over 350,000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT) and followed up for an average of 12 years revealed that the risk of death by suicide was significantly greater in the men with serum cholesterol levels $< 4.14 \text{ mmol L}^{-1}$ than in those in each of the upper three cholesterol level strata [76]. A Canadian retrospective cohort study by Ellison and Morrison [80] found that individuals in the lowest quartile of serum cholesterol concentration ($< 4.27 \text{ mmol L}^{-1}$) had a six times greater risk of committing suicide than subjects in the highest quartile ($> 5.77 \text{ mmol L}^{-1}$).

Several cohort studies have examined psychological data in addition to mortality data with respect to cholesterol levels. In a study of 29,133 men followed up for 5–8 years, Partonen et al. [78] found that low serum cholesterol was associated with depressed mood (based on self-reports of depression) and a subsequent increased risk of hospitalization due to major depression and death from suicide. Freedman et al. [81] examined psychological characteristics of 3490 men and found that those who were diagnosed with antisocial personality disorder had significantly lower cholesterol levels than the rest of the men.

The association between low cholesterol and high relative risk of suicide has not been replicated in every cohort study [82], thereby adding to the controversy. One possible reason for the inconsistency is that suicide is relatively rare in the general population and may represent an event whose rate is too small to be detected in these studies. One approach that many investigators have taken to circumvent this limitation is to examine cholesterol levels in populations at risk of suicide, namely suicide attempters [83–88], psychiatric populations [89–94], and violent offenders [95–98].

Kunugi et al. [84] found that the mean cholesterol level of patients admitted to an emergency ward following a suicide attempt was significantly lower than in both nonsuicidal psychiatric patients and normal controls. Garland et al. [87] reported similar findings and additionally demonstrated that higher impulsivity scores were associated with low cholesterol. Among suicide attempters, Alvarez et al. [86] found that the mean cholesterol level of violent attempters was significantly lower than that of the suicide attempters who used less violent means.

Among psychiatric patients, Golier et al. [91] found that male patients with low cholesterol were twice as likely to have made a serious suicide attempt than male patients with cholesterol levels in the highest quartile. In a large sample of psychiatric inpatients, Modai et al. [89] showed that the mean cholesterol level of those who had attempted suicide at least once was significantly lower than that of the nonsuicidal psychiatric inpatients.

Virkkunen [95] examined a sample of male homicidal offenders and found that those with antisocial personality disorder and a habitual violent tendency when under the influence of alcohol had a lower mean serum cholesterol level than did the other offenders in the sample.

11.4.1

A Causal Relationship?

The majority of studies have demonstrated an association between low cholesterol level and violent, impulsive–aggressive, or suicidal behavior, providing consistent evidence in support of this relationship [99, 100] (Table 11.2). In a thorough review, Golomb [101] systematically evaluated the relevant medical literature and concluded that there is a significant association between low or lowered cholesterol level and violence (including suicide). Evidence was also presented demonstrating that this relationship may be causal. This conclusion is supported by several studies in humans [102, 103] and nonhuman primates [104, 105] showing a relationship between low or lowered cholesterol levels and low measures of serotonergic activity. Low serotonergic activity has been linked to impulsive–aggressive and suicidal behaviors.

Kaplan et al. [105] showed that juvenile cynomolgus monkeys fed low-cholesterol diets displayed lower serotonergic activity (as determined by lower CSF 5-HIAA measures), lower cholesterol levels, less affiliated interaction, and higher levels of aggression than monkeys fed high-cholesterol diets. These results suggest an association among low cholesterol, low serotonergic activity, and impulsive–aggressive behaviors, but they do not reveal the biological mechanisms behind this apparent association.

Table 11.2 Summary of the main lines of evidence supporting a relationship between low levels of serum cholesterol and suicidal behavior

<i>Study Approach and Evidence</i>	<i>Selected References</i>
Intervention trials	
• early trials using statins: ↑ violence-related deaths	71–73
Epidemiological cohort studies	
• ↑ risk of death from suicide in low-cholesterol group	75–78, 80
Observational/case-control studies	
Lower cholesterol levels in:	
• suicide attempters vs. nonsuicidal controls	83, 84, 87, 88
• psychiatric populations with suicide attempt/ideation vs. nonsuicidal psychiatric patients and controls	89–92, 155
• violent populations vs. controls	79, 95, 97, 98
• violent suicide attempters vs. nonviolent attempters	85, 86, 156
Experimental studies in animals	
• ↓ 5-HT response, ↓ CSF concentration of 5-HIAA, and ↑ aggression in monkeys fed low-cholesterol diet vs. high-cholesterol diet	104, 105, 157

11.4.2

Hypothetical Mechanisms

Several hypotheses have been presented in an effort to explain the mechanism underlying this putative association. One of the most widely quoted hypotheses is that of Engelberg [106], who proposed that low serum cholesterol may reduce the amount of cholesterol in brain cell membranes (through free exchange with peripheral cholesterol), thereby lowering the lipid microviscosity. This in turn would decrease the exposure of the serotonin receptors on the membrane surface, resulting in decreased serotonin binding. The result would be a reduced uptake of serotonin from the blood and less serotonin entry into brain cells, and consequently an impairment of inhibition of harmful behavioral impulses. As support, Engelberg cited an *in vitro* study [107] that demonstrated a significant decrease in serotonin binding resulting from a reduction in the lipid microviscosity of synaptic membranes in the mouse brain. However, this hypothesis has received much criticism and lacks experimental testing.

An *in vivo* study by Terao et al. [108] that investigated the effects of cholesterol on serotonergic receptor function lends support to the relationship among serotonin, cholesterol, and suicidal behavior. Terao et al. performed neuroendocrine challenge tests as a probe for serotonergic receptor function in healthy subjects by examining their cortisol responses to *m*-CPP, which has a particular agonist effect on 5-HT_{2C} receptors. They found that cortisol responses to *m*-CPP were positively associated with serum cholesterol level, suggesting that low cholesterol may be associated with low serotonergic receptor function.

A second hypothesis put forth to explain the relationship between suicide and low cholesterol also implicates a role for serotonin. In this hypothesis, Salter [109] proposed that low serum cholesterol levels may be associated with a decrease in serum fatty acids. Fatty acids and tryptophan compete for a binding site on albumin. A decreased serum concentration of fatty acids would result in a larger amount of albumin-bound tryptophan, which is not readily transported into the brain, thus decreasing the amount of free tryptophan available in the brain for synthesis of serotonin. This lack of serotonin synthesis would result in impaired serotonergic activity and suicidal behavior.

Penttinen [110] suggested a different hypothesis that ties in the possible relationship that has been observed between interleukin-2 (IL-2) and suicide in depressed people [111]. Penttinen proposed that increased production of IL-2 leads to a decrease in serum cholesterol [112] and, subsequently, a suppression of melatonin secretion [113]. Decreased melatonin secretion may play a causal role in depression and suicidal behavior. This hypothesis incorporates concepts that have not been validated and also fails to account for the important relationship between low cholesterol, impulsive-aggression, and suicide independent of depression.

A relationship between low cholesterol level and suicidal behavior mediated by reduced serotonergic function is biologically plausible and fits well with what is currently known about cholesterol, serotonin, and suicidal behavior. There is still

certainly a considerable amount of knowledge that remains to be gained in this field to fully understand the biological mechanisms.

11.5

Genetic Factors

A large body of evidence has accumulated indicating that a strong genetic component exists for suicidal behavior. These genetic factors are likely involved in mediating the neurotransmitter systems and endogenous substances related to suicidal behavior. The evidence supporting this continues to expand as the search for specific genetic markers of suicide risk advances.

11.5.1

Family Studies

It has been observed that suicidal behavior tends to run in families. Beyond notable observations of this tendency, evidence has been collected from family studies and population studies of suicide that have consistently shown that suicide tends to aggregate in families [114]. These studies revealed that biological relatives of adolescent and adult suicide completers have higher rates of suicidal behavior than do relatives of nonsuicidal controls [115–117]. Studies that have examined the family history of adolescents and adults who have attempted suicide have also found higher rates of suicidal behaviors among the relatives of suicide attempters [118–122].

In a study of psychiatric patients with a family history of suicide, Roy [123] found that 48.6% of the patients attempted suicide, compared to 21.8% of control patients without a family history of suicide. This was a highly significant difference, which persisted across different psychiatric diagnoses. Similarly and more specifically, Linkowski et al. [124] found that a family history of violent suicide is associated with violent suicidal behavior in patients with major depression. A positive family history was found in 32% of violent suicide attempters, compared with 16% of nonviolent suicide attempters. Thus, the presence of a family history of suicidal behavior is an important risk factor that should be used in a clinical setting to identify patients who may be at greater risk. However, psychiatric disorders are frequent in the majority of suicide attempters and completers; clustering of psychiatric disorders among their relatives is also observed [125]. One could argue that what is being genetically transmitted within families is the predisposition to the psychiatric illness, which in turn is responsible for the observed familial aggregation of suicidal behaviors. A few studies have been conducted to address this issue.

One of the first studies that was able to disentangle familial transmission of psychiatric disorder from familial aggregation of suicide was a study carried out by Egeland and Sussex [126] on the Old Order Amish, a conservative religious community in southeastern Pennsylvania, USA. Although suicide is rare in the Amish, they have kept extensive genealogical and medical records, enabling the identification of all suicides that occurred during a 100-year period (1880 to 1980).

In all, there were 26 suicides. These suicides were clustered in only four families that also had heavy loading for affective disorders; however, no suicides occurred in several other families that also showed a heavy loading for affective disorders. This striking finding is strongly suggestive of a discrete genetic influence that mediates the inclination to suicide, with an underlying affective disorder being an important but insufficient contributing factor.

In another key study, Brent et al. [116] investigated familial rates of suicide and measures of aggression in adolescent probands who had committed suicide and compared these measures with those of a sample of demographically similar controls who had never exhibited suicidal behaviors. A higher rate of suicide attempts was found in the first-degree relatives of suicide probands than in the relatives of controls. This finding persisted even after controlling for increased rates of Axis I and II disorders in probands and families, supporting the notion that a genetic liability to suicide may be transmitted by a mechanism separate from the familial transmission of psychiatric (Axis I and II) disorders. Of further interest is the finding that a higher familial loading of suicide attempts among suicide probands was associated with higher scores on aggression measures in the probands, even after controlling for family loading of aggression. This implies that the genetic transmissions of suicidal behavior and of aggressive traits are related.

11.5.2

Twin Studies

Most of the twin studies suggest that genes account for at least part of the familial aggregation of suicidal behavior, consistently indicating that concordance rates for monozygotic (MZ) twins are higher than for dizygotic (DZ) twins [127–131].

Roy et al. [127] looked at concordance rates in a sample of 176 twin pairs in which at least one twin from each pair had committed suicide and found that 7 of the 62 MZ twin pairs (11.3%) were concordant for suicide, while concordance was observed for only 2 of the 114 DZ twin pairs (1.8%). In a separate study, Roy et al. [128] examined the frequency of attempted suicide in a sample of living twins whose co-twins had committed suicide and found that 38% of MZ co-twins had a history of attempted suicide, while none of the DZ twins did. Thus, higher concordance rates are again observed in MZ twins, particularly when a broader spectrum of suicidal behavior is considered.

A large epidemiological and genetic study conducted in an Australian community-based sample of MZ and DZ twin pairs examined suicidal behavior and considered a number of important risk factors, including psychiatric history, personality traits, traumatic life experiences, and certain sociodemographic variables [129]. It was found that even after adjustment for these risk factors, a history of suicidal behavior in one MZ twin remained a powerful predictor of suicidal behavior in the other MZ co-twin, while failing to be consistently predictive in DZ twin pairs. Furthermore, heritability of serious suicidal behavior was estimated at 55%.

Further support for the role of genetic factors in the etiology of suicidal behavior comes from other recent studies in large epidemiological twin samples. Fu et al.

[132] conducted a study on male twins. They found that a suicide attempt in one MZ twin was predictive of suicide attempt or ideation in the co-twin, even after controlling for other risk factors, including psychiatric history. They concluded that the genetic liability to suicidal behavior is likely independent of the genetic predisposition to psychiatric illness. Glowinski et al. [131] reported similar findings in an adolescent female twin sample.

11.5.3

Adoption Studies

Another line of evidence that complements the data from twin studies and supports the role of genes in the etiology of suicidal behavior comes from adoption studies. The first adoption study on suicide was carried out by Schulsinger et al. [133] using the Danish case registry of adoptions: 57 records were found of adoptees who had committed suicide. These were matched to a control sample of 57 adoptees. Examination of the biological relatives of these adoptees revealed significantly more suicides among the biological relatives of the suicide adoptees than among the biological relatives of the control adoptees. There were 12 suicides among the 269 biological relatives of the suicide adoptees and only 2 suicides among the 269 biological relatives of the control adoptees. No instances of suicide were found among the adoptive relatives of either the suicide or control adoptees. These findings provide strong evidence that the tendency to suicide is influenced by genetic factors.

In another adoption study, Wender et al. [134] selected 71 index adoptees with affective disorders and 71 control adoptees from the same Danish adoption registry and examined the frequency of psychiatric disorders among the biological and adoptive relatives. They found that the frequency of suicide among the biological relatives of the index adoptees was 15 times that of the biological relatives of the control adoptees, with no differential risk between the adoptive relatives of index and control adoptees. Moreover, they noted an especially high frequency of suicide among the biological relatives of a subset of index adoptees who were characterized as 'affect reaction' type (i.e., more prone to make an impulsive suicide attempt in response to an emotional setback). In addition to providing further robust evidence for a genetic predisposition to suicide that is transmitted independently of the genetic liability to psychopathology, this study goes one step further, to suggest that the genetic element in suicide may be related to impulse control.

Taken together, family, twin, and adoption studies provide consistent evidence that there is an underlying genetic predisposition to suicidal behavior that is distinct from, although perhaps contingent upon, the genetic liability to psychiatric illness. Suicidal behavior, as a complex trait, is likely to be the result of numerous environmental factors and multiple genes.

Table 11.3 Summary of selected studies investigating variation at 5-HT receptors in suicide attempters and completers

Study	Receptor	Polymorphism	Subjects (S) and Controls (C)	Origin	Main Findings
Nishiguchi et al., 2002 [158]	1A	Pro16Leu, Gly272Asp	S: suicide completers (N = 163) C: healthy volunteers (N = 163)	Japanese	No association with either polymorphism examined
Huang et al., 1999 [139]	1B	G861C	S: suicide completers (N = 71) C: nonsuicides died by natural causes or accidents (N = 107)	USA (mixed races)	No association found
Nishiguchi et al., 2001 [159]	1B	G861C	S: suicide completers (N = 163) C: healthy volunteers (N = 163)	Japanese	No association found
Turecki et al., 2003 [160]	1B	G861C	S: suicide completers (N = 106) C: healthy volunteers (N = 120)	French-Canadian	No association found
Rujescu et al., 2003 [161]	1B	G861C	S: suicide attempters (N = 148) C: healthy volunteers (N = 327)	German	No association found
Huang et al., 2003 [162]	1B	G861C	S: psychiatric patients w/ suicide attempts (N = 132) C: healthy volunteers (N = 96); psychiatric patients w/ no suicide history (N = 262)	USA (mixed races)	No association between suicide attempts and this polymorphism
Turecki et al., 2003 [160]	1D α , 1E, 1F	T1350C, C117T, C-78T, C528T	S: suicide completers (N = 106) C: healthy volunteers (N = 120)	French-Canadian	No association found with any of the polymorphisms examined
Zhang et al., 1997 [140]	2A	T102C	S: mood disorder patients w/ suicide attempts (N = 15) C: healthy volunteers (N = 150)	Japanese	Association found between the genotype and suicide attempts ($P = 0.016$)
Ohara et al., 1998 [163]	2A	G-1438A	S: mood disorder patients w/ suicide attempts (N = 14) C: healthy volunteers (N = 106)	Japanese	No association found
Du et al., 1999 [164]	2A	T102C, His452Tyr	S: suicide completers (N = 24) C: nonsuicides, no PH, died by CVD (N = 31)	Hungarian	No association with either polymorphism examined
Turecki et al., 1999 [61]	2A	T102C, G-1438A	S: suicide completers (N = 54) C: nonsuicides, died by CVD, nonimpulsive accident (N = 126)	French-Canadian	No association found

Table 11.3 (continued)

Study	Receptor	Polymorphism	Subjects (S) and Controls (C)	Origin	Main Findings
Tsai et al., 1999 [165]	2A	T102C	S: mood disorder patients w/ suicide attempts (N = 61) C: healthy volunteers (N = 96)	Taiwanese	No association found
Geijer et al., 2000 [142]	2A	T102C	S: suicide attempters (N = 165) C: healthy volunteers (N = 99)	Swedish	No association found
Preuss et al., 2000 [166]	2A	T102C	S: alcohol dependants w/ suicide attempts (N = 45) C: general population, no PH (N = 117)	German	No association found
Crawford et al., 2000 [167]	2A	T102C	S: suicide completers (N = 68) C: anonymous blood donors (N = 95)	Australian (mostly Caucasian)	No association found
Bondy et al., 2000 [168]	2A	T102C	S: suicide completers (N = 131) C: general population, no PH (N = 125)	German	No association found
Ono et al., 2001 [169]	2A	G-1438A	S: suicide completers (N = 151) C: healthy volunteers (N = 163)	Japanese	No association found
Arias et al., 2001 [170]	2A	T102C	S: MDD patients w/ suicide attempts (N = 33) C: MDD patients w/ no suicide attempts (N = 126); healthy controls (N = 164)	Spanish	Significant differences in allele ($P = 0.04$) and genotype ($P = 0.04$) frequencies between MDD attempters and MDD non-attempters
Correa et al., 2002 [171]	2A	T102C	S: psychiatric patients w/ suicide attempts (N = 66) C: psychiatric patients w/ no suicide history (N = 107); healthy volunteers (N = 52)	Brazilian	No association found
Turecki et al., 2003 [160]	2C, 5A, 6	G-995A G-19C C267T	S: suicide completers (N = 106) C: healthy volunteers (N = 120)	French-Canadian	No association found with any of the polymorphisms examined

Abbreviations:

w/ = with; CVD = cardiovascular disease; PH = psychiatric history; MDD = major depressive disorder

11.5.4

Molecular Genetics Studies

Because of the nature of suicide and related behaviors, most molecular studies carried out have primarily been association studies. Studies have been focusing on genes involved in the serotonergic system as candidates, because of the evidence for serotonin involvement in suicidal behavior and the fact that serotonergic activity is likely to be partially controlled by genetic factors.

The first report of an association between suicidal behavior and a polymorphism in a serotonergic-system gene involved the gene for tryptophan hydroxylase (*TPH*). Tryptophan hydroxylase is the rate-limiting enzyme in the biosynthesis of serotonin and is important in determining the amount of serotonin synthesized, making the *TPH* gene a good candidate to investigate in relation to suicidal behavior. Initial evidence of an association between *TPH* and suicidal behavior came from a study by Nielsen et al. [135]. They investigated the A779C polymorphism located in intron 7 of the *TPH* gene in a Finnish sample of violent alcoholics and found an association between the 779C allele (also referred to as the *L* allele) and a positive history of attempted suicide. They also demonstrated that this same allele was associated with a low concentration of 5-HIAA in the CSF of subjects characterized as impulsive.

The *TPH* gene has been examined in numerous studies since the initial report, and the findings from subsequent studies have not been entirely consistent. The results of 17 independent association studies examining the A779C variant in suicide attempters or completers were combined by means of meta-analysis, and no significant association between suicidal behavior and the A779C polymorphism in *TPH* was found [136]. This conclusion is consistent with the recent report of a second *TPH* gene, referred to as *TPH2*, which is predominantly expressed in the brain. The previously known *TPH* isoform, now referred to as *TPH1*, has not been detected in the brain and has been shown to be expressed peripherally [137]. Therefore, it is likely that the *TPH1* findings were primarily spurious results.

The genes encoding the various 5-HT receptor subtypes have been investigated as candidates in numerous studies, since alterations in several 5-HT receptor subtypes have been demonstrated in the brains of suicide victims. Table 11.3 lists and describes case-control studies that examined variation at a number of genes encoding the different 5-HT receptor subtypes. The 5-HT_{1B} receptor gene is an interesting candidate, because increased aggressive behavior has been reported in 5-HT_{1B} receptor gene knockout mice [138]. Huang et al. [139] investigated two common polymorphisms in the 5-HT_{1B} receptor gene and found no evidence for an association in suicide completers. Increased binding of the 5-HT_{1A} and 5-HT_{2A} receptors has been reported in the brains of suicide completers [56], thus making the 5-HT_{1A} and 5-HT_{2A} receptor genes good candidates for further investigation. Whereas the existence of an association between suicidal behavior and the 5-HT_{2A} receptor gene variant remains uncertain [61, 140–142], recent findings with a functional promoter variant in the 5-HT_{1A} receptor gene are very promising [143].

The serotonin transporter (5-HTT) gene is also an important candidate for obtaining promising results [144–147]. Case-control studies examining a functional 44-base-pair insertion/deletion polymorphism located in the promoter region of the 5-HTT gene in subjects with suicidal behavior are summarized in Table 11.4. A recent quantitative synthesis of these studies indicates an overall positive association with the *short* (s) allele [148]. The s allele is associated with reduced transcriptional efficiency of the 5-HTT promoter compared to the *long* (l) allele [149]. Moreover, added support for the association between the s allele and suicidal behavior comes from a recent methodologically robust cohort study that tested whether variation at the 5-HTT promoter moderates the influence of an environmental factor such as life stress on depression [150]. In that study, Caspi et al. showed that stressful life events predicted suicidal behavior among individuals carrying an s allele, but not among l/l homozygotes.

11.6 Conclusions

An abundance of research has been carried out over the last few decades focusing on the neurobiology and genetics of suicidality. These studies have provided consistent evidence indicating that abnormalities in serotonergic system functioning are involved in influencing suicide risk. More recent studies have been demonstrating a relationship between lower levels of serum cholesterol and suicidality. Although the mechanism for this putative association is unclear, one possibility is that the serotonergic system plays a role in mediating the inhibition of aggressive impulses, which are correlated with both suicidality and low cholesterol levels. Data from family, twin, and adoption studies provide convincing evidence that a genetic predisposition underlies suicidal behavior, and familial transmission of suicide risk is discrete from that of psychiatric illness. Given the evidence suggesting reduced serotonergic activity in persons exhibiting suicidal behavior and the fact that serotonergic activity is under partial genetic control, the selection of serotonergic-system genes as candidates for investigation in association studies is logical. The data from many of these studies are promising, particularly results relating to the serotonin transporter gene. Further work involving the serotonergic-system genes, as well as the identification and investigation of novel candidate genes, is necessary. The use of innovative molecular profiling techniques, such as cDNA microarrays, to screen for abnormalities in gene expression will be instrumental in advancing our knowledge about the numerous genes and their complex interactions involved in the predisposition to suicidal behavior. Finally, the merger of data from molecular studies and multiple domains of suicide research will be the key to synthesizing a more complete understanding of this complex and tragic behavior.

Table 11.4 Summary of studies investigating variation at the promoter insertion/deletion polymorphism of the 5-HTT in suicide attempters and completers

Study	Subjects (S) and Controls (C)	Origin	Main Findings
Du et al., 1999 [164]	S: suicide completers w/ depression ($N = 24$) C: nonsuicides, died by CVD	Hungarian	Higher frequency of <i>l</i> allele in depressed suicides ($P = 0.048$)
Bellivier et al., 2000 [144]	S: AD patients w/ nonviolent suicide attempts ($N = 73$); w/ violent suicide attempts ($N = 26$) C: healthy volunteers ($N = 187$)	French	Significant association of the <i>s</i> allele only w/ violent suicide attempt vs. controls ($P = 0.023$)
Bondy et al., 2000 [145]	S: suicide completers ($N = 58$) C: healthy volunteers ($N = 110$)	German	Higher frequency of <i>s</i> allele in suicide completers ($P = 0.0019$)
Chong et al., 2000 [172]	S: schizophrenia patients w/ suicide attempt ($N = 76$) C: nonsuicidal schizophrenia patients ($N = 262$); controls ($N = 103$)	Chinese	No association found
Geijer et al., 2000 [142]	S: suicide attempters ($N = 165$) C: healthy volunteers ($N = 99$)	Swedish	No association found
Gorwood et al., 2000 [173]	S: alcoholic patients w/ suicide attempts ($N = 55$) C: nonsuicidal alcoholics ($N = 55$); nonsuicidal blood donors w/ no alcohol dependence ($N = 61$)	French	Genotypes w/ <i>s</i> allele more frequent in suicide attempters than nonalcoholic controls ($P = 0.04$)
Russ et al., 2000 [174]	S: psychiatric inpatients at risk of suicide ($N = 51$); 84% w/ suicide attempt history C: healthy volunteers ($N = 51$)	USA (80% Caucasian, 20% other)	No association found; <i>ll</i> genotype related to higher suicidal ideation and hopelessness scores
Courtet et al., 2001 [146]	S: violent suicide attempters ($N = 51$); w/ AD ($N = 40$); w/ no AD ($N = 11$) C: controls w/ no suicide history ($N = 139$); w/ AD ($N = 44$); w/ no AD ($N = 95$)	West European	Higher frequency of <i>s</i> allele in violent attempters vs. non-attempters ($P = 0.02$)
Fitch et al., 2001 [175]	S: suicide completers ($N = 95$) C: healthy volunteers ($N = 120$)	French-Canadian	Non-significant higher frequency of <i>l</i> allele in suicides ($P = 0.09$)

Table 11.4 (continued)

Study	Subjects (S) and Controls (C)	Origin	Main Findings
Preuss et al., 2001 [147]	S: alcoholic patients w/ suicide attempts ($N = 52$) C: nonsuicidal alcoholic patients ($N = 111$); general population, no PH ($N = 117$)	German	Higher frequency of s allele in alcoholic patients w/ suicide attempts vs. without ($P = 0.019$); No difference w/ healthy controls
Rujescu et al., 2001 [176]	S: suicide attempters ($N = 124$) C: healthy volunteers ($N = 185$)	German	No association found
Baca-Garcia et al., 2002 [177]	S: suicide attempters ($N = 180$) C: blood donors ($N = 212$)	Spanish	Significantly higher frequency of s allele only in female attempters vs. female controls ($P = 0.02$)
Bayle et al., 2003 [178]	S: schizophrenia patients w/ nonviolent suicide attempts ($N = 51$); w/ violent attempts ($N = 18$) C: nonsuicidal schizophrenia patients ($N = 112$); healthy volunteers ($N = 159$)	French	Genotype with s allele more frequent in violent attempters vs. nonviolent attempters ($P = 0.013$) and nonsuicidal schizophrenia patients ($P = 0.007$); No difference w/ healthy controls
Courtet et al., 2003 [179]	S: nonviolent suicide attempters ($N = 166$); w/ AD ($N = 108$); w/ no AD ($N = 58$) C: controls w/ no suicide history ($N = 139$); w/ AD ($N = 44$); w/ no AD ($N = 95$)	West European	No association found

Abbreviations:

w/ = with; CVD = cardiovascular disease; AD = affective disorder; PH = psychiatric history

References

- 1 LONNQVIST, J. K., Psychiatric aspects of suicidal behaviour: depression. In: HAWTON, K., VAN HEERINGEN, K. (Eds.), *Suicide and Attempted Suicide*. Chichester: Wiley, 2000, p. 107–120.
- 2 WHO, *Preventing Suicide: A Resource for General Physicians*. Geneva: World Health Organization, 2000.
- 3 MARIS, R. W., Suicide. *Lancet* 2002, 360, 319–326.
- 4 CAVANAGH, J. T., CARSON, A. J., SHARPE, M., LAWRIE, S. M., Psychological autopsy studies of suicide: a systematic review. *Psychol. Med.* 2003, 33, 395–405.
- 5 BECK, A. T., DAVIS, J. H., FREDERICK, C. J., et al., Classification and nomenclature. In: RESNICK, H., HATHORNE, B. (Eds.), *Suicide Prevention in the Seventies*. Washington DC: US Government Printing Office, 1973, p. 7–12.
- 6 ROSENBERG, M. L., DAVIDSON, L. E., SMITH, J. C., BERMAN, A. L., BUZBEE, H., GANTNER, G., et al., Operational criteria for the determination of suicide. *J. Forensic Sci.* 1988, 33, 1445–1456.
- 7 O'CARROLL, P. W., BERMAN, A. L., MARIS, R. W., MOSCICKI, E. K., TANNEY, B. L., SILVERMAN, M. M., Beyond the Tower of Babel: a nomenclature for suicidology. *Suicide Life Threat. Behav.* 1996, 26, 237–252.
- 8 BECK, A. T., WEISSMAN, A., LESTER, D., TREXLER, L., CLASSIFICATION OF SUICIDAL BEHAVIORS., I. I., Dimensions of suicidal intent. *Arch. Gen. Psychiatry* 1976, 33, 835–837.
- 9 PAYKEL, E. S., RASSABY, E., Classification of suicide attempters by cluster analysis. *Br. J. Psychiatry* 1978, 133, 45–52.
- 10 ISOMETSA, E. T., LONNQVIST, J. K., Suicide attempts preceding completed suicide. *Br. J. Psychiatry* 1998, 173, 531–535.
- 11 US PUBLIC HEALTH SERVICE, *The Surgeon General's Call to Action to Prevent Suicide*. Washington DC, 1999.
- 12 WEISSMAN, M. M., BLAND, R. C., CANINO, G. J., GREENWALD, S., HWU, H. G., JOYCE, P. R., et al., Prevalence of suicide ideation and suicide attempts in nine countries. *Psychol. Med.* 1999, 29, 9–17.
- 13 HAWTON, K., APPLEBY, L., PLATT, S., FOSTER, T., COOPER, J., MALMBERG, A., et al., The psychological autopsy approach to studying suicide: a review of methodological issues. *J. Affect Disord.* 1998, 50, 269–276.
- 14 CONWELL, Y., DUBERSTEIN, P. R., COX, C., HERRMANN, J. H., FORBES, N. T., CAINE, E. D., Relationships of age and axis I diagnoses in victims of completed suicide: a psychological autopsy study. *Am. J. Psychiatry* 1996, 153, 1001–1008.
- 15 ARSENAULT-LAPIERRE, G., KIM, C., TURECKI, G., 3500 cases of suicide: a systematic review. Submitted.
- 16 ISOMETSA, E. T., Psychological autopsy studies: a review. *Eur. Psychiatry* 2001, 16, 379–385.
- 17 GUZE, S. B., ROBINS, E., Suicide and primary affective disorders. *Br. J. Psychiatry* 1970, 117, 437–438.
- 18 BLAIR-WEST, G. W., MELLISOP, G. W., EYESON-ANNAN, M. L., Down-rating lifetime suicide risk in major depression. *Acta Psychiatr. Scand.* 1997, 95, 259–263.
- 19 BROWN, G. L., EBERT, M. H., GOYER, P. F., JIMERSON, D. C., KLEIN, W. J., BUNNEY, W. E., et al., Aggression, suicide, and serotonin: relationships to CSF amine metabolites. *Am. J. Psychiatry* 1982, 139, 741–746.
- 20 APTER, A., PLUTCHIK, R., VAN PRAAG, H. M., Anxiety, impulsivity and depressed mood in relation to suicidal and violent behavior. *Acta Psychiatr. Scand.* 1993, 87, 1–5.
- 21 PLUTCHIK, R., Outward and inward directed aggressiveness: the interaction between violence and suicidality. *Pharmacopsychiatry* 1995, 28, (Suppl. 2), 47–57.
- 22 BRENT, D. A., JOHNSON, B. A., PERPER, J., CONNOLLY, J., BRIDGE, J., BARTLE, S., et al., Personality disorder, personality traits, impulsive violence, and completed suicide in adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 1994, 33, 1080–1086.
- 23 MANN, J. J., WATERNAUX, C., HAAS, G. L., MALONE, K. M., Toward a clinical model of suicidal behavior in psychiatric patients. *Am. J. Psychiatry* 1999, 156, 181–189.
- 24 APTER, A., VAN PRAAG, H. M., PLUTCHIK, R., SEVY, S., KORN, M., BROWN, S. L., Interrelationships among anxiety,

- aggression, impulsivity, and mood: a serotonergically linked cluster? *Psychiatry Res.* **1990**, *32*, 191–199.
- 25 STANLEY, M., TRASKMAN-BENDZ, L., DOROVINI-ZIS, K., Correlations between aminergic metabolites simultaneously obtained from human CSF and brain. *Life Sci.* **1985**, *37*, 1279–1286.
 - 26 ASBERG, M., TRASKMAN, L., THOREN, P., 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? *Arch. Gen. Psychiatry* **1976**, *33*, 1193–1197.
 - 27 ASBERG, M., Neurotransmitters and suicidal behavior: the evidence from cerebrospinal fluid studies. *Ann. NY Acad. Sci.* **1997**, *836*, 158–181.
 - 28 COOPER, S. J., KELLY, C. B., KING, D. J., 5-Hydroxyindoleacetic acid in cerebrospinal fluid and prediction of suicidal behaviour in schizophrenia. *Lancet* **1992**, *340*, 940–941.
 - 29 BANKI, C. M., ARATO, M., PAPP, Z., KURCZ, M., Biochemical markers in suicidal patients: investigations with cerebrospinal fluid amine metabolites and neuroendocrine tests. *J. Affect Disord.* **1984**, *6*, 341–350.
 - 30 BROWN, G. L., GOODWIN, F. K., BALLENGER, J. C., GOYER, P. F., MAJOR, L. F., Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Res.* **1979**, *1*, 131–139.
 - 31 ROY-BYRNE, P., POST, R. M., RUBINOW, D. R., LINNOILA, M., SAVARD, R., DAVIS, D., CSF 5HIAA and personal and family history of suicide in affectively ill patients: a negative study. *Psychiatry Res.* **1983**, *10*, 263–274.
 - 32 BERRETTINI, W. H., NURNBERGER, J. I. JR., SCHEININ, M., SEPPALA, T., LINNOILA, M., NARROW, W., et al., Cerebrospinal fluid and plasma monoamines and their metabolites in euthymic bipolar patients. *Biol. Psychiatry* **1985**, *20*, 257–269.
 - 33 TRASKMAN, L., ASBERG, M., BERTILSSON, L., SJOSTRAND, L., Monoamine metabolites in CSF and suicidal behavior. *Arch. Gen. Psychiatry* **1981**, *38*, 631–636.
 - 34 ROY, A., AGREN, H., PICKAR, D., LINNOILA, M., DORAN, A. R., CUTLER, N. R., et al., Reduced CSF concentrations of homovanillic acid and homovanillic acid to 5-hydroxyindoleacetic acid ratios in depressed patients: relationship to suicidal behavior and dexamethasone nonsuppression. *Am. J. Psychiatry* **1986**, *143*, 1539–1545.
 - 35 SEDVALL, G., FYRO, B., GULLBERG, B., NYBACK, H., WIESEL, F. A., WODE-HELGODT, B., Relationships in healthy volunteers between concentrations of monoamine metabolites in cerebrospinal fluid and family history of psychiatric morbidity. *Br. J. Psychiatry* **1980**, *136*, 366–374.
 - 36 LINNOILA, M., VIRKKUNEN, M., SCHEININ, M., NUUTILA, A., RIMON, R., GOODWIN, F. K., Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non-impulsive violent behavior. *Life Sci.* **1983**, *33*, 2609–2614.
 - 37 ROWLAND, N. E., CARLTON, J., Neurobiology of an anorectic drug: fenfluramine. *Prog. Neurobiol.* **1986**, *27*, 13–62.
 - 38 QUATTRONE, A., TEDESCHI, G., AGUGLIA, U., SCOPACASA, F., DIRENZO, G. F., ANNUNZIATO, L., Prolactin secretion in man: a useful tool to evaluate the activity of drugs on central 5-hydroxytryptaminergic neurons. Studies with fenfluramine. *Br. J. Clin. Pharmacol.* **1983**, *16*, 471–475.
 - 39 MANN, J. J., MCBRIDE, P. A., MALONE, K. M., DEMEO, M., KEILP, J., Blunted serotonergic responsivity in depressed inpatients. *Neuropsychopharmacology* **1995**, *13*, 53–64.
 - 40 CORREA, H., DUVAL, F., MOKRANI, M., BAILEY, P., TREMEAU, F., STANER, L., et al., Prolactin response to D-fenfluramine and suicidal behavior in depressed patients. *Psychiatry Res.* **2000**, *93*, 189–199.
 - 41 NEW, A. S., TRESTMAN, R. L., MITROPOULOU, V., BENISHAY, D. S., COCCARO, E., SILVERMAN, J., et al., Serotonergic function and self-injurious behavior in personality disorder patients. *Psychiatry Res.* **1997**, *69*, 17–26.
 - 42 SOLOFF, P. H., KELLY, T. M., STROTMAYER, S. J., MALONE, K. M., MANN, J. J., Impulsivity, gender, and response to fenfluramine challenge in borderline personality disorder. *Psychiatry Res.* **2003**, *119*, 11–24.
 - 43 COCCARO, E. F., SIEVER, L. J., KLAR, H. M., MAURER, G., COCHRANE, K., COOPER, T. B., et al., Serotonergic studies in patients with affective and personality

- disorders: correlates with suicidal and impulsive aggressive behavior. *Arch. Gen. Psychiatry* **1989**, *46*, 587–599.
- 44 MALONE, K. M., CORBITT, E. M., LI, S., MANN, J. J., Prolactin response to fenfluramine and suicide attempt lethality in major depression. *Br. J. Psychiatry* **1996**, *168*, 324–329.
 - 45 STAHL, S. M., The human platelet: a diagnostic and research tool for the study of biogenic amines in psychiatric and neurologic disorders. *Arch. Gen. Psychiatry* **1977**, *34*, 509–516.
 - 46 ANDRES, A. H., RAO, M. L., OSTROWITZKI, S., ENTZIAN, W., Human brain cortex and platelet serotonin-2 receptor binding properties and their regulation by endogenous serotonin. *Life Sci.* **1993**, *52*, 313–321.
 - 47 PANDEY, G. N., PANDEY, S. C., JANICAK, P. G., MARKS, R. C., DAVIS, J. M., Platelet serotonin-2 receptor binding sites in depression and suicide. *Biol. Psychiatry* **1990**, *28*, 215–222.
 - 48 ARORA, R. C., MELTZER, H. Y., Serotonin-2 receptor binding in blood platelets of schizophrenic patients. *Psychiatry Res.* **1993**, *47*, 111–119.
 - 49 PANDEY, G. N., PANDEY, S. C., DWIVEDI, Y., SHARMA, R. P., JANICAK, P. G., DAVIS, J. M., Platelet serotonin-2A receptors: a potential biological marker for suicidal behavior. *Am. J. Psychiatry* **1995**, *152*, 850–855.
 - 50 PANDEY, G. N., Altered serotonin function in suicide: evidence from platelet and neuroendocrine studies. *Ann. NY Acad. Sci.* **1997**, *836*, 182–200.
 - 51 MARAZZITI, D., DE LEO, D., CONTI, L., Further evidence supporting the role of the serotonin system in suicidal behavior: a preliminary study of suicide attempters. *Acta Psychiatr. Scand.* **1989**, *80*, 322–324.
 - 52 MARAZZITI, D., PRESTA, S., SILVESTRI, S., BATTISTINI, A., MOSTI, L., BALESTRI, C., et al., Platelet markers in suicide attempters. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1995**, *19*, 375–383.
 - 53 MELTZER, H. Y., ARORA, R. C., Platelet markers of suicidality. *Ann. NY Acad. Sci.* **1986**, *487*, 271–280.
 - 54 ROY, A., EVERETT, D., PICKAR, D., PAUL, S. M., Platelet tritiated imipramine binding and serotonin uptake in depressed patients and controls: relationship to plasma cortisol levels before and after dexamethasone administration. *Arch. Gen. Psychiatry* **1987**, *44*, 320–327.
 - 55 MANN, J. J., UNDERWOOD, M. D., ARANGO, V., Postmortem studies of suicide victims. In: Watson, S. J. (Ed.), *Biology of Schizophrenia and Affective Disease*. Washington, DC: American Psychiatric Press, **1996**, p. 197–221.
 - 56 ARANGO, V., UNDERWOOD, M. D., MANN, J. J., Postmortem findings in suicide victims: implications for in vivo imaging studies. *Ann. NY Acad. Sci.* **1997**, *836*, 269–287.
 - 57 GROSS-ISSEROFF, R., BIEGON, A., VOET, H., WEIZMAN, A., The suicide brain: a review of postmortem receptor/transporter binding studies. *Neurosci. Biobehav. Rev.* **1998**, *22*, 653–661.
 - 58 ARANGO, V., UNDERWOOD, M. D., GUBBI, A. V., MANN, J. J., Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Res.* **1995**, *688*, 121–133.
 - 59 STANLEY, M., MANN, J. J., Increased serotonin-2 binding sites in frontal cortex of suicide victims. *Lancet* **1983**, *1*, 214–216.
 - 60 HRDINA, P. D., DEMETER, E., VU, T. B., SOTONYI, P., PALKOVITS, M., 5-HT uptake sites and 5-HT₂ receptors in brain of antidepressant-free suicide victims/depressives: increase in 5-HT₂ sites in cortex and amygdala. *Brain Res.* **1993**, *614*, 37–44.
 - 61 TURECKI, G., BRIERE, R., DEWAR, K., ANTONETTI, T., LESAGE, A. D., SEGUIN, M., et al., Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in post-mortem brain samples from subjects who did or did not commit suicide. *Am. J. Psychiatry* **1999**, *156*, 1456–1458.
 - 62 OWEN, F., CHAMBERS, D. R., COOPER, S. J., CROW, T. J., JOHNSON, J. A., LOFTHOUSE, R., et al., Serotonergic mechanisms in brains of suicide victims. *Brain Res.* **1986**, *362*, 185–188.
 - 63 ARORA, R. C., MELTZER, H. Y., ³H-imipramine binding in the frontal cortex of suicides. *Psychiatry Res.* **1989**, *30*, 125–135.

- 64 CHEETHAM, S. C., CROMPTON, M. R., KATONA, C. L., HORTON, R. W., Brain 5-HT₁ binding sites in depressed suicides. *Psychopharmacology (Berl.)* **1990**, *102*, 544–548.
- 65 GROSS-ISSEROFF, R., SALAMA, D., ISRAELI, M., BIEGON, A., Autoradiographic analysis of [³H]ketanserin binding in the human brain postmortem: effect of suicide. *Brain Res.* **1990**, *507*, 208–215.
- 66 ARRANZ, B., ERIKSSON, A., MELLERUP, E., PLENGE, P., MARCUSSEN, J., Brain 5-HT_{1A}, 5-HT_{1D}, and 5-HT₂ receptors in suicide victims. *Biol. Psychiatry* **1994**, *35*, 457–463.
- 67 LITTLE, K. Y., McLAUGHLIN, D. P., RANC, J., GILMORE, J., LOPEZ, J. F., WATSON, S. J., et al., Serotonin transporter binding sites and mRNA levels in depressed persons committing suicide. *Biol. Psychiatry* **1997**, *41*, 1156–1164.
- 68 SHALLICE, T., BURGESS, P., The domain of supervisory processes and temporal organization of behaviour. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **1996**, *351*, 1405–1411.
- 69 MANN, J. J., The neurobiology of suicide. *Nat. Med.* **1998**, *4*, 25–30.
- 70 VIRKKUNEN, M., Serum cholesterol in antisocial personality. *Neuropsychobiology* **1979**, *5*, 27–30.
- 71 LIPID RESEARCH CLINICS PROGRAM, The Lipid Research Clinics Coronary Primary Prevention Trial results I, Reduction in incidence of coronary heart disease. *JAMA* **1984**, *251*, 351–364.
- 72 FRICK, M. H., ELO, O., HAAPA, K., HEINONEN, O. P., HEINSALMI, P., HELO, P., et al., Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N. Engl. J. Med.* **1987**, *317*, 1237–1245.
- 73 MULDOON, M. F., MANUCK, S. B., MATTHEWS, K. A., Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *Br. Med. J.* **1990**, *301*, 309–314.
- 74 VIRKKUNEN, M., Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA* **1985**, *253*, 635–636.
- 75 LINDBERG, G., RASTAM, L., GULLBERG, B., EKLUND, G. A., Low serum cholesterol concentration and short term mortality from injuries in men and women. *Br. Med. J.* **1992**, *305*, 277–279.
- 76 NEATON, J. D., BLACKBURN, H., JACOBS, D., KULLER, L., LEE, D. J., SHERWIN, R., et al., Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch. Intern. Med.* **1992**, *152*, 1490–1500.
- 77 ZUREIK, M., COURBON, D., DUCIMETIERE, P., Serum cholesterol concentration and death from suicide in men: Paris prospective study I. *Br. Med. J.* **1996**, *313*, 649–651.
- 78 PARTONEN, T., HAUKKA, J., VIRTAMO, J., TAYLOR, P. R., LONNQVIST, J., Association of low serum total cholesterol with major depression and suicide. *Br. J. Psychiatry* **1999**, *175*, 259–262.
- 79 GOLOMB, B. A., STATTIN, H., MEDNICK, S., Low cholesterol and violent crime. *J. Psychiatr. Res.* **2000**, *34*, 301–309.
- 80 ELLISON, L. F., MORRISON, H. I., Low serum cholesterol concentration and risk of suicide. *Epidemiology* **2001**, *12*, 168–172.
- 81 FREEDMAN, D. S., BYERS, T., BARRETT, D. H., STROUP, N. E., EAKER, E., MONROE-BLUM, H., Plasma lipid levels and psychologic characteristics in men. *Am. J. Epidemiol.* **1995**, *141*, 507–517.
- 82 IRIBARREN, C., REED, D. M., WERGOWSKIE, G., BURCHFIELD, C. M., DWYER, J. H., Serum cholesterol level and mortality due to suicide and trauma in the Honolulu Heart Program. *Arch. Intern. Med.* **1995**, *155*, 695–700.
- 83 GALLERANI, M., MANFREDINI, R., CARACCILO, S., SCAPOLI, C., MOLINARI, S., FERSINI, C., Serum cholesterol concentrations in parasuicide. *Br. Med. J.* **1995**, *310*, 1632–1636.
- 84 KUNUGI, H., TAKEI, N., AOKI, H., NANKO, S., Low serum cholesterol in suicide attempters. *Biol. Psychiatry* **1997**, *41*, 196–200.
- 85 ALVAREZ, J. C., CREMNITER, D., LESIEUR, P., GREGOIRE, A., GILTON, A., MACQUIN-MAVIER, I., et al., Low blood cholesterol and low platelet serotonin levels in violent suicide attempters. *Biol. Psychiatry* **1999**, *45*, 1066–1069.

- 86 ALVAREZ, J. C., CREMNITER, D., GLUCK, N., QUINTIN, P., LEBOYER, M., BERLIN, I., et al., Low serum cholesterol in violent but not in non-violent suicide attempters. *Psychiatry Res.* **2000**, 95, 103–108.
- 87 GARLAND, M., HICKEY, D., CORVIN, A., GOLDEN, J., FITZPATRICK, P., CUNNINGHAM, S., et al., Total serum cholesterol in relation to psychological correlates in parasuicide. *Br. J. Psychiatry* **2000**, 177, 77–83.
- 88 SARCHIAPONE, M., ROY, A., CAMARDESE, G., DE RISIO, S., Further evidence for low serum cholesterol and suicidal behaviour. *J. Affect Disord.* **2000**, 61, 69–71.
- 89 MODAI, I., VALEVSKI, A., DROR, S., WEIZMAN, A., Serum cholesterol levels and suicidal tendencies in psychiatric inpatients. *J. Clin. Psychiatry* **1994**, 55, 252–254.
- 90 SULLIVAN, P. F., JOYCE, P. R., BULIK, C. M., MULDER, R. T., OAKLEY-BROWNE, M., Total cholesterol and suicidality in depression. *Biol. Psychiatry* **1994**, 36, 472–477.
- 91 GOLIER, J. A., MARZUK, P. M., LEON, A. C., WEINER, C., TARDIFF, K., Low serum cholesterol level and attempted suicide. *Am. J. Psychiatry* **1995**, 152, 419–423.
- 92 MUFTI, R. M., BALON, R., ARFKEN, C. L., Low cholesterol and violence. *Psychiatr. Serv.* **1998**, 49, 221–224.
- 93 NEW, A. S., SEVIN, E. M., MITROPOULOU, V., REYNOLDS, D., NOVOTNY, S. L., CALLAHAN, A., et al., Serum cholesterol and impulsivity in personality disorders. *Psychiatry Res.* **1999**, 85, 145–150.
- 94 ATMACA, M., KULOGLU, M., TEZCAN, E., GECICI, O., USTUNDAG, B., Serum cholesterol and leptin levels in patients with borderline personality disorder. *Neuropsychobiology* **2002**, 45, 167–171.
- 95 VIRKKUNEN, M., Serum cholesterol levels in homicidal offenders: a low cholesterol level is connected with a habitually violent tendency under the influence of alcohol. *Neuropsychobiology* **1983**, 10, 65–69.
- 96 VIRKKUNEN, M., PENTTINEN, H., Serum cholesterol in aggressive conduct disorder: a preliminary study. *Biol. Psychiatry* **1984**, 19, 435–439.
- 97 HILLBRAND, M., SPITZ, R. T., FOSTER, H. G., Serum cholesterol and aggression in hospitalized male forensic patients. *J. Behav. Med.* **1995**, 18, 33–43.
- 98 REPO-TIIHONEN, E., HALONEN, P., TIIHONEN, J., VIRKKUNEN, M., Total serum cholesterol level, violent criminal offences, suicidal behavior, mortality and the appearance of conduct disorder in Finnish male criminal offenders with antisocial personality disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* **2002**, 252, 8–11.
- 99 APTER, A., LAUFER, N., BAR-SEVER, M., HAR-EVEN, D., OFEK, H., WEIZMAN, A., Serum cholesterol, suicidal tendencies, impulsivity, aggression, and depression in adolescent psychiatric inpatients. *Biol. Psychiatry* **1999**, 46, 532–541.
- 100 TANSKANEN, A., VARTIAINEN, E., TUOMILEHTO, J., VIINAMAKI, H., LEHTONEN, J., PUSKA, P., High serum cholesterol and risk of suicide. *Am. J. Psychiatry* **2000**, 157, 648–650.
- 101 GOLOMB, B. A., Cholesterol and violence: is there a connection? *Ann. Intern. Med.* **1998**, 128, 478–487.
- 102 RINGO, D. L., LINDLEY, S. E., FAULL, K. F., FAUSTMAN, W. O., Cholesterol and serotonin: seeking a possible link between blood cholesterol and CSF 5-HIAA. *Biol. Psychiatry* **1994**, 35, 957–959.
- 103 STEEGMANS, P. H., HOES, A. W., BAK, A. A., VAN DER, D. E., GROBBEE, D. E., Higher prevalence of depressive symptoms in middle-aged men with low serum cholesterol levels. *Psychosom. Med.* **2000**, 62, 205–211.
- 104 MULDOON, M. F., KAPLAN, J. R., MANUCK, S. B., MANN, J. J., Effects of a low-fat diet on brain serotonergic responsivity in cynomolgus monkeys. *Biol. Psychiatry* **1992**, 31, 739–742.
- 105 KAPLAN, J. R., SHIVELY, C. A., FONTENOT, M. B., MORGAN, T. M., HOWELL, S. M., MANUCK, S. B., et al., Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. *Psychosom. Med.* **1994**, 56, 479–484.
- 106 ENGELBERG, H., Low serum cholesterol and suicide. *Lancet* **1992**, 339, 727–729.
- 107 HERON, D. S., SHINITZKY, M., HERSHKOWITZ, M., SAMUEL, D., Lipid fluidity markedly modulates the binding of serotonin to mouse brain membranes.

- Proc. Natl. Acad. Sci. USA* **1980**, *77*, 7463–7467.
- 108 TERA0, T., NAKAMURA, J., YOSHIMURA, R., OHMORI, O., TAKAHASHI, N., KOJIMA, H., et al., Relationship between serum cholesterol levels and meta-chlorophenyl-piperazine-induced cortisol responses in healthy men and women. *Psychiatry Res.* **2000**, *96*, 167–173.
 - 109 SALTER, M., Low serum cholesterol and suicide. *Lancet* **1992**, *339*, 1169.
 - 110 PENTTINEN, J., Hypothesis: low serum cholesterol, suicide, and interleukin-2. *Am. J. Epidemiol.* **1995**, *141*, 716–718.
 - 111 BARON, D. A., HARDIE, T., BARON, S. H., Possible association of interleukin-2 treatment with depression and suicide. *J. Am. Osteopath. Assoc.* **1993**, *93*, 799–800.
 - 112 WILSON, D. E., BIRCHFIELD, G. R., HEJAZI, J. S., WARD, J. H., SAMLOWSKI, W. E., Hypocholesterolemia in patients treated with recombinant interleukin-2: appearance of remnant-like lipoproteins. *J. Clin. Oncol.* **1989**, *7*, 1573–1577.
 - 113 LISSONI, P., BARNI, S., ROVELLI, F., CRISPINO, S., FUMAGALLI, G., PESCIA, S., et al., Neuroendocrine effects of subcutaneous interleukin-2 injection in cancer patients. *Tumori* **1991**, *77*, 212–215.
 - 114 TURECKI, G., Suicidal behavior: is there a genetic predisposition? *Bipolar Disord.* **2001**, *3*, 335–349.
 - 115 TSUANG, M. T., Risk of suicide in the relatives of schizophrenics, manics, depressives, and controls. *J. Clin. Psychiatry* **1983**, *44*, 396–400.
 - 116 BRENT, D. A., BRIDGE, J., JOHNSON, B. A., CONNOLLY, J., Suicidal behavior runs in families: a controlled family study of adolescent suicide victims. *Arch. Gen. Psychiatry* **1996**, *53*, 1145–1152.
 - 117 CHENG, A. T., CHEN, T. H., CHEN, C. C., JENKINS, R., Psychosocial and psychiatric risk factors for suicide: case-control psychological autopsy study. *Br. J. Psychiatry* **2000**, *177*, 360–365.
 - 118 MURPHY, G. E., WETZEL, R. D., Family history of suicidal behavior among suicide attempters. *J. Nerv. Ment. Dis.* **1982**, *170*, 86–90.
 - 119 PFEFFER, C. R., NORMANDIN, L., KAKUMA, T., Suicidal children grow up: suicidal behavior and psychiatric disorders among relatives. *J. Am. Acad. Child Adolesc. Psychiatry* **1994**, *33*, 1087–1097.
 - 120 MALONE, K. M., HAAS, G. L., SWEENEY, J. A., MANN, J. J., Major depression and the risk of attempted suicide. *J. Affect Disord.* **1995**, *34*, 173–185.
 - 121 JOHNSON, B. A., BRENT, D. A., BRIDGE, J., CONNOLLY, J., The familial aggregation of adolescent suicide attempts. *Acta Psychiatr. Scand.* **1998**, *97*, 18–24.
 - 122 ROY, A., Relation of family history of suicide to suicide attempts in alcoholics. *Am. J. Psychiatry* **2000**, *157*, 2050–2051.
 - 123 ROY, A., Family history of suicide. *Arch. Gen. Psychiatry* **1983**, *40*, 971–974.
 - 124 LINKOWSKI, P., DE, M., V, MENDLEWICZ, J., Suicidal behaviour in major depressive illness. *Acta Psychiatr. Scand.* **1985**, *72*, 233–238.
 - 125 BARRACLOUGH, B., BUNCH, J., NELSON, B., SAINSBURY, P., A hundred cases of suicide: clinical aspects. *Br. J. Psychiatry* **1974**, *125*, 355–373.
 - 126 EGELAND, J. A., SUSSEX, J. N., Suicide and family loading for affective disorders. *JAMA* **1985**, *254*, 915–918.
 - 127 ROY, A., SEGAL, N. L., CENTERWALL, B. S., ROBINETTE, C. D., Suicide in twins. *Arch. Gen. Psychiatry* **1991**, *48*, 29–32.
 - 128 ROY, A., SEGAL, N. L., SARCHIAPONE, M., Attempted suicide among living co-twins of twin suicide victims. *Am. J. Psychiatry* **1995**, *152*, 1075–1076.
 - 129 STATHAM, D. J., HEATH, A. C., MADDEN, P. A., BUCHOLZ, K. K., BIERUT, L., DINWIDDIE, S. H., et al., Suicidal behaviour: an epidemiological and genetic study. *Psychol. Med.* **1998**, *28*, 839–855.
 - 130 ROY, A., SEGAL, N. L., Suicidal behavior in twins: a replication. *J. Affect Disord.* **2001**, *66*, 71–74.
 - 131 GLOWINSKI, A. L., BUCHOLZ, K. K., NELSON, E. C., FU, Q., MADDEN, P. A., REICH, W., et al., Suicide attempts in an adolescent female twin sample. *J. Am. Acad. Child Adolesc. Psychiatry* **2001**, *40*, 1300–1307.
 - 132 FU, Q., HEATH, A. C., BUCHOLZ, K. K., NELSON, E. C., GLOWINSKI, A. L., GOLDBERG, J., et al., A twin study of genetic and environmental influences on suicidality in men. *Psychol. Med.* **2002**, *32*, 11–24.

- 133 SCHULSINGER, F., KETY, S., ROSENTHAL, D., WENDER, P., A family study of suicide. In: SCHOU, M., STROMGREN, E. (Eds.), *Origins, Prevention and Treatment of Affective Disorders*. New York: Academic Press, 1979, p. 277–287.
- 134 WENDER, P. H., KETY, S. S., ROSENTHAL, D., SCHULSINGER, F., ORTMANN, J., LUNDE, I., Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Arch. Gen. Psychiatry* 1986, 43, 923–929.
- 135 NIELSEN, D. A., GOLDMAN, D., VIRKKUNEN, M., TOKOLA, R., RAWLINGS, R., LINNOILA, M., Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. *Arch. Gen. Psychiatry* 1994, 51, 34–38.
- 136 LALOVIC, A., TURECKI, G., Meta-analysis of the association between tryptophan hydroxylase and suicidal behavior. *Am. J. Med. Genet.* 2002, 114, 533–540.
- 137 WALTHER, D. J., PETER, J. U., BASHAMMAKH, S., HORTNAGL, H., VOITS, M., FINK, H., et al., Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science* 2003, 299, 76.
- 138 SAUDOU, F., AMARA, D. A., DIERICH, A., LEMEUR, M., RAMBOZ, S., SEGU, L., et al., Enhanced aggressive behavior in mice lacking 5-HT1B receptor. *Science* 1994, 265, 1875–1878.
- 139 HUANG, Y. Y., GRAILHE, R., ARANGO, V., HEN, R., MANN, J. J., Relationship of psychopathology to the human serotonin1B genotype and receptor binding kinetics in postmortem brain tissue. *Neuropsychopharmacology* 1999, 21, 238–246.
- 140 ZHANG, H. Y., ISHIGAKI, T., TANI, K., CHEN, K., SHIH, J. C., MIYASATO, K., et al., Serotonin 2A receptor gene polymorphism in mood disorders. *Biol. Psychiatry* 1997, 41, 768–773.
- 141 DU, L., BAKISH, D., LAPIERRE, Y. D., RAVINDRAN, A. V., HRDINA, P. D., Association of polymorphism of serotonin 2A receptor gene with suicidal ideation in major depressive disorder. *Am. J. Med. Genet.* 2000, 96, 56–60.
- 142 GEIJER, T., FRISCH, A., PERSSON, M. L., WASSERMAN, D., ROCKAH, R., MICHAELOVSKY, E., et al., Search for association between suicide attempt and serotonergic polymorphisms. *Psychiatr. Genet.* 2000, 10, 19–26.
- 143 LEMONDE, S., TURECKI, G., BAKISH, D., DU, L., HRDINA, P. D., BASAK, A., KUSHWAHA, N., SEQUEIRA, A., MORRIS, S. J., OU, X. M., DAIGLE, M., ALBERT, P. R., Impaired trans-repression at a 5-HT1A receptor gene polymorphism associated with major depression and suicide. *J. Neurosci.* 2003, 23, 8788–8799.
- 144 BELLIVIER, F., SZOKE, A., HENRY, C., LACOSTE, J., BOTTOS, C., NOSTEN-BERTRAND, M., et al., Possible association between serotonin transporter gene polymorphism and violent suicidal behavior in mood disorders. *Biol. Psychiatry* 2000, 48, 319–322.
- 145 BONDY, B., ERFURTH, A., DE JONGE, S., KRUGER, M., MEYER, H., Possible association of the short allele of the serotonin transporter promoter gene polymorphism (5-HTTLPR) with violent suicide. *Mol. Psychiatry* 2000, 5, 193–195.
- 146 COURTET, P., BAUD, P., ABBAR, M., BOULENGER, J. P., CASTELNAU, D., MOUTHON, D., et al., Association between violent suicidal behavior and the low activity allele of the serotonin transporter gene. *Mol. Psychiatry* 2001, 6, 338–341.
- 147 PREUSS, U. W., KOLLER, G., SOYKA, M., BONDY, B., Association between suicide attempts and 5-HTTLPR S allele in alcohol-dependent and control subjects: further evidence from a German alcohol-dependent inpatient sample. *Biol. Psychiatry* 2001, 50, 636–639.
- 148 ANGUELOVA, M., BENKELFAT, C., TURECKI, G., A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter II, Suicidal behavior. *Mol. Psychiatry* 2003, 8, 646–653.
- 149 LESCH, K. P., BENDEL, D., HEILS, A., SABOL, S. Z., GREENBERG, B. D., PETRI, S., et al., Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996, 274, 1527–1531.
- 150 CASPI, A., SUGDEN, K., MOFFITT, T. E., TAYLOR, A., CRAIG, I. W., HARRINGTON, H., et al., Influence of life stress on

- depression: moderation by a polymorphism in the 5-HTT gene. *Science* **2003**, *301*, 386–389.
- 151 VIRKKUNEN, M., DE JONG, J., BARTKO, J., LINNOILA, M., Psychobiological concomitants of history of suicide attempts among violent offenders and impulsive fire setters. *Arch. Gen. Psychiatry* **1989**, *46*, 604–606.
 - 152 CROW, T. J., CROSS, A. J., COOPER, S. J., DEAKIN, J. F., FERRIER, I. N., JOHNSON, J. A., et al., Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicides. *Neuropharmacology* **1984**, *23*, 1561–1569.
 - 153 MATSUBARA, S., ARORA, R. C., MELTZER, H. Y., Serotonergic measures in suicide brain: 5-HT1A binding sites in frontal cortex of suicide victims. *J. Neural Transm. Gen Sect* **1991**, *85*, 181–194.
 - 154 ARANGO, V., ERNSBERGER, P., MARZUK, P. M., CHEN, J. S., TIERNEY, H., STANLEY, M., et al., Autoradiographic demonstration of increased serotonin 5-HT2 and beta-adrenergic receptor binding sites in the brain of suicide victims. *Arch. Gen. Psychiatry* **1990**, *47*, 1038–1047.
 - 155 GUILLEM, E., PELISSOLO, A., NOTIDES, C., LEPINE, J. P., Relationship between attempted suicide, serum cholesterol level and novelty seeking in psychiatric in-patients. *Psychiatry Res.* **2002**, *112*, 83–88.
 - 156 VEVERA, J., ZUKOV, I., MORCINEK, T., PAPEZOVA, H., Cholesterol concentrations in violent and non-violent women suicide attempters. *Eur. Psychiatry* **2003**, *18*, 23–27.
 - 157 KAPLAN, J. R., MANUCK, S. B., SHIVELY, C., The effects of fat and cholesterol on social behavior in monkeys. *Psychosom. Med.* **1991**, *53*, 634–642.
 - 158 NISHIGUCHI, N., SHIRAKAWA, O., ONO, H., NISHIMURA, A., NUSHIDA, H., UENO, Y., et al., Lack of an association between 5-HT1A receptor gene structural polymorphisms and suicide victims. *Am. J. Med. Genet.* **2002**, *114*, 423–425.
 - 159 NISHIGUCHI, N., SHIRAKAWA, O., ONO, H., NISHIMURA, A., NUSHIDA, H., UENO, Y., et al., No evidence of an association between 5HT1B receptor gene polymorphism and suicide victims in a Japanese population. *Am. J. Med. Genet.* **2001**, *105*, 343–345.
 - 160 TURECKI, G., SEQUEIRA, A., GINGRAS, Y., SEGUIN, M., LESAGE, A., TOUSIGNANT, M., et al., Suicide and serotonin: study of variation at seven serotonin receptor genes in suicide completers. *Am. J. Med. Genet.* **2003**, *118B*, 36–40.
 - 161 RUJESCU, D., GIEGLING, I., SATO, T., MOLLER, H. J., Lack of association between serotonin 5-HT1B receptor gene polymorphism and suicidal behavior. *Am. J. Med. Genet.* **2003**, *116B*, 69–71.
 - 162 HUANG, Y. Y., OQUENDO, M. A., FRIEDMAN, J. M., GREENHILL, L. L., BRODSKY, B., MALONE, K. M., et al., Substance abuse disorder and major depression are associated with the human 5-HT1B receptor gene (HTR1B) G861C polymorphism. *Neuropsychopharmacology* **2003**, *28*, 163–169.
 - 163 OHARA, K., NAGAI, M., TSUKAMOTO, T., TANI, K., SUZUKI, Y., OHARA, K., 5-HT2A receptor gene promoter polymorphism: 1438G/A and mood disorders. *Neuroreport* **1998**, *9*, 1139–1141.
 - 164 DU, L., FALUDI, G., PALKOVITS, M., DEMETER, E., BAKISH, D., LAPIERRE, Y. D., et al., Frequency of long allele in serotonin transporter gene is increased in depressed suicide victims. *Biol. Psychiatry* **1999**, *46*, 196–201.
 - 165 TSAI, S. J., HONG, C. J., HSU, C. C., CHENG, C. Y., LIAO, W. Y., SONG, H. L., et al., Serotonin-2A receptor polymorphism (102T/C) in mood disorders. *Psychiatry Res.* **1999**, *87*, 233–237.
 - 166 PREUSS, U. W., KOLLER, G., BAHLMANN, M., SOYKA, M., BONDY, B., No association between suicidal behavior and 5-HT2A-T102C polymorphism in alcohol dependents. *Am. J. Med. Genet.* **2000**, *96*, 877–878.
 - 167 CRAWFORD, J., SUTHERLAND, G. R., GOLDNEY, R. D., No evidence for association of 5-HT2A receptor polymorphism with suicide. *Am. J. Med. Genet.* **2000**, *96*, 879–880.
 - 168 BONDY, B., KUZNIK, J., BAGHAI, T., SCHULE, C., ZWANZGER, P., MINOV, C., et al., Lack of association of serotonin-2A receptor gene polymorphism (T102C) with suicidal ideation and suicide. *Am. J. Med. Genet.* **2000**, *96*, 831–835.

- 169 ONO, H., SHIRAKAWA, O., NISHIGUCHI, N., NISHIMURA, A., NUSHIDA, H., UENO, Y., et al., Serotonin 2A receptor gene polymorphism is not associated with completed suicide. *J. Psychiatr. Res.* **2001**, 35, 173–176.
- 170 ARIAS, B., GASTO, C., CATALAN, R., GUTIERREZ, B., PINTOR, L., FANANAS, L., The 5-HT (2A) receptor gene 102T/C polymorphism is associated with suicidal behavior in depressed patients. *Am. J. Med. Genet.* **2001**, 105, 801–804.
- 171 CORREA, H., DE MARCO, L., BOSON, W., VIANA, M. M., LIMA, V. F., CAMPI-AZEVEDO, A. C., et al., Analysis of T102C 5HT2A polymorphism in Brazilian psychiatric inpatients: relationship with suicidal behavior. *Cell Mol. Neurobiol.* **2002**, 22, 813–817.
- 172 CHONG, S. A., LEE, W. L., TAN, C. H., TAY, A. H., CHAN, A. O., TAN, E. C., Attempted suicide and polymorphism of the serotonin transporter gene in Chinese patients with schizophrenia. *Psychiatry Res.* **2000**, 97, 101–106.
- 173 GORWOOD, P., BATEL, P., ADES, J., HAMON, M., BONI, C., Serotonin transporter gene polymorphisms, alcoholism, and suicidal behavior. *Biol. Psychiatry* **2000**, 48, 259–264.
- 174 RUSS, M. J., LACHMAN, H. M., KASHDAN, T., SAITO, T., BAJMAKOVIC-KACILA, S., Analysis of catechol-O-methyltransferase and 5-hydroxytryptamine transporter polymorphisms in patients at risk for suicide. *Psychiatry Res.* **2000**, 93, 73–78.
- 175 FITCH, D., LESAGE, A., SEGUIN, M., TROUSIGNANT, M., BANKELFAT, C., ROULEAU, G. A., et al., Suicide and the serotonin transporter gene. *Mol. Psychiatry* **2001**, 6, 127–128.
- 176 RUJESCU, D., GIEGLING, I., SATO, T., MOELLER, H. J., A polymorphism in the promoter of the serotonin transporter gene is not associated with suicidal behavior. *Psychiatr. Genet.* **2001**, 11, 169–172.
- 177 BACA-GARCIA, E., VAQUERO, C., DIAZ-SASTRE, C., SAIZ-RUIZ, J., FERNANDEZ-PIQUERAS, J., DE LEON, J., A gender-specific association between the serotonin transporter gene and suicide attempts. *Neuropsychopharmacology* **2002**, 26, 692–695.
- 178 BAYLE, F. J., LEROY, S., GOURION, D., MILLET, B., OLIE, J. P., POIRIER, M. F., et al., 5HTTLPR polymorphism in schizophrenic patients: further support for association with violent suicide attempts. *Am. J. Med. Genet.* **2003**, 119B, 13–17.
- 179 COURTET, P., BURESI, C., ABBAR, M., BAUD, P., BOULENGER, J. P., CASTELNAU, D., et al., No association between non-violent suicidal behavior and the serotonin transporter promoter polymorphism. *Am. J. Med. Genet.* **2003**, 116B, 72–76.

12

Geriatric Depression

Bindu Shanmugham and George Alexopoulos

Abstract

Geriatric depression has a diverse etiology. The estimated prevalence of geriatric major depression is 1–2%. Depression occurs at higher rates among elders treated in medical settings. Depressive symptoms overlap with manifestations of medical and neurological disorders and pose a diagnostic challenge. Geriatric depression exacerbates medical morbidity and increases mortality. Elderly depressed patients are more likely to present with somatic or cognitive complaints when compared to the younger population.

Elderly individuals have the highest risk for suicide than any other age group. Suicidal ideation is a risk factor for suicide. Depressive symptoms may occur in the context of common stressors experienced by the elderly including socio-economic problems, medical illness or disability, and relocation to a long-term care facility. Adverse biological, psychological or social events can affect the timing, course and prognosis of the depression. The severity of disability follows the course of depressive symptoms.

Several geriatric depressive syndromes described in literature have guided treatment and prevention strategies as well as research on the mechanisms of depression. Clinical, as well as structural and functional neuroimaging studies suggest that dysfunction of frontostriatal-limbic neural systems contribute to the pathogenesis of late-life depressive syndromes. Cerebrovascular disease is a common cause of frontostriatal-limbic dysfunction. Knowledge of risk factors and periods of high risk for particular adverse outcomes can aid clinicians in selecting appropriate diagnostic methods and preventive treatments.

12.1

Introduction

Depression occurring in persons aged 60 years or older is referred to as geriatric depression. Geriatric depression refers to disorders ranging from clinically

significant depressive symptomatology to depressive syndromes defined according to the *Diagnostic and Statistical Manual of Mental Disorders*—Fourth edition (DSM-IV) criteria. This chapter reviews the epidemiology, clinical presentation, comorbidity, course and etiological theories of geriatric depression with attention to characteristics distinguishing it from depression occurring earlier in life.

12.2 Epidemiology

In the general elderly population the estimated prevalence of geriatric major depression is 1–2%. The prevalence of geriatric depression is estimated to be 1.4% in women and 0.4% in men. Depressive symptoms not meeting criteria for major depression occur in 15% of elderly persons [1]. A review of 34 studies of community-residing elders showed that the prevalence of depressive disorders varies from 0.4–35% [2]. Moreover a weighted average of the rates estimated the prevalence for major depression as 1.8%, minor depression as 9.8% and clinically significant depressive symptoms as 13.5% [2].

Depression occurs at higher rates in medical settings than in community settings thus suggesting that depression is associated with medical comorbidity. A review of the literature on mixed-aged patients in primary care settings identified clinically significant depressive symptomatology in 17–37% of the patients [3]. A study of elderly patients treated in a primary care setting showed that the prevalence of major depression was 6.5% and of minor depression was 5.2% [4]. Another study showed that about 9% of elderly primary care patients meet the criteria for major depression [5]. In a medical inpatient setting, 25% of the population had clinically significant depressive symptomatology and 11% had major depression [1]. The elderly in long-term care settings experience higher rates of depression when compared to the elderly in community settings. In nursing homes, the prevalence of major depression ranges from 12–22.4% and minor depression from 17–30% [6, 7]. In a study of the elderly living in public housing 26.6% of the elderly residents reported a lifetime prevalence of mood disorders [8]. The higher prevalence of depression in public housing-residing elders is only partly explained by socioeconomic stressors. In a home health care setting, 13.5% of elderly patients receiving care for medical or surgical problems were found to have major depression [9].

12.3 Clinical Presentation

Geriatric depressive disorders are defined according to the same DSM-IV diagnostic criteria used in younger adults. However, as DSM-IV criteria result in clinically heterogeneous groups, this section focuses on clinical characteristics relevant to geriatric depression. The classification of depressive syndromes per DSM-IV and ICD-10 are reviewed in Chapter 3.

12.3.1

Major Depressive Disorder

Elderly patients with major depression often present with more somatic features or cognitive complaints when compared to the younger population. Some of the somatic symptoms are changes in body weight, sleep pattern and appetite. Older depressed patients often deny having depressed mood and report a lack of feeling/emotion or acknowledge a loss of interest/pleasure in activities. “Depression without sadness” has been identified in elderly primary care populations and consists of apathy, loss of interest, fatigue, trouble sleeping, and other somatic symptoms, but not sad mood [10]. These symptoms may be accompanied by avoidance of social interactions as well as feelings of worthlessness, hopelessness or guilt as well as difficulties with concentration, making plans, and completing tasks. It is unclear whether and in what percentage of patients “depression without sadness” is an idiopathic depression, a depression secondary to medical illness, or a non-affective syndrome related to chronic medical disease.

The overlap of depressive symptoms with manifestations of medical and neurological disorders may interfere with the diagnosis of depression. Clinicians may dismiss depressive symptoms especially in elders with co-existing medical illnesses, dementing disorders or pronounced disability. Similarly, patients may attribute depressive symptoms to their other medical conditions. In an elderly population receiving home health care, only 22% of the elderly meeting criteria for major depression were identified and received treatment [9].

12.3.2

Major Depression with Psychotic Features

Psychotic depression, also known as Kraepelin’s melancholia gravis, occurs in 6.3% of elderly depressives living in the community [11] and in 20–45% of hospitalized elderly depressives [12]. Psychotic depression is a severe illness with profound depressive symptomatology accompanied by delusions and less frequently by hallucinations. The delusional themes are of guilt, hypochondriasis, nihilism, persecution and jealousy. Psychomotor retardation and/or agitation are more pronounced and frequent in psychotic compared to non-psychotic elderly depressives [13]. A study comparing delusional and non-delusional depression, found that the delusional depression group had a shorter duration of depression history, a higher number of vascular risk factors and was more frequently treated with electroconvulsive therapy [14]. The study identified a trend for more prevalence of deep white matter lesions in the delusional depression group.

Delusions occur in successive episodes of geriatric depression if the severity of episodes is high [13, 15]. However, in geriatric patients, psychotic depression is not merely a consequence of high severity of depression since high percentages of severely depressed elderly patients do not develop delusions [13, 15]. Psychotic depression poses a risk for suicide [16] usually with violent means [17]. For this reason, recognition and treatment of psychotic depression can be life saving.

12.3.3

Dysthymic Disorder

Dysthymic disorder is a depression of low severity that lasts 2 or more years. The DSM-IV diagnosis requires the presence of persistently depressed mood and at least two or more of the following symptoms: poor or increased appetite, increased or decreased sleep, low energy or fatigue, low self-esteem, poor concentration or difficulty in making decisions and feelings of hopelessness. The depressed mood and two other depressive symptoms need not be absent for more than 2 months in the 2-year period. In elderly patients, major depression, dysthymia and even clinically significant depressive symptomatology that does not meet criteria for a distinct depressive syndrome occur frequently in the context of neurological and medical disorders and pose diagnostic difficulties. Episodes of major depression are more likely to occur in dysthymic patients than in patients with subsyndromal depressive symptoms [18]. Since there are difficulties in identifying depressive features in the elderly, it is possible that dysthymia persists for long periods prior to diagnosis.

12.3.4

Adjustment Disorder with Depressed Mood

By DSM-IV criteria, adjustment disorder should be diagnosed when emotional or behavioral symptoms develop within 3 months of the occurrence of a stressor. Among older women, the effects of aging, mood and chronic life stress are interactive and may affect regulation of interleukin-6, a cytokine that is implicated in both the aging process and health problems such as osteoporosis [19]. Stressors commonly experienced by the elderly include socio-economic problems [20], development of new medical problems or disabilities, social isolation, and relocation to a long-term care facility [21, 22]. An involuntary relocation to a long-term care facility is often followed by a marked increase in the risk for medical morbidity and mortality [23]. However relocation can sometimes have a neutral or a beneficial effect. The morbidity and mortality risk is reduced if the elderly have control over the decision and move into a high quality institution [24].

12.3.4.1 **Caregiver Depression**

Older persons often have to care for family members who have developed a disability. Caregiving often leads to depressive symptoms or syndromes [25]. Depressive symptoms are twice as common among caregivers than non-caregivers [26], especially when care is provided for long periods of time [27]. Moreover, 25% of caregivers develop significant symptoms of depression following nursing home placement of the care recipient. Behavioral problems of the care recipient and limited help from family and friends predispose caregivers to symptoms of depression [28]. The course of caregiver depression remains relatively unchanged overtime in female caregivers but worsens in male caregivers [29].

Psychiatric symptoms related to caregiving often escape attention. Male caregivers under-report depression compared to female caregivers. Similarly, African American

caregivers report less depression and role strain than their white counterparts, although there was no interaction between race and caregiver distress [30]. Family education and involvement in the treatment of the depressed elderly can be useful approaches. Pharmacotherapy, psychotherapy, family intervention and support groups can be used effectively to address the emotional burden experienced by caregivers.

12.3.5

Depressive Disorder Not Otherwise Specified

Minor depression (three depressive symptoms according to DSM-IV) and subsyndromal depression are common in elderly populations and have adverse health consequences. About one-quarter of minor depression cases identified in a medical population, developed major depression within 2 years [31]. Minor depression is commonly the diagnosis of elderly suicide victims [32]. Subsyndromal depression has a point prevalence of 9.9% among elderly primary care patients [4]. Elderly individuals with subsyndromal depression had higher rates of functional disability and medical comorbidity when compared to the elderly individuals without depressive symptoms [4].

12.3.6

Dementing Disorders with Depressed Mood

Major depression and subsyndromal depression are both common in Alzheimer's disease. In a study of long-term care patients with dementia, the incidence of depression over a 1-year period was 6% [33]. The annual cumulative likelihood of depression for this population was 26.4%.

Among demented patients diagnosed with Alzheimer's disease, the point prevalence of major depression or depressive symptoms in Alzheimer's patients is about 17% [34]. About 23% of depressed Alzheimer's patients were found to have major depression [35]. In order to assist in diagnosis, provisional diagnostic criteria for depression in Alzheimer's disease were developed [36]. The criteria require both the diagnosis of dementia of the Alzheimer type and clinically significant depressive symptoms. Three or more depressive symptoms are sufficient as long as they have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms must be either depressed mood or decreased positive affect or pleasure. Depressive symptoms are: (1) depressed or sad mood, discouraged state, and tearfulness; (2) decreased positive affect or pleasure derived from social contacts and usual activities; (3) social isolation or withdrawal; (4) appetite disturbance; (5) sleep disturbance; (6) psychomotor agitation or retardation; (7) irritability; (8) fatigue; (9) ideational disturbances including worthlessness, hopelessness, or excessive or inappropriate guilt; (10) recurrent thoughts of death, suicidal ideation, plan or attempt. Symptoms due to a medical condition and non-affective dementia symptoms (e.g. loss of weight due to difficulties with food intake) should not be used in making the diagnosis of

depression in Alzheimer's disease. Clinical assessment should focus on the temporal associations between the onset and course of the depression and the dementia in order to establish that the depression is not better accounted for by an idiopathic depression, other mental disorders, other medical conditions, or adverse effects of medication.

12.4

Clinical Presentation of Non-DSM IV Syndromes

Several geriatric depressive syndromes have been described in the literature. These syndromes have not replaced the DSM-IV classification system but their clinical characteristics have guided treatment and prevention strategies as well as research focusing on the mechanisms of depression.

12.4.1

Late-onset Depression

Depression with the onset of the first episode in late-life includes a large subgroup of patients with neurological brain disorders [37]. The brain abnormalities are either identified prior to or after the diagnosis of depressive disorders. Patients with late-onset depression have higher rates of dementing disorders, hearing impairment, dementia development, large lateral brain ventricles, white matter hyperintensities, poor performance on neuropsychological tests and lower rates of family history of mood disorders than elderly patients with early onset depression.

Findings on late-onset depression have guided research on the role of neurological abnormalities in the development of depression. However, there are two important limitations in using the onset of depression as the principal clinical feature identifying depressive syndromes resulting from aging-related brain abnormalities. First, the onset of depression is difficult to identify, especially in patients whose early episodes are of mild severity [38]. Second, a depressive episode occurring in late life may be due to aging-related brain changes even in patients with depressive episodes in early life. Indeed, early-onset depression may contribute to brain abnormalities by reducing neurotrophic factor secretion, and ultimately decreasing neurogenesis [39]. Therefore, in some cases early-onset depression may predispose individuals to depressive syndromes contributed to by aging-related abnormalities later in life.

12.4.2

Depression-executive Dysfunction Syndrome

Studies using diverse methodology suggest that dysfunction of frontostriatal-limbic neural systems contribute to the pathogenesis of late-life depressive syndromes. Frontostriatal dysfunction often results in impairment of executive cognitive functions. In depressed elders with executive impairment, executive functions usually improve to some extent after amelioration of depressive symptoms, but do

not reach normal levels [40]. Based on such findings, it was proposed that a “depression-executive dysfunction” syndrome exists and that this syndrome has a distinct clinical presentation with poor short-term and long-term outcomes [41]. Later studies have shown that the depression-executive dysfunction syndrome is characterized by psychomotor retardation, reduced interest in activities, disability disproportional to the severity of depression, and a rather mild vegetative syndrome. There is evidence that the syndrome has a poor or slow response to antidepressants [42] and early relapse and recurrence [43]. In contrast, a recent study showed that the syndrome responds well to problem-solving therapy modified to remedy the behavioral deficits resulting from both depression and executive dysfunction [44].

12.4.3

Depression with Reversible Dementia

A syndrome of dementia may develop during episodes of geriatric depression and subside after the resolution of depression. Commonly referred to as “pseudodementia”, this dementia syndrome has also been described as dementia of depression and depression with reversible dementia and mainly occurs in patients with late-onset depression [45]. Depressed elderly patients in whom some cognitive impairment remains even after improvement of depression, usually have an early stage dementing disorder whose cognitive manifestations are exaggerated when the depressive syndrome is superimposed. It appears that even patients with more or less complete cognitive recovery have high rates of irreversible dementia (about 40% within 3 years) on follow-up. Most of these patients do not meet criteria for dementia for 1 to 2 years after the initial episode of depression with reversible dementia [46]. Therefore, identification of a “reversible dementia” syndrome in elderly depressives constitutes an indication for thorough diagnostic work-up aimed at the identification of treatable dementing disorders and frequent follow-up.

12.4.4

Depression without Sadness

The term “depression without sadness” has been proposed to describe depression in which depressed mood is not a prominent symptom [10]. There is evidence that “depression without sadness” occurs principally in elderly populations. Individuals aged 65 years and older were less likely to report sadness or dysphoria compared to persons aged 64 years or younger [47]. However some other studies have shown no difference in the complaint of sadness by the elderly versus those in mid-life [48, 49].

12.4.5

Vascular Depression

Cerebrovascular disease and risk factors as well as ischemic brain lesions have been associated with the development of depression. Based on these observations,

the “vascular depression” hypothesis has been proposed, which postulates that cerebrovascular disease predisposes, precipitates or perpetuates some geriatric depressive syndromes [50, 51]. The clinical presentation of vascular depression is characterized by apathy, retardation, and pronounced functional disability, while agitation and feelings of guilt are less pronounced. Elderly patients with vascular depression have greater overall cognitive impairment than the non-vascular depression group [50, 51]. Executive functions are disproportionately impaired. Two mechanisms were proposed as the pathophysiological basis of vascular depression: (1) single lesions disrupting critical frontostriatal-limbic pathways, and (2) an accumulation of lesions exceeding a threshold.

12.4.6

Spousal Bereavement

Loss of a spouse commonly occurs in late life and leads to depressive symptoms or syndromes. Approximately 10–20% of persons who experience spousal bereavement develop clinically significant depressive symptoms during the ensuing year. There is a difference between older and younger individuals in that the elderly are at lower risk for developing depressive symptoms during the first months of widowhood. However, the rates of depression continue to increase in the older individuals and at the end of 2 years both older and younger individuals have similar rates of major depression [52]. In fact, the prevalence of major depression continues to increase during the second year of bereavement [52]. At the end of the second year after the loss of a spouse, 14% of the bereaved individuals have major depression, a percentage much higher than the 1% prevalence of major depression in the elderly community population. If left untreated, the depression frequently persists [53]. Bereaved elderly individuals with depressive symptomatology that does not meet criteria for major depression have compromised function and impaired quality of life.

12.5

Comorbidity

Geriatric depressive disorders and subsyndromal depressive states commonly occur in the context of medical and neurological disorders. Attention to the medical and neurological comorbidity of geriatric depression is important because depression exacerbates the medical morbidity and increases mortality.

12.5.1

Medical Illness

Geriatric depression has a reciprocal relationship with medical morbidity. Depression often occurs in elders with significant medical burden. It promotes medical morbidity, worsens the outcome of medical illnesses, and increases mortality [54].

Epidemiological and clinical studies suggest that medical burden is associated with high prevalence of depression. Major depression affects 1–2% of community-residing elders, while the prevalence of major depression ranges from 6 to 12% in medical patient populations and in nursing home residents [4, 9, 55]. A clinical study showed that patients with any medical diagnosis were twice as likely to have depression than patients without a medical diagnosis [56]. The total mean number of medical diagnoses in depressed patients was 7.9 compared to 3.0 medical diagnoses in non-depressed patients.

Besides predisposition to depression conferred by overall medical burden, some medical illnesses are more likely to contribute to depression than others. Vascular diseases are among them. A meta-analysis showed that on average 14% of diabetic patients suffer from depression [57]. Stroke victims also experience high rates of depression. Localization of lesions at the left frontal pole or the basal ganglia is associated with the highest incidence of depression [58]. Post-stroke sequelae can further influence the course of depression. Depression occurring in the context of cancer, thyroid status and heart disease is addressed in other chapters of this book.

Depression increases medical morbidity. Among the psychiatric symptoms of late life, chronic depressive symptoms are associated with the highest medical morbidity compared with other psychiatric disorders of late life [59]. Chronic depressive symptoms have an adverse impact on medical health in older community residents, while medical burden contributes only to short-lived depressive symptoms [60]. In elderly medical inpatients, those with six depressive symptoms had greater comorbid illness, cognitive impairment, and functional impairment [61].

Depression worsens the prognosis of comorbid medical illnesses. Depression is associated with prolonged medical recovery, increased medical complications, long hospitalization, and higher mortality [62]. Depressed elderly primary-care patients had more than twice the number of hospital days over the expected length of stay compared to non-depressed patients [63]. Depressed medical patients stay in bed more days compared to patients with chronic diseases, such as chronic lung disease, diabetes, arthritis and hypertension [64]. Among patients hospitalized after hip fractures, those with depressive and cognitive symptoms had poorer functional recovery 1 year after discharge than those who did not [65]. Depression after surgery has been associated with poorer recovery in both functional and psychosocial status [66].

Depression increases mortality. Increased mortality risk has been reported in depressed compared to non-depressed medical and psychiatric patients [67–69]. In medically hospitalized patients, depression increased mortality even when the severity of medical illnesses and disability is controlled [61]. Similarly, depression increased mortality in institutionalized elders [70]. Presence of major depression on admission to a nursing home leads to a 59% increase in mortality during the first year of institutionalization [71].

12.5.2

Cognitive Impairment

Depressed elders often present with cognitive impairment. The cognitive impairment is characterized by disturbances in attention, speed of mental processing and executive function and may not be severe enough to be called dementia [72, 73]. The deficits in working memory and speed of mental processing can persist even after the remission of the depression [74, 75]. The cognitive impairment of depressed elders may be an expression of aging-related brain changes or dementing disorders at a preclinical stage [37]. Cognitive impairment occurring in the context of geriatric depression is a risk factor for later development of irreversible or progressive dementing disorders. Moreover, impairment of executive functions may be associated with poor short- and long-term outcomes of the depressive syndrome. In a mixed age population severity of cognitive impairment was correlated with mortality [76].

12.5.3

Disability

The World Health Organization defined disability as problems in self-care, household activities, getting around, understanding and communicating, getting along with others, and participating in society. Depression is the second most common cause of disability in the United States [77]. Depression directly confers disability in medically healthy elderly individuals [78]. Depression may lead to disability indirectly by exacerbating medical morbidity. Finally, medical or neurological illnesses accompanied by disability are a risk factor for late-life depression, which in turn exacerbates disability.

In elderly populations, disability often has been divided into two categories: (1) impairment in self-care functions (ability to eat, dress, groom, bathe, use the toilet and ambulate), and (2) impairment in instrumental activities of daily living (IADL), including ability to go to places out of walking distance, shop for groceries, prepare meals, do housework, launder clothes, use the telephone, take medications, and manage money. Among older depressed adults, impairment in self-care was associated with advanced age, medical burden, psychomotor retardation and inadequate subjective social support, while depressed mood had a lower impact [79, 80]. In contrast the IADLs were significantly influenced by depressive symptoms and signs [79, 80].

Some depressive symptoms and not others may have a pronounced influence on IADL impairment. Severity of depression, cognitive impairment, and medical burden, appear to predict approximately 40% of the variance in instrumental activities of daily living [80]. Among elderly patients with major depression, IADL impairment is associated with anxiety, depressive ideation, apathy, psychomotor retardation, and weight loss but less pathological guilt [79, 80]. Similar findings have been reported in older community residents, in whom IADL impairment was correlated with dysphoria, sleep disturbance, appetite disturbance, feelings of guilt, death wishes and suicidal thoughts, loss of interest, concentration difficulties,

psychomotor change and loss of energy [81]. Cognitive impairment and in particular executive dysfunction, has a strong relationship to IADL impairment in depressed elderly patients [80, 82, 83].

The severity of disability follows the course of depressive symptoms. Residual depressive symptomatology parallels the course disability over time [84, 85]. Reduction in severity of depression leads to reduction in days burdened by disability by 50% over a period of 1 year [85]. In depressed medically ill patients, antidepressant treatment can improve disability without changing the physiologic measures of the underlying medical illness [86].

12.6

Course of Illness

Knowledge of risk factors and periods of high risk for particular adverse outcomes enable the clinician to use appropriate diagnostic methods and offer preventive treatments with favorable benefit to risk ratios. Despite advances in antidepressant therapies, a recent meta-analysis suggests that among community-residing depressed elders 33% remain depressed, 33% are well and 21% die during a 2-year follow-up [87]. Physical illness, disability, cognitive impairment, and more severe depression are associated with worse outcomes.

Dementia is not an outcome of depression among intact elderly patients. However, a large proportion of geriatric depressives have cognitive dysfunction or dementia. The large percentage of elderly depressives with evidence of brain disease suggests that it is clinically meaningful to examine predictors of dementia in these populations. With some exceptions, recent follow-up data observed that elderly depressives who initially had “reversible dementia” develop permanent dementia at a rate of 9–25% per year [46]. Presence of an initially “reversible dementia” leads to a yearly rate of irreversible dementia 2.5 to 6 times higher than that of the general geriatric population. In non-demented depressives late age of depression onset and cortical brain atrophy were significant predictors of development of dementia over a 38-month average follow-up period.

12.6.1

Chronicity

Despite advances in antidepressant treatment, longitudinal studies of 1 to 6 years duration suggest that 7–30% of geriatric patients have a chronic major depression [88]. If partially remitted subjects are considered chronic, the rate of chronicity reaches 40%. Even patients who have achieved remission can still experience some residual symptoms. At the end of 9 months of treatment, 82.3% of geriatric depressives who achieved remission still had one or more residual symptoms [89]. Chronicity of depression may be predicted by history of a long current episode or long previous episodes, co-existing medical illness, high severity of depression, non-melancholic presentation, and delusions. Executive dysfunction [42, 90] and

white matter hyperintensities [90–92] have been associated with chronicity of geriatric depression. These findings suggest that frontostriatal dysfunction influences the clinical course of geriatric depression as executive dysfunction is a clinical expression of frontostriatal pathway impairment, and frontostriatal impairment is often associated with subcortical white matter lesions.

12.6.2

Relapse and Recurrence

Uncontrolled treatment studies suggest that 13–19% of depressed elderly patients who achieve remission have a relapse or a recurrence 1 year later, while a 15% relapse rate is observed in patients receiving controlled antidepressant treatment [88]. This percentage is lower than the 34% relapse/recurrence rate reported in younger adults. However, during 3- to 6-year longitudinal observations, the recurrence rate of depressed elders is 38%. Finally, 95% of mixed age depressed patients experience a recurrence if the observation period is extended to 20 years. Some of the predictors of relapse and recurrence are different from the predictors of remission. The likelihood of relapse/recurrence is high in patients with a history of frequent episodes, late age of illness onset, history of dysthymia, intercurrent medical illness, and possibly high severity and chronicity of the index depressive episode. There is some evidence that executive dysfunction is a predictor of early relapse and recurrence of geriatric major depression [43].

12.6.3

Dementia

Dementia may precede, co-exist with or follow depression. The relationship of depression to dementia may be specific as patients with mood disorders are more likely to develop dementia than medical illnesses like diabetes and osteoarthritis [93]. Depressive symptoms were associated with cognitive impairment (Mini-Mental State Examination, Trails B, Digit Symbol) at baseline and with cognitive decline 4 years later [94]. In another study, depressive symptoms, and depressed mood in particular, predicted cognitive decline during a 3-year follow-up [95]. Depressed mood was associated with development of dementia 5 years later [96]. In individuals with sub-clinical cognitive dysfunction, those who developed dementia 3 years later had more depressive symptoms. As subjects were progressing to dementia, they exhibited fewer affective symptoms and more agitation and psychomotor slowing. These changes paralleled reduction of cerebral blood flow in the left temporal region. [97]. Among 142 elderly twins, those without an APOE4 allele and late-onset depression had 2.95 times higher risk for Alzheimer's disease than those without a history of depression [98]. These findings suggest that depressive symptoms are often a prodrome of dementing disorders.

There is some evidence that depression is a risk factor for dementing disorders. A meta-analysis showed that depression with onset more than 10 years before the diagnosis of dementia was found to be associated with onset of Alzheimer's disease

at any age [67]. More recent studies suggest that a history of depression increases the risk of Alzheimer's disease, regardless of presence or absence of a family history of dementing disorders [99]. Furthermore, depressive symptoms occurring more than 10 years before the onset of dementia represents a risk factor for Alzheimer's disease [100].

12.6.4

Mortality

Depression increases mortality rates among community-dwelling elderly [101]. Even after controlling for medical illness and disability, depressed hospitalized patients had higher mortality rates than patients without significant depression [61]. Nursing home patients who met criteria for major depression at the time of admission had a 59% increased likelihood of death [71]. In a prospective follow-up of depressed persons with a mean age of 67.2 years, mortality was associated with factors such as male gender, advanced age, and late age of depression onset. The relationship of baseline depressive symptoms to mortality was stronger among men than among women. Vascular risk factors and late onset of depression were strong predictors of mortality among women.

12.6.5

Suicide

Elderly individuals as a group are more at risk for suicide than any other age group. In 2000, the suicide rate for the elderly was 15.3% as opposed to 10.7% of the general United States population [102]. Suicide rates of older Americans are twice that of younger Americans. In intra-group comparisons of the elderly, older white men lead with a rate of 43.5/100 000, followed by non-white men at 15.7/100 000, white women at 6.3/100 000 and non-white women at 2.8/100 000 [103]. While elderly men have the highest suicide rate among all male age groups, the suicide rate of elderly women peaks in middle age and declines later [103, 104].

The suicide rate for persons aged 65 years and older decreased from 20.5% in 1990 to 15.3% in 2000 [102]. The frequency of suicide attempts and suicidal ideation in the elderly is lower than that of the young. However the ratio of completed suicides to suicide attempts is 1 : 4 in the elderly compared to 1 : 100–200 in younger adults. [102]. It appears that older adults carefully plan their suicide, do not share their suicidal ideation and use lethal means [105, 106].

Suicide attempters have different demographic characteristics and use different means for suicide than those who commit suicide [102]. While 60% of those who commit suicide are men, about 75% of those who attempt suicide are women. Those who commit suicide use more lethal means such as guns or hanging and 72.9% of the suicides among the elderly used firearms. Those who attempt suicide unsuccessfully commonly overdose on medications or slash themselves.

Suicidal ideation is a risk factor for suicide. The rate of suicidal ideation is lower in the elderly than in the young [107, 108]. However suicidal ideation has a higher

sensitivity and predictive value in geriatric psychiatric outpatients than in younger outpatients. Suicidal ideation in younger psychiatric outpatients showed a 53% sensitivity and 4.2% predictive value [109] whereas in geriatric psychiatric outpatients it had a higher sensitivity of 80% and a higher predictive value of 5.6%.

12.7 Etiology

Geriatric depression has a diverse etiology. Patients may have depressive symptoms in the prodromal phase for many years before adverse events exacerbate the prodrome to a syndromal phase. Adverse biological, psychological or social events can affect the timing, course and prognosis of the depression.

12.7.1 Biological Factors

Dysfunction in corticostriatal neural systems and their limbic connections contribute to the development of some geriatric depressive syndromes [110]. In support of this view, are observations relating dysfunction of these structures to depressive symptoms. Of the five cortico–striato–pallido–cortical pathways described originally by Alexander [111], three pathways, when disrupted, result in behavioral abnormalities reminiscent of depressive manifestations. Disruption of the orbitofrontal pathway leads to disinhibition, irritability and decreased sensitivity to social cues. Impairment of the anterior cingulate pathway results in apathy and decreased initiative. Dorsolateral pathway disruption can lead to cognitive impairment principally expressed as difficulties with set shifting, learning and word list generation.

Patients with disorders affecting the basal ganglia and their frontal and limbic connections often develop depression [112]. Ischemic lesions in the basal ganglia and frontal projections are correlated with a high incidence of depression [113]. Patients with basal ganglia disorders develop executive dysfunction that is similar to the executive abnormalities identified in geriatric depression [114].

Structural imaging studies identified abnormalities in the frontostriatal-limbic pathways of elders suffering from depression. White matter hyperintensities commonly occur in the frontal projections of the subcortical structures in depressed elders [51, 115–117]. White matter abnormalities have been correlated with executive dysfunction [116]. In patients with familial major depression, there was decreased subgenual anterior cingulate volume, a structure of the limbic system [118].

Neuropathological studies in depressed patients showed a reduction in the glia in the subgenual prelimbic anterior cingulate gyrus [119, 120]. Neuronal abnormalities in the dorsal prefrontal cortex have also been identified in depressed patients [119, 121].

Findings of functional neuroimaging studies support the role of subcortical-limbic structures in the pathogenesis of depression. Abnormal metabolism in the

subgenual anterior cingulate, amygdala, and posterior orbital cortex has been associated with depression [122]. Severely depressed elderly patients performing a word activation task had reduced bilateral activation of the dorsal anterior cingulate and the hippocampus [123]. When performing a Stroop interference task, younger patients with mood disorders had a blunted activation of the left anterior cingulate and minimal activation of the right anterior cingulate gyrus [124].

Changes in frontostriatal-limbic function influence the course of depression. Depression is associated with increased metabolism in limbic regions and reduced metabolism in the lateral and dorsolateral prefrontal cortex, the dorsal anterior cingulate, and the caudate regions [125]. During remission of depression, these abnormalities are reversed [122, 126–129]. Hypometabolism of rostral anterior cingulate is associated with treatment resistance [130]. There is evidence that disruption in the regulation of dorsal cortical and ventral limbic areas influences the response to antidepressants. A preliminary diffusion tensor imaging study showed microstructural abnormalities in the white matter lateral to the anterior cingulate in patients with depression and executive dysfunction [131]. It has been proposed that this area is critical for the reciprocal regulation between ventral limbic and dorsal neocortical structures.

The etiology of frontostriatal-limbic dysfunction in geriatric depression may be multifactorial. In some patients, the presence of vascular lesions in the perforating artery territory is the principal cause of frontostriatal-limbic dysfunction. In others, inhibition of neurogenesis has been hypothesized to contribute to dysfunction of the hippocampus and its frontostriatal connections. Inhibition of neurogenesis may result from hypercortesolemia occurring during depressive episodes and may lead to hippocampal atrophy [132, 133]; it has been documented that the presence of high levels of stress-related hormones may decrease neurotrophic factor secretion and thus effect neural growth [39]. Animal studies have shown preliminary evidence linking antidepressant usage to hippocampal neurogenesis [134]. Treatment with fluoxetine has been shown to reverse the decrease in neural cells [135] and neurogenesis has been proposed to be a mechanism of antidepressant action [136].

12.7.2

Social Factors

Social factors increase the risk of depression [137]. The prevalence of depressive symptoms appeared to be lower in affluent older communities than prevalence estimates of depression in non-affluent older populations [20]. Lack of acculturation and loss of traditional roles can lead to loneliness and depression among ethnic elders [138]. Older persons who have experienced a large number of negative life events in the previous year have a wide range of depressive symptoms [22]. Advanced age, history of depression, death of a spouse, health-related factors, and comorbid anxiety are all associated with late-life depression [139, 140]. Depressive symptoms often occur in the context of poor physical health, physical disability and social isolation [21]. Spousal bereavement increases the risk for depressive symptoms and syndromes. Identified risk factors for depression post bereavement include

pre-bereavement depression, financial pressures, global stress, and fewer social supports [141]. Nortriptyline alone or in combination with interpersonal psychotherapy was found to be more effective than placebo in bereavement-related major depression [142].

Social support, defined as instrumental support, tangible/instrumental assistance, emotional support, esteem support, and social integration, is both a “vulnerability” and a “protective” factor for depression in later life. High levels of social support identified in persons with late-life depression [143, 144] may be due to an increased need for support rather than a cause of depressive symptoms [22]. Social support has also been shown to moderate the effects of pain, functional limitations, and depression on patients’ quality of life [145]. Social support may buffer the adverse effects of stressors [146], of which undesired/unscheduled (non-normative) life events are the most stressful.

Social support may influence the treatment outcomes of depression [137]. Among elders who underwent treatment based on a standardized algorithm, those who reported a lower subjective social support at baseline were less likely to be in remission from depression 1 year later [147]. Having a marital partner, and if unmarried, having social support significantly reduces the impact of stress on the incidence of depression.

12.8

Conclusion

A large literature suggests that depressive disorders of late life are biologically heterogeneous and are contributed by a multitude of clinical and social factors. The clinical manifestation of geriatric depression often overlaps with symptoms of medical comorbidity, cognitive impairment and disability. Effective treatment planning has to rely on a comprehensive analysis of contributors to the development of depression in an individual patient and of factors influencing antidepressant response, relapse, recurrence, risk of suicide, disability and increased medical morbidity.

In geriatric depression treatment approaches aim for (1) improvement of cognitive and functional status, and (2) development of skills needed for coping with psychosocial stressors. The goals of treatment for late-life depression include reduction of depressive symptoms and suicidal ideation, and the prevention of relapse and recurrence.

Treatment of depression is discussed in detail elsewhere in this volume. We hope, however, that the above review will function as a conceptual guide to treatment strategies for elders suffering from depression.

References

- 1 NIH CONSENSUS CONFERENCE, Diagnosis and treatment of depression in late life. *JAMA* **1992**, *268*, 1018–1024.
- 2 BEEKMAN, A. T., COPELAND, J. R., PRINCE, M. J., Review of community prevalence of depression in later life. *Br. J. Psychiatry* **1999**, *174*, 307–311.
- 3 ALEXOPOULOS, G. S., Geriatric depression in primary care. *Int. J. Geriatr. Psychiatry* **1996**, *11*, 397–400.
- 4 LYNES, J. M., KING, D. A., COX, C., YOEDIONO, Z., CAINE, E. D., The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. *J. Am. Geriatr. Soc.* **1999**, *47*, 647–652.
- 5 OXMAN, T. E., BARRETT, J. E., BARRETT, J., GERBER, P., Symptomatology of late-life minor depression among primary care patients. *Psychosomatics* **1990**, *31*, 174–180.
- 6 BURROWS, A. B., SATLIN, A., SALZMAN, C., NOBEL, K., LIPSITZ, L. A., Depression in a long-term care facility: Clinical features and discordance between nursing assessment and patient interviews. *J. Am. Geriatr. Soc.* **1995**, *43*, 1118–1122.
- 7 KATZ, I. R., PARMELEE, P. A., STREIM, J. E., Depression in older patients in residential care: Significance of dysphoria and dimensional assessment. *Am. J. Geriatr. Psychiatry* **1995**, *3*, 161–169.
- 8 RABINS, P. V., BLACK, B., GERMAN, P., et al., The prevalence of psychiatric disorders in elderly residents of public housing. *J. Gerontol. A Biol. Sci. Med. Sci.* **1996**, *51*, M319–M324.
- 9 BRUCE, M. L., McAVAY, G. J., RAUE, P. J., et al., Major depression in elderly home health care patients. *Am. J. Psychiatry* **2002**, *159*, 1367–1374.
- 10 GALLO, J. J., RABINS, P. V., Depression without sadness: Alternative presentations of depression in late life. *Am. Family Physician* **1999**, *60*, 820–826.
- 11 KIVELA, S. L., PAHKALA, K., Hallucinatory depression in the elderly: a community study. *ZFA* **1988**, *43*, 331–339.
- 12 MEYERS, B. S., Late-life delusional depression: Acute and long-term treatment. *Int. Psychogeriatr.* **1995**, *7* (Suppl.), 113–124.
- 13 BALDWIN, R. C., Delusional and non-delusional depression in late life. Evidence for distinct subtypes. *Br. J. Psychiatry* **1988**, *152*, 39–44.
- 14 O'BRIEN, J. T., AMES, D., SCHWEITZER, I., DESMOND, P., COLEMAN, P., TRESS, B., Clinical, magnetic resonance imaging and endocrinological differences between delusional and non-delusional depression in the elderly. *Int. J. Geriatr. Psychiatry* **1997**, *12*, 211–218.
- 15 SANDS, J. R., HARROW, M., Psychotic unipolar depression at follow-up: factors related to psychosis in the affective disorders. *Am. J. Psychiatry* **1994**, *151*, 995–1000.
- 16 ROOSE, S. P., GLASSMAN, A. H., WALSH, B. T., WOODRING, S., VITAL-HERNE, J., Depression, delusions, and suicide. *Am. J. Psychiatry* **1983**, *140*, 1159–1162.
- 17 ISOMETSA, E., HENRIKSSON, M., ARO, H., HEIKKINEN, M., KUOPPASALMI, K., LONNQVIST, J., Suicide in psychotic major depression. *J. Affect Disord.* **1994**, *31*, 187–191.
- 18 MURPHY, J. M., NIERENBERG, A. A., LAIRD, N. M., MONSON, R. R., SOBOLE, A. M., LEIGHTON, A. H., Incidence of major depression: prediction from subthreshold categories in the Stirling County Study. *J. Affect Disord.* **2002**, *68*, 251–259.
- 19 LUTGENDORF, S. K., GARAND, L., BUCKWALTER, K. C., REIMER, T. T., HONG, S. Y., LUBAROFF, D. M., Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. *J. Gerontol. A Biol. Sci. Med. Sci.* **1999**, *54*, M434–M439.
- 20 WILSON, K. C., CHEN, R., TAYLOR, S., MCCracken, C. F., COPELAND, J. R., Socio-economic deprivation and the prevalence and prediction of depression in older community residents. The MRC-ALPHA Study. *Br. J. Psychiatry* **1999**, *175*, 549–553.
- 21 WEST, C. G., REED, D. M., GILDENGORIN, G. L., Can money buy happiness? Depressive symptoms in an affluent older population. *J. Am. Geriatr. Soc.* **1998**, *46*, 49–57.
- 22 HAYS, J. C., LANDERMAN, L. R., GEORGE, L. K., et al., Social correlates of the

- dimensions of depression in the elderly. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **1998**, *53*, P31–P39.
- 23 PARMELEE, P. A., KATZ, I. R., LAWTON, M. P., Depression among institutionalized aged: Assessment and prevalence estimation. *J. Gerontology* **1989**, *44*, M22–M29.
 - 24 ARMER, J., Elderly relocation to a congregate setting: Factors influencing adjustment. *Issues Mental Health Nurs.* **1993**, *14*, 157–172.
 - 25 GALLANT, M. P., CONNELL, C. M., Predictors of decreased self-care among spouse caregivers of older adults with dementing illnesses. *J. Aging Health* **1997**, *9*, 373–395.
 - 26 BAUMGARTEN, M., BATTISTA, R. N., INFANTE-RIVARD, C., HANLEY, J. A., BECKER, R., GAUTHIER, S., The psychological and physical health of family members caring for an elderly person with dementia. *J. Clin. Epidemiol.* **1992**, *45*, 61–70.
 - 27 COLLINS, C., STOMMEL, M., WANG, S., GIVEN, C. W., Caregiving transitions: changes in depression among family caregivers of relatives with dementia. *Nurs. Res.* **1994**, *43*, 220–225.
 - 28 CLYBURN, L. D., STONES, M. J., HADJISTAVROPOULOS, T., TUOKKO, H., Predicting caregiver burden and depression in Alzheimer's disease. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **2000**, *55*, S2–S13.
 - 29 SCHULZ, R., WILLIAMSON, G. M., A 2-year longitudinal study of depression among Alzheimer's caregivers. *Psychol. Aging* **1991**, *6*, 569–578.
 - 30 FARRAN, C. J., MILLER, B. H., KAUFMAN, J. E., DAVIS, L., Race, finding meaning, and caregiver distress. *J. Aging Health* **1997**, *9*, 316–333.
 - 31 KATON, W., SCHULBERG, H., Epidemiology of depression in primary care. *Gen. Hosp. Psychiatry* **1992**, *14*, 237–242.
 - 32 CONWELL, Y., Suicide in the elderly. In: *Diagnosis and Treatment of Depression in Late Life. Results of the NIH Consensus Development Conference*, SCHNEIDER, L. S., REYNOLDS, C. F., LEBOWITZ, B. D., FRIEDHOFF, A. J. (Eds.). Washington DC: American Psychiatric Press, **1994**, pp. 397–418.
 - 33 PAYNE, J. L., SHEPPARD, J. M., STEINBERG, M., et al., Incidence, prevalence, and outcomes of depression in residents of a long-term care facility with dementia. *Int. J. Geriatr. Psychiatry* **2002**, *17*, 247–253.
 - 34 WRAGG, R. E., JESTE, D. V., Overview of depression and psychosis in Alzheimer's disease. *Am. J. Psychiatry* **1989**, *146*, 577–589.
 - 35 MIGLIORELLI, R., TESON, A., SABE, L., PETRACCHI, M., LEIGUARDA, R., STARKSTEIN, S. E., Prevalence and correlates of dysthymia and major depression among patients with Alzheimer's disease. *Am. J. Psychiatry* **1995**, *152*, 37–44.
 - 36 OLIN, J. T., SCHNEIDER, L. S., KATZ, I. R., et al., National Institute of Mental Health – Provisional Diagnostic Criteria for Depression of Alzheimer Disease. *Am. J. Geriatr. Psychiatry* **2002**, *10*, 125–128.
 - 37 ALEXOPOULOS, G. S., *Clinical and Biological Findings in Late-Onset Depression*. TASMAN, A., GOLDFINGER, S. M., KAUFMANN, C. A. (Eds.). Washington DC: American Psychiatric Press Review of Psychiatry, Vol. 9, **1990**.
 - 38 WIENER, P., ALEXOPOULOS, G. S., KAKUMA, T., MEYERS, B. S., ROSENTHAL, E., CHESTER, J., The limits of history-taking in geriatric depression. *Am. J. Geriatr. Psychiatry* **1997**, *5*, 116–125.
 - 39 DUMAN, R. S., HENINGER, G. R., NESTLER, E. J., A molecular and cellular theory of depression. *Arch. Gen. Psychiatry* **1997**, *54*, 597–606.
 - 40 LOCKWOOD, K. A., ALEXOPOULOS, G. S., VAN GORP, W. G., Executive dysfunction in geriatric depression. *Am. J. Psychiatry* **2002**, *159*, 1119–1126.
 - 41 ALEXOPOULOS, G. S., The depression-executive dysfunction syndrome of late life: A target for D3 receptor agonists. *Am. J. Geriatr. Psychiatry* **2001**, *9*, 1–8.
 - 42 KALAYAM, B., ALEXOPOULOS, G. S., Prefrontal dysfunction and treatment response in geriatric depression. *Arch. Gen. Psychiatry* **1999**, *56*, 713–718.
 - 43 ALEXOPOULOS, G. S., MEYERS, B. S., YOUNG, R. C., et al., Executive dysfunction and long-term outcomes of geriatric depression. *Arch. Gen. Psychiatry* **2000**, *57*, 285–290.
 - 44 ALEXOPOULOS, G. S., RAUE, P., AREAN, P., Problem-solving therapy versus

- supportive therapy in geriatric major depression with executive dysfunction. *Am. J. Geriatr. Psychiatry* 2003, 11, 46–52.
- 45 ALEXOPOULOS, G., YOUNG, R., MEYERS, B., Geriatric depression: Age of onset and dementia. *Biol. Psychiatry* 1993, 34, 141–145.
 - 46 ALEXOPOULOS, G. S., MEYERS, B. S., YOUNG, R. C., MATTIS, S., KAKUMA, T., The course of geriatric depression with “reversible dementia”: A controlled study. *Am. J. Psychiatry* 1993, 150, 1693–1699.
 - 47 GALLO, J. J., ANTHONY, J. C., MUTHEN, B. O., Age differences in the symptoms of depression: a latent trait analysis. *J. Gerontol.* 1994, 49, P251–P264.
 - 48 BLAZER, D. G., GEORGE, L., LANDERMAN, R., The phenomenology of late life depression. In: *Psychiatric Disorder of the Elderly*, BEBBINGTON, P. E., JACOBY, R. (Eds.). London: Mental Health Foundation, 1984, pp. 143, 152.
 - 49 BLAZER, D. G., BACHAR, J. R., HUGHES, D. C., Major depression with melancholia: a comparison of middle-aged and elderly adults. *J. Am. Geriatr. Soc.* 1987, 35, 927–932.
 - 50 ALEXOPOULOS, G. S., MEYERS, B. S., YOUNG, R. C., KAKUMA, T., SILBERSWEIG, D., CHARLSON, M., Clinically defined vascular depression. *Am. J. Psychiatry* 1997, 154, 562–565.
 - 51 KRISHNAN KRR, HAYS, J. C., BLAZER, D. G., MRI-defined vascular depression. *Am. J. Psychiatry* 1997, 154, 497–500.
 - 52 ZISOOK, S., SCHUCHTER, S. R., SLEDGE, R., Diagnostic and treatment considerations in depression associated with late-life bereavement. In: *Diagnosis and Treatment of Depression in Late Life. Results of the NIH Consensus Development Conference*, SCHNEIDER, L. S., REYNOLDS, C. F., LEBOWITZ, B. D., FRIEDHOFF, A. J. (Eds.). Washington DC: American Psychiatric Press, 1994, pp. 419–435.
 - 53 ZISOOK, S., SHUCHTER, S. R., SLEDGE, P. A., PAULUS, M., JUDD, L. L., The spectrum of depressive phenomena after spousal bereavement. *J. Clin. Psychiatry* 1994, 55 (Suppl.), 29–36.
 - 54 ALEXOPOULOS, G. S., BUCKWALTER, K., OLIN, J., MARTINEZ, R., WAINSCOTT, C., KRISHNAN, K. R., Comorbidity of late-life depression: An opportunity for research in mechanisms and treatment. *Biol. Psychiatry* 2002, 52, 543–558.
 - 55 LYNESS, J. M., CAINE, E. D., KING, D. A., COX, C., YOEDIONO, Z., Psychiatric disorders in older primary care patients. *J. Gen. Intern. Med.* 1999, 14, 249–254.
 - 56 LUBER, M. P., HOLLENBERG, J. P., WILLIAMS-RUSO, P., et al., Diagnosis, treatment, comorbidity, and resource utilization of depressed patients in a general medical practice. *Int. J. Psychiatry Med.* 2000, 30, 1–13.
 - 57 ANDERSON, R. J., FREEDLAND, K. E., CLOUSE, R. E., LUSTMAN, P. J., The prevalence of comorbid depression in adults with diabetes: A meta-analysis. *Diabetes Care* 2001, 24, 1069–1078.
 - 58 CARSON, A. J., MACHALE, S., ALLEN, K., et al., Depression after stroke and lesion location: A systematic review. *Lancet* 2000, 356, 122–130.
 - 59 LACRO, J. P., JESTE, D. V., Physical comorbidity and polypharmacy in older psychiatric patients. *Biol. Psychiatry* 1994, 36, 146–152.
 - 60 MEEKS, S., MURRELL, S. A., MEHL, R. C., Longitudinal relationships between depressive symptoms and health in normal older and middle-aged adults. *Psychol. Aging* 2000, 15, 100–109.
 - 61 COVINSKY, K. E., KAHANA, E., CHIN, M. H., PALMER, R. M., FORTINSKY, R. H., LANDEFELD, C. S., Depressive symptoms and 3-year mortality in older hospitalized medical patients. *Ann. Int. Med.* 1999, 130, 563–569.
 - 62 COOPER, P. L., CRUM, R. M., FORD, D. E., Characteristics of patients with major depression who received care in general medical and specialty mental health settings. *Med. Care* 1994, 32, 15–24.
 - 63 LUBER, M. P., MEYERS, B. S., WILLIAMS-RUSO, P. G., et al., Depression and service utilization in elderly primary care patients. *Am. J. Geriatr. Psychiatry* 2001, 9, 169–176.
 - 64 WELLS, K. B., GOLDING, J. M., BURNAM, M. A., Affective, substance use, and anxiety disorders in persons with arthritis, diabetes, heart disease, high blood pressure, or chronic lung conditions. *Gen. Hosp. Psychiatry* 1989, 11, 320–327.
 - 65 MAGAZINER, J., SIMONSICK, E. M., KASHNER, T. M., HEBEL, J. R., KENZORA,

- J. E., Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. *J. Gerontol.* **1990**, *45*, M101–M107.
- 66 MOSSEY, J. M., MUTRAN, E., KNOTT, K., CRAIK, R., Determinants of recovery 12 months after hip fracture: the importance of psychosocial factors. *Am. J. Public Health* **1989**, *79*, 279–286.
 - 67 JORM, A. F., VAN DUIJN, C. M., CHANDRA, V., et al., Psychiatric history and related exposures as risk factors for Alzheimer's disease: A collaborative re-analysis of case-control studies. *Int. J. Epidemiol.* **1991**, *20* (Suppl. 2), S43–S47.
 - 68 MURPHY, E., SMITH, R., LINDESAY, J., SLATTERY, J., Increased mortality rates in late-life depression. *Br. J. Psychiatry* **1988**, *152*, 347–353.
 - 69 SHAMASH, K., O'CONNELL, K., LOWY, M. M., KATONA CLE. Psychiatric morbidity and outcome in elderly patients undergoing emergency hip surgery: A one-year follow-up study. *Int. J. Geriatr. Psychiatry* **1992**, *7*, 505–509.
 - 70 SAMUELS, S. C., KATZ, I. R., PARMELEE, P. A., BOYCE, A. A., Di Filippo. Use of the Hamilton and Montgomery-Asberg depression scales in institutionalized elderly patients. *Am. J. Geriatr. Psychiatry* **1996**, *4*, 237–246.
 - 71 ROVNER, B. W., Depression and increased risk of mortality in the nursing home patient. *Am. J. Medicine* **1993**, *94*, 19–22.
 - 72 LOCKWOOD, K. A., ALEXOPOULOS, G. S., KAKUMA, T., VAN GORP, W. G., Subtypes of cognitive impairment in depressed older adults. *Am. J. Geriatr. Psychiatry* **2000**, *8*, 201–208.
 - 73 KINDERMANN, S. S., KALAYAM, B., BROWN, G. G., BURDICK, K. E., ALEXOPOULOS, G. S., Executive functions and P300 latency in elderly depressed patients and control subjects. *Am. J. Geriatr. Psychiatry* **2000**, *8*, 57–65.
 - 74 BUTTERS, M. A., BECKER, J. T., NEBES, R. D., et al., Changes in cognitive functioning following treatment of late-life depression. *Am. J. Psychiatry* **2000**, *157*, 1949–1954.
 - 75 NEBES, R. D., BUTTERS, M. A., MULSANT, B. H., et al., Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychol. Med.* **2000**, *30*, 679–691.
 - 76 BRUCE, M. L., HOFF, R. A., JACOBS, S. C., LEAF, P. J., The effects of cognitive impairment on 9-year mortality in a community sample. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **1995**, *50*, P289–P296.
 - 77 MURRAY CGL, LOPEZ, A. D., Alternative projections of mortality and disability by cause 1990–2020, Global burden of disease study. *Lancet* **1997**, *349*, 1498–1504.
 - 78 BRUCE, M. L., SEEMAN, T. E., MERRILL, S. S., BLAZER, D. G., The impact of depressive symptomatology on physical disability: MacArthur studies of successful aging. *Am. J. Public Health* **1994**, *84*, 1796–1799.
 - 79 STEFFENS, D. C., HAYS, J. C., Krishnan KRR. Disability in geriatric depression. *Am. J. Geriatr. Psychiatry* **1999**, *7*, 34–40.
 - 80 ALEXOPOULOS, G. S., VRONTOU, C., KAKUMA, T., et al., Disability in geriatric depression. *Am. J. Psychiatry* **1996**, *153*, 877–885.
 - 81 FORSELL, Y., JORM, A. F., WINBLAD, B., Association of age, sex, cognitive dysfunction, and disability with major depressive symptoms in an elderly sample. *Am. J. Psychiatry* **1994**, *151*, 1600–1604.
 - 82 KIOSSES, D. N., ALEXOPOULOS, G. S., MURPHY, C., Symptoms of striatofrontal dysfunction contribute to disability in geriatric depression. *Int. J. Geriatr. Psychiatry* **2000**, *15*, 992–999.
 - 83 KIOSSES, D. N., KLIMSTRA, S., MUPHY, C., ALEXOPOULOS, G. S., Executive dysfunction and disability in elderly patients with major depression. *Am. J. Geriatr. Psychiatry* **2001**, *9*, 269–274.
 - 84 ORMEL, J., VON KOROFF, M., VAN DEN BRINK, W., KATON, W., BRILMAN, E., OLDEHINKEL, T., Depression, anxiety and social disability show synchrony of change in primary care patients. *Am. J. Public Health* **1993**, *83*, 385–390.
 - 85 VON KORFF, M., OMEL, J., KATON, W., Lin EHB. Disability and depression among high utilizers of health care: A longitudinal analysis. *Arch. Gen. Psychiatry* **1992**, *49*, 91–100.
 - 86 BORSON, S., McDONALD, G. J., GAYLE, T., DEFFENBACH, M., LAKSHMINARAYAN, S., VAN TUINEN, C., Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients

- with chronic obstructive pulmonary disease. *Psychosomatics* **1992**, *33*, 190–201.
- 87 COLE, M. G., BELLAVANCE, F., MANSOUR, A., Prognosis of depression in elderly community and primary care populations: A systematic review and meta-analysis. *Am. J. Psychiatry* **1999**, *156*, 1182–1189.
 - 88 ALEXOPOULOS, G. S., CHESTER, J. G., Outcomes of geriatric depression. *Clinics Geriatr. Med.* **1992**, *8*, 363–376.
 - 89 GASTO, C., NAVARRO, V., CATALAN, R., PORTELLA, M. J., MARCOS, T., Residual symptoms in elderly major depression remitters. *Acta Psychiatr. Scand.* **2003**, *108*, 15–19.
 - 90 SIMPSON, S. W., JACKSON, A., BALDWIN, R. C., BURNS, A., Subcortical hyperintensities in late-life depression: acute response to treatment and neuropsychological impairment. *Int. Psychogeriatr.* **1997**, *9*, 257–275.
 - 91 HICKIE, I., SCOTT, E., MITCHELL, P., WILHELM, K., AUSTIN, M. P., BENNETT, B., Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol. Psychiatry* **1995**, *37*, 151–160.
 - 92 O'BRIEN, J., AMES, D., CHIU, E., SCHWEITZER, I., DESMOND, P., TRESS, B., Severe deep white matter lesions and outcome in elderly patients with major depressive disorder: follow up study. *BMJ* **1998**, *317*, 982–984.
 - 93 KESSING, L. V., NILSSON, F. M., Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. *J. Affect Disord.* **2003**, *73*, 261–269.
 - 94 YAFFE, K., BLACKWELL, T., GORE, R., SANDS, L., REUS, V., BROWNER, W. S., Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. *Arch. Gen. Psychiatry* **1999**, *56*, 425–430.
 - 95 BASSUK, S. S., BERKMAN, L. F., WYPIJ, D., Depressive symptomatology and incident cognitive decline in an elderly community sample. *Arch. Gen. Psychiatry* **1998**, *55*, 1073–1081.
 - 96 DEVANAND, D. P., SANO, M., TANG, M. X., et al., Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch. Gen. Psychiatry* **1996**, *53*, 175–182.
 - 97 RITCHIE, K., GILHAM, C., LEDESERT, B., TOUCHON, J., KOTZKI, P. O., Depressive illness, depressive symptomatology and regional cerebral blood flow in elderly people with sub-clinical cognitive impairment. *Age Ageing* **1999**, *28*, 385–391.
 - 98 STEFFENS, D. C., PIASSMAN, B. L., HELMS, M. J., WELSH-BOHMER, K. A., SAUNDERS, A. M., BREITNER, J. C., A twin study of late-onset depression and apolipoprotein E epsilon 4 as risk factors for Alzheimer's disease. *Biol. Psychiatry* **1997**, *41*, 851–856.
 - 99 VAN DUIJN, C. M., CLAYTON, D. G., CHANDRA, V., et al., Interaction between genetic and environmental risk factors for Alzheimer's disease: a reanalysis of case-control studies. *Genet. Epidemiol.* **1994**, *11*, 539–551.
 - 100 SPECK, C. E., KUKULL, W. A., BRENNER, D. E., et al., History of depression as a risk factor for Alzheimer's disease. *Epidemiology* **1995**, *6*, 366–369.
 - 101 FU, C. C., LEE, Y. M., CHEN, J. D., Association between depressive symptoms and twelve-year mortality among elderly in a rural community in Taiwan. *J. Formos. Med. Assoc.* **2003**, *102*, 234–239.
 - 102 MININO, A. M., ARIAS, E., KOCHANEK, K. D., MURPHY, S. L., SMITH, B. L., Deaths: final data for 2000. *Natl. Vital Stat. Rep.* **2002**, *50*, 1–119.
 - 103 MCINTOSH, J. L., SANTOS, J. F., HUBBARD, R. W., et al., *Elder Suicide: Research, Theory, and Treatment*. American Psychological Association APA, July **1994**.
 - 104 NATIONAL CENTER FOR HEALTH STATISTICS, Advance report of final mortality statistics, 1989. *NCHS Monthly Vital Statistics Report* **1992**, *40* (8, Suppl. 2).
 - 105 CARNEY, S. S., RICH, C. L., BURKE, P. A., FOWLER, R. C., Suicide over 60, The San Diego Study. *JAGS* **1994**, *42*, 174–180.
 - 106 CONWELL, Y., DUBERSTEIN, P. R., HERRMANN, J., FORBES, N., CAINE, E. D., Age differences in behaviors leading to completed suicide. *Am. J. Geriatr. Psychiatry* **1998**, *6*, 122–126.
 - 107 WALLACE, J., PFOHL, B., Age-related differences in the symptomatic expression of major depression. *J. Nerv. Ment. Dis.* **1995**, *183*, 99–102.

- 108 MOSCICKI, E. K., Epidemiologic surveys as tools for studying behavior: A review. *Suic. Life Threat. Behav.* **1989**, *19*, 131–146.
- 109 BECK, A. T., BROWN, G., STEER, R. A., DAHLGAARD, K. K., GRISHAM, J., Suicide ideation at its worst point: a predictor of eventual suicide in psychiatric outpatients. *Suic. Life Threat. Behav.* **1999**, *29*, 1–9.
- 110 ALEXOPOULOS, G. S., Frontostriatal and limbic dysfunction in late-life depression. *Am. J. Geriatr. Psychiatry* **2002**, *10*, 687–695.
- 111 ALEXANDER, G. E., DELONG, M. R., STRICK, P. L., Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann. Rev. Neurosci.* **1986**, *9*, 357–381.
- 112 SOBIN, C., SACHEIM, H. A., Psychomotor symptoms of depression. *Am. J. Psychiatry* **1997**, *154*, 4–17.
- 113 CHERMERINSKI, E., ROBINSON, R. G., The neuropsychiatry of stroke. *Psychosomatics* **2000**, *41*, 5–14.
- 114 MASSMAN, P. J., DELIS, D. C., BUTTERS, N., DUPONT, R. M., GILLIN, J. C., The subcortical dysfunction hypothesis of memory deficits in depression: Neuropsychological validation in a subgroup of patients. *J. Clin. Exp. Neuropsychol.* **1992**, *14*, 687–706.
- 115 LESSER, I., BOONE, K. B., MEHRINGER, C. M., WOHL, M. A., MILLER, B. L., BERMAN, N. G., Cognition and white matter hyperintensities in older depressed adults. *Am. J. Psychiatry* **1996**, *153*, 1280–1287.
- 116 BOONE, K. B., MILLER, B. L., LESSER, I. M., et al., Neuropsychological correlates of white matter lesions in healthy elderly subjects. *Arch. Neurol.* **1992**, *49*, 549–554.
- 117 KUMAR, A., BILKER, W., JIN, Z., et al., Atrophy and high intensity lesions: Complementary neurobiological mechanisms in late-life depression. *Neuropsychopharmacology* **2000**, *22*, 264–274.
- 118 DREVETS, W. C., PRICE, J. L., SIMPSON, J. R., et al., Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **1997**, *386*, 824–827.
- 119 RAJKOWSKA, G., MIGUEL-HIDALGO, L. L., WEI, J., Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol. Psychiatry* **1999**, *45*, 1085–1098.
- 120 LAI, T.-J., PAYNE, M. E., BYRUM, C. E., STEFFENS, D. C., Krishnan KRR. Reduction of orbital frontal cortex volume in geriatric depression. *Biol. Psychiatry* **2000**, *48*, 971–975.
- 121 ONGUR, D., DREVETS, W. C., Price JL: Glial reduction in the prefrontal cortex in mood disorders. *Proc. Natl. Acad. Sci. USA* **95**, 13290–13295.22, **1998**.
- 122 DREVETS, W. C., Neuroimaging studies of mood disorders. *Biol. Psychiatry* **2000**, *48*, 813–819.
- 123 DE ASIS, J. M., STERN, E., ALEXOPOULOS, G. S., et al., Hippocampal and anterior cingulate activation deficits in patients with geriatric depression. *Am. J. Psychiatry* **2001**, *158*, 1321–1323.
- 124 ROGERS, M. A., BRADSHAW, J. L., PANTELIS, C., PHILLIPS, J. G., Frontostriatal deficits in unipolar major depression. *Brain Res. Bull.* **1998**, *47*, 297–310.
- 125 DREVETS, W. C., VIDEEN, T. O., PRICE, J. L., PRESKORN, S. H., CARMICHAEL, S. T., RAICHLE, M. E., A functional anatomical study of unipolar depression. *J. Neurosci.* **1992**, *12*, 3628–3641.
- 126 KENNEDY, S. H., EVANS, K. R., KRUGER, S., et al., Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am. J. Psychiatry* **2001**, *158*, 899–905.
- 127 MAYBERG, H. S., LIOTTI, M., BRANNAN, S. K., et al., Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry* **1999**, *156*, 675–682.
- 128 PIZZAGALLI, D., PASCUAL-MARQUI, R. D., NITSCHKE, J. B., et al., Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am. J. Psychiatry* **2001**, *158*, 405–415.
- 129 BRODY, A. L., SAXENA, S., MANDELKERN, M. A., FAIRBANKS, L. A., HO, M. L., BAXTER, L. R., Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biol. Psychiatry* **2001**, *50*, 171–178.
- 130 MAYBERG, H. S., Depression and frontal-subcortical circuits. Focus on prefrontal–

- limbic interactions. In: *Frontal-Subcortical Circuits in Psychiatric and Neurological Disorders*, LICHTER, D. C., CUMMINGS, J. L. (Eds.). New York: The Guilford Press, 2001, pp. 177–206.
- 131 ALEXOPOULOS, G. S., KIOSSES, D., KLIMSTRA, S., KALAYAM, B., BRUCE, M. L., Clinical presentation of “depression-executive dysfunction syndrome” of late life. *Am. J. Geriatr. Psychiatry* 2002, 10, 98–102.
- 132 SHELINE, Y. I., WANG, P. W., GADO, M. H., CSERNANSKY, J. G., VANNIER, M. W., Hippocampal atrophy in recurrent major depression. *Proc. Natl. Acad. Sci. USA* 1996, 93, 3908–3913.
- 133 SHELINE, Y. I., SANGHAVI, M., MINTUN, M. A., GADO, M. H., Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J. Neurosci.* 1999, 19, 5034–5043.
- 134 SANTARELLI, L., SAXE, M., GROSS, C., et al., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 2003, 301, 805–809.
- 135 MALBERG, J. E., DUMAN, R. S., Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. *Neuropsychopharmacology* 2003, 28, 1562–1571.
- 136 LEE, J., DUMAN, R., ARANCIO, O., BELZUNG, C., HEN, R., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 2003, 301, 805–809.
- 137 FELD, S., GEORGE, L. K., Moderating effects of prior social resources on the hospitalizations of elders who become widowed. *J. Aging Health* 1994, 6, 275–295.
- 138 ARANDA, M. P., KNIGHT, B. G., The influence of ethnicity and culture on the caregiver stress and coping process: a sociocultural review and analysis. *Gerontologist* 1997, 37, 342–354.
- 139 SCHOEVERS, R. A., BEEKMAN, A. T., DEEG, D. J., GEERLINGS, M. I., JONKER, C., VAN TILBURG, W., Risk factors for depression in later life; results of a prospective community based study (AMSTEL). *J. Affect Disord.* 2000, 59, 127–137.
- 140 SCHOEVERS, R. A., GEERLINGS, M. I., BEEKMAN, A. T., et al., Association of depression and gender with mortality in old age. Results from the Amsterdam Study of the Elderly (AMSTEL). *Br. J. Psychiatry* 2000, 177, 336–342.
- 141 NORRIS, F. H., MURRELL, S. A., Social support, life events, and stress as modifiers of adjustment to bereavement by older adults. *Psychol. Aging* 1990, 5, 429–436.
- 142 REYNOLDS, C. F. 3RD, MILLER, M. D., PASTERNAK, R. E., et al., Treatment of bereavement-related major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. *Am. J. Psychiatry* 1999, 156, 202–208.
- 143 KOENIG, H., Depression and dysphoria among the elderly: dispelling a myth. *J. Family Pract.* 1986, 23, 383–385.
- 144 KRAUSE, N., Life stress, social support, and self-esteem in an elderly population. *Psychol. Aging* 1987, 2, 349–356.
- 145 BLIXEN, C. E., KIPPES, C., Depression, social support, and quality of life in older adults with osteoarthritis. *Image J. Nurs. Sc.* 1999, 31, 221–226.
- 146 KRAUSE, N., Stressors in salient social roles and well-being in later life. *J. Gerontol.* 1994, 49, P137–P148.
- 147 BOSWORTH, H. B., HAYS, J. C., GEORGE, L. K., STEFFENS, D. C., Psychosocial and clinical predictors of unipolar depression outcome in older adults. *Int. J. Geriatr. Psychiatry* 2002, 17, 238–246.

13

Comorbidity of Depression and Substance Abuse

Edward V. Nunes and Wilfred N. Raby

Abstract

Substance use and substance-use disorders, including those involving alcohol, nicotine, and other drugs, are prevalent in patients with mood disorders. Understanding this co-occurrence is important, both to improve treatment for patients with depression and to advance our models of the etiology and pathophysiology of mood disorders. This chapter reviews several areas of convergence between substance abuse and mood disorders, highlighting the following main findings: (1) increased prevalence of addictive disorders among depressed persons; (2) adverse prognostic effects when both disorders are combined; (3) benefits of joint treatment for depression and addiction; (4) depressogenic effects of chronic substance exposure and withdrawal and time course of resolution with abstinence; (5) effects of depressed mood in heightening euphoric response and reward value of addictive substances; (6) evidence from developmental and longitudinal studies that early substance exposure and abuse increase risk of subsequent development of depression and other psychiatric disorders and, conversely, that prior depression and other psychiatric disorders increase risk for subsequent substance-use disorders; and (7) evidence regarding risk factors shared by both depression and substance-use disorders, including common genetic underpinnings and potential related endophenotypes, and the role of stress and response to stress in promoting both depression and addictions. We hope that the discussion stimulates interest in the study of comorbidity and new lines of research that may ultimately deepen our understanding of both mood and substance-use disorders and their treatment.

13.1

Introduction

This book is focused on summarizing and furthering our understanding of depression from a biopsychosocial perspective. Why is it important, as part of such an effort, to consider the role of addictive substances and the co-occurrence between

depression and addictions? First, there are important clinical reasons. Substance use and substance-use disorders are common in depressed patients. Thus, to competently treat depression, it is important to be able to evaluate and treat substance-use disorders and to understand the possible relationships between substance abuse and depression and the implications for the patient. The importance of substance-use disorders in depression is highlighted by the consistent finding that the comorbidity of substance-use disorders and depression adversely affects prognosis.

The second reason to study comorbid substance-use disorders among depressed patients is that such comorbidity may offer insights into the biology of depression. Substance intoxication produces euphoria, and withdrawal from substances usually produces dysphoria, often mimicking depression or anxiety. Thus, understanding the biology of intoxication and withdrawal may offer insights into the underlying mechanisms of mood disorders. Depressed mood affects response to intoxicating substances, perhaps offering insights into the interplay between mood and the brain-reward circuitry that is directly affected by substances. Depression and substance-use disorders share some common risk factors, including shared genetic factors and psychological stress, an environmental risk factor that predisposes to both disorders.

Finally, there are a number of interesting relationships between substance abuse and depression over the course of development, including findings on early-onset substance use and subsequent risk of psychopathology and effects of early onset of depression and other psychopathologies on subsequent risk of substance-use disorders.

This chapter begins by describing the clinical context for comorbid substance-use disorders and depression, describing the epidemiology, prognostic effects, and treatment implications of this comorbidity. We then explore a number of the interesting relationships between intoxicating substances and mood that may have implications for understanding the etiology and psychobiology of depression. These include acute effects of drugs on mood and of mood on drug response, shared genetic and environmental risk factors, including stress, and the interplay of substance abuse and mood over the course of development. We hope that this discussion will stimulate new thinking and new lines of research that may ultimately deepen our understanding of mood disorders.

13.2

Epidemiology and Treatment

Table 13.1 presents data from the Epidemiologic Catchment Area (ECA) Study (Regier et al. 1990) on the lifetime prevalence of DSM-III drug- and alcohol-use disorders in representative samples from five communities and the odds ratios representing the extent to which the prevalence of substance-use disorders is increased in the presence of depressive disorders, as well as other psychiatric disorders. As can be seen from Table 13.1, substance-use disorders are common in the general population across the lifetime, and the presence of major depression or

Table 13.1 Lifetime prevalence of substance use disorders in the general population and in the presence of lifetime co-occurring psychiatric disorders according to the Epidemiologic Catchment Area (ECA) study^{a)}.

	Any Substance Use Disorder	Alcohol		Other Drug	
	% (OR)	Dependence % (OR)	Abuse Only % (OR)	Dependence % (OR)	Abuse Only % (OR)
General Population:	16.7	7.9	5.6	3.5	2.6
Among Respondents with Mood Disorders:					
Any Affective Disorder	32.0 (2.6)	14.9 (2.2)	6.9 (1.3)	11.3 (4.4)	8.1 (4.1)
Any Bipolar Disorder	56.1 (6.6)	27.6 (4.6)	16.1 (3.3)	21.8 (8.3)	11.7 (5.2)
Major Depression ^{b)}	27.2 (1.9)	11.6 (1.6)	5.0 (0.9)	10.7 (3.7)	7.3 (3.3)
Dysthymia	31.4 (2.4)	16.1 (2.3)	4.8 (0.8)	10.8 (3.6)	8.1 (3.6)
Among Respondents with Other Disorders:					
Any Anxiety Disorder	23.7 (1.7)	12.2 (1.8)	5.8 (1.0)	6.9 (2.4)	5.0 (2.3)
Panic Disorder	35.8 (2.9)	21.7 (3.3)	7.0 (1.3)	13.3 (4.4)	3.4 (1.4)
Schizophrenia	47.0 (4.6)	24.0 (3.8)	9.7 (1.9)	12.9 (4.2)	14.6 (6.9)
Antisocial Personality	83.6 (29.6)	51.5 (14.7)	22.1 (5.4)	30.8 (15.6)	11.2 (5.2)

^{a)} From Regier et al., 1990; values in the table are prevalence rates in percent and odds ratios (OR). Prevalence rates are from 5 communities surveyed in the ECA and standardized to US general population based on age, gender and ethnicity; odds ratios (OR) represent the increased risk (odds) of substance use disorder in respondents with, versus without, the co-occurring psychiatric disorder.

^{b)} Major depression is unipolar.

dysthymia roughly doubles the odds of having an alcohol or drug disorder. The increased risk is greater for drug- than for alcohol-use disorders. These findings have been replicated fairly consistently across several large community-based surveys of psychiatric diagnoses, including the National Comorbidity Survey (Kessler 1995), the National Longitudinal Alcohol Epidemiology Survey (Grant 1995, Grant and Harford 1995), and the National Epidemiologic Survey on Alcohol and Related Conditions (Grant et al. 2004), despite differences in criteria sets (DSM-III vs. DSM-III-R or DSM-IV) and diagnostic interviews. Thus, among individuals with major depression or dysthymia, a lifetime history of alcohol or drug abuse or dependence can be expected to occur in around 20% or more of them. These high prevalences highlight the fundamental importance of inquiring about substance-use disorders during the routine history and evaluation of patients with mood disorders.

The data from the community surveys also raise several caveats. First, as can be seen in Table 13.1, unipolar major depression and dysthymia actually display smaller degrees of association with substance-use disorders than do many other less-common psychiatric disorders, including bipolar disorder, panic disorder, schizophrenia, and antisocial personality disorder, for which the odds ratios, particularly for alcohol or drug dependence, vary from 2 to 6 or more. Thus, the phenomenon of comorbidity of substance-use disorders is not unique to depression and, in fact,

the relationships appear to be stronger for most other psychiatric disorders. These other disorders have high rates of comorbidity among themselves and with depression. Thus, although depression has been the most extensively studied with respect to its comorbidity with substance-use disorders, partly because of its greater prevalence, it must be born in mind that the relationships explored in this chapter may have implications not only for depression but also for anxiety disorders and other commonly co-occurring disorders. Although these community surveys sampled adults, a number of similar community surveys have also been conducted on adolescents and have found a similar degree of association between substance-use disorder and depression, with odds ratios in the range of 2 (for a review see Armstrong and Costello 2002). Similarly, strong associations between anxiety disorders and disruptive disorders with substance-use disorders were also found among the adolescents.

Another caveat concerns diagnosis. The problem of how to diagnose depression in the setting of substance abuse has been an ongoing source of controversy. The problem is how to distinguish symptoms of depression, which may merely represent toxic effects of ongoing substance use or withdrawal, from a diagnosis of an independent depressive disorder. All of the community surveys cited above used structured clinical interviews, and in each study additional efforts were made to provide guidelines for the interviewers as to how to establish whether a mood or other comorbid disorder that was independent of substance use existed. *The Diagnostic and Statistical Manual for Mental Disorders*, 4th Edition (American Psychiatric Association 1994) has gone further than any previous diagnostic system in classifying depressive and other psychiatric symptoms in the setting of substance abuse into three categories:

Symptoms that are expected to be toxic or withdrawal effects of substances.

Substance-induced depression that indicates a substantial depressive syndrome that nonetheless has not occurred independently of drug or alcohol use, although the depressive symptoms exceed what would be expected from the usual toxic withdrawal effects of the substances.

Primary depression that indicates a depressive disorder that has clearly been independent of the substance use over time, persisting after a period of abstinence in the present, or having clearly occurred during past periods of abstinence, or having clearly preceded the onset of substance use over the lifetime.

Data on the predictive utility and validity of these distinctions are just beginning to emerge (Hasin et al. 2002).

Clinical samples also highlight the high rates of comorbidity between depression and substance-use disorders. A large number of studies have accumulated in the literature examining the prevalence of depression in patients seeking treatment for drug or alcohol problems (for review see Hasin et al. 2004). Lifetime prevalence rates for depression across these samples range from 30% to 50%, and current prevalence rates for depression range from 10% to 30%. Fewer studies have examined the prevalence of substance-use disorders in patients seeking treatment for psychiatric problems, but high rates of substance-abuse disorders in such patients have been documented (Havassy et al. 2004).

13.2.1

Comorbidity and Prognosis

The clinical importance of comorbid mood and substance-use disorders is also highlighted by the fairly consistent finding that the combination of the disorders is associated with greater overall illness severity and poor prognosis for treatment outcome. In patients in treatment for substance-use disorders, a number of studies have found that depression has a negative effect on treatment outcome and that this effect is strongest when depressive disorders are diagnosed with careful clinical or structured interview methods (for review see Hasin et al. 2004). Studies in which depressive symptoms are examined as prognostic indicators have shown less-consistent results, suggesting the clinical importance of making distinctions between symptoms and of carefully ascertaining a history of a mood disorder. A concurrent substance-use disorder has been found to predict worse outcome for the treatment of bipolar illness and severe mental illness (Rachbeisel et al. 1999; Salloum and Thase 2000). There are fewer such data with respect to the effect of substance use or abuse on the treatment outcome for unipolar depressive illness in routine outpatient populations.

For the prognostic effects of combined nicotine dependence and depression, the effects are more complicated. The findings are similar in some respects to those for depression and other drug or alcohol dependencies, in that the prevalence of a lifetime history of depression is elevated among cigarette smokers, and smoking is more likely among patients seeking treatment for depression (Glassman et al. 1990), although a history of depression does not consistently predict reduced likelihood of successfully quitting smoking (Hitsman et al. 2003). What is most interesting is that dysphoric symptoms tend to emerge after a patient has quit smoking, regardless of history of depression (Hall et al. 1998), and that these symptoms predict relapse (Kenford et al. 2002); in a subgroup of such patients there is even relapse to or emergence of major depression, which can be quite severe in some patients and which can include significant suicidal ideation (Covey et al. 1997). The implication here is that nicotine for some patients might exert a favorable effect on the tendency toward depression, almost looking as if it functions as an antidepressant (Glassman 1993). Thus, it is important at a clinical level and in terms of scientific inquiry to remain aware that addictive substances may exert beneficial effects for some patients. This notion is embodied in the so-called self medication hypothesis of substance abuse (Khantzian 1985), which holds that substance abuse may be driven to some extent by a need or an effort to achieve relief from symptoms of depression or other emotional pain.

13.2.2

Comorbidity and Treatment

The foregoing review of findings on the prevalence and adverse prognostic effects of co-occurring depression and substance-use disorders may suggest that concurrent treatment of both sets of disorders would be important for optimal clinical outcome.

Unfortunately, patients with drug- or alcohol-use disorders have been excluded from most studies of pharmacotherapy or psychotherapy for depression. One important exception is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a large community-based, multisite trial that examines different sequences of treatments for outpatient depression, and which sought to recruit a sample that would be as representative as possible of patients seen in routine clinical settings (Rush et al. 2004). Patients not requiring emergency treatment for drug or alcohol problems were included. Results are expected in the near future and should include analyses of whether concurrent substance use or use disorders affect treatment outcome for outpatient depression.

In contrast, a number of studies in the literature have examined the treatment of depression among patients seeking treatment for drug- and alcohol-use problems. These studies were recently reviewed in a meta-analysis of placebo-controlled trials of antidepressant medication in drug- or alcohol-dependent patients in whom a depressive syndrome, major depression, or dysthymia, was diagnosed with clinical history or structured interview (Nunes and Levin 2004). Eight out of fourteen studies found significant or trend-significant favorable effects of antidepressant medication on mood outcome in such patients. A number of the negative studies exhibited high placebo-response rates, which the authors attributed to either difficulties in making a diagnosis of a true depressive disorder among substance-dependent patients or to favorable effects of concurrent psychotherapeutic interventions offered to all patients in some of the trials. Studies that demonstrated medium-to-large effects of medication on mood outcome also tended to show that medication treatment reduced self-reported quantity of substance use, although rates of sustained abstinence tended to remain low and to differ relatively little between treatment groups. Taken together, the data support a combined treatment strategy in which depressive disorders among substance-dependent patients are carefully diagnosed (by clinical history and observation of depression during a period of abstinence if possible) and treated in conjunction with treatment for the substance-use disorder.

Studies of the treatment of nicotine-dependent patients have routinely excluded patients with current major depression. With mixed results, some of these studies have examined the prognostic effects of a history of major depression on treatment outcome (Hitsman et al. 2003). Most studies suggest that psychosocial and pharmacologic treatments, including nicotine replacement or antidepressant medications (bupropion or nortriptyline), are effective regardless of whether or not there is a history of major depression. Interestingly, one study that examined the separate and joint effects of cognitive behavior therapy and/or nortriptyline for treatment of outpatient smokers found that cognitive therapy was more effective among patients with a history of depression, but nortriptyline, although equally effective in patients with and without a depression history, appeared to function by reducing the dysphoric moods that emerge after smoking cessation (Hall et al. 1998).

The notion of combined or integrated treatment for mood and substance-use disorders has found support in studies examining the treatment of severely mentally

ill populations with combinations of schizophrenia, bipolar disorder, and unipolar mood disorders. Studies of combined-treatment strategies have generally been found superior to strategies in which patients are referred to one agency for treatment of substance use and to another for treatment of psychiatric disorder (Hellerstein et al. 2001). Studies have supported the utility of case-management strategies, in which case managers individualize care and work to assure that both psychiatric and substance-use disorders receive adequate treatment (Drake et al. 1998).

Studies have also examined the effect of purely treating drug or alcohol dependence on the outcome of mood symptoms. An example of such studies are those that examine the effect of enforced abstinence through hospitalization upon the outcome of depressive symptoms, which is reviewed in more detail in the next section. These studies, carried out mainly without alcohol- or cocaine-dependent patients, suggest a relatively dramatic effect of achieving abstinence upon improvement in depressive symptoms. Some studies of outpatient treatments for drug dependence also suggest that such treatment is associated with improvement in depression (Carroll et al. 1995; Tidey et al. 1998). These data highlight an important principle in treatment planning in patients with comorbid disorders, namely, that treatment of drug or alcohol dependence may turn out to be very effective and that clinicians ought to be prepared to implement such treatments as part of routine care or to make appropriate referrals.

13.2.3

Summary

The foregoing brief review of epidemiologic and clinical data suggests that substance-use disorders commonly co-occur with depression, that the combination confers a worse prognosis, and that combined or integrated treatment addressing both sets of disorders simultaneously is likely to be important for achieving optimal treatment outcome. The data also suggest questions about what the fundamental relationships may be at a psychological or biological level between addictions and mood disorders. In the next sections, we take a closer look at several lines of inquiry on the effects of substances or their comorbidity with mood disorders that may shed light on the psychobiology of depression.

13.3

Acute Effects of Substances on Mood

Perusal of the DSM-IV criteria for substance intoxication and withdrawal reveals substantial overlap with depressive symptoms (American Psychiatric Association 1994). In particular, withdrawal symptoms from alcohol and drugs typically involve dysphoric mood, low energy and/or motivation, and changes in sleep and appetite, reminiscent of symptoms of depression. Such depressive symptoms are often thought of clinically as a kind of nuisance factor, in that they can be expected to

resolve with abstinence and can confuse the effort to establish accurate diagnosis of co-occurring psychiatric disorders. However, an alternative view of such withdrawal symptoms is that they represent a kind of biological challenge that induces depression, and, as such, careful study of their manifestations and time course may help to further understand the neurobiology of depression.

Table 13.2 summarizes studies that have examined the course of depressive symptoms after enforced abstinence due to hospitalization or entry into abstinence-promoting treatments, such as methadone maintenance. As can be seen from Table 13.2, patients hospitalized for treatment of alcoholism typically show moderate to high levels of depressive symptoms at baseline upon admission to treatment. Within two to three weeks, overall symptom levels are reduced by around 50%, and within one month, overall symptoms are reduced by closer to 75% and few of these patients still score in the severe range. The one exception to this pattern was a small group of patients with primary major depression (unipolar or bipolar) reported by Brown et al. (1995), in whom there was little change in moderate-to-severe depressive symptoms with abstinence, suggesting the importance of distinguishing primary from secondary depression among alcoholics. Among cocaine-dependent patients without other psychiatric disorders, levels of depressive symptoms were lower initially than among the alcoholics, but followed a similar time course of improvement. Similarly, in opiate dependence, moderate levels of depressive symptoms were observed at baseline, but reductions during the first month after entry into treatment were less marked.

From a clinical perspective, the data shown in Table 13.2 are unique, in that currently, in most treatment systems it is not possible to hospitalize substance-dependent patients for more than a few days at a time due to fiscal constraints. Thus, the ability to observe the course of prolonged enforced abstinence has been largely lost. Data such as these have been used to derive the recommendation found in DSM-IV that abstinence of at least one-month duration be established before determining that persistent depressive symptoms indicate a primary depressive disorder rather than a substance-induced depression. However, standard deviations, when reported, indicated considerable individual differences. For some patients, depressive symptoms may resolve within a few days, while for others symptoms may be more persistent.

From a neurobiological standpoint, the data suggest that exposure to substances induces neural adaptations that might parallel those seen in depression. The variable time course of resolution, from days to weeks, suggests that the neural adaptations might involve synthesis or renewal of stores of neurotransmitters by intra-cellular synthesis or conformational changes in receptors as explanations for the more rapid resolution or changes in gene expression and protein synthesis for the more slowly resolving symptoms. Markou and colleagues (1998) conducted an extensive review of the neurochemical changes typically observed during depressive illness and compared these to the neurochemical changes observed during drug or alcohol withdrawal, drawing heavily on animal studies that have allowed fairly precise characterization of the neurochemistry of withdrawal. They found striking parallels between depression and substance withdrawal: depression was typically charac-

Table 13.2 Time course of depressive symptoms after enforced abstinence or entry into treatment for substance abuse.

Substance/ Author, year	Sample and Setting	Depression Outcome Measure	Mean Depression Scores by Week					Comment
			baseline	wk 1	wk 2	wk 3	wk 4	
Alcohol								
Brown et al., 1988	N = 177 male, alcohol dependent patients, admitted to VA inpatient unit, major depression excluded	Hamilton	18.3	11.6	10.2	8.8		Only 6% had HamD score greater than 20 during 4 th week. All subscales decreased.
Liappas et al., 2002	N = 34 alcohol dependent patients, 86% male, admitted to inpatient unit, prior onset major depression excluded	Hamilton	37.2	29.0	20.8	8.9		Anxiety and GAS also improved. Younger age at onset alcoholism correlated with greater depression at end of study.
Brown et al., 1995	N = 15 male inpatient alcoholics with no affective disorder	Hamilton	15.7	9.9	10.4	8.1		No patients had Hamilton score > 20 at end of study
Brown et al., 1995	N = 12 male inpatient alcoholics with a secondary affective disorder	Hamilton	16.2	12.1	7.9	5.9		No patients had Hamilton score > 20 at end of study
Brown et al., 1995	N = 12 men with primary affective disorder and secondary alcoholism	Hamilton	23.8	21.9	19.5	20.4		67% had Hamilton score > 20 at end of study
Cocaine								
Weddington et al., 1990	N = 12 male, cocaine dependent patients, 71% male, admitted to inpatient research unit	Beck	8.5	4.0	2.5	2.0	2.0	Drug craving and POMS subscales improved similarly with greatest drop over 1 st week.
Satel et al., 1991	N = 22 cocaine dependent patients, 86% male, admitted to inpatient unit, other psychiatric disorders excluded	Beck	15.0	8.5	11.0	10.5		Anxiety, abstinence symptom ratings also mild and decreased rapidly in 1 st week.
Opiate								
DeLeon et al., 1973	N = 200 opiate dependent patients in residential therapeutic community, assessed cross-sectionally at different time points.	Beck	23.2				19.2	Beck dropped to 14 by 9 months; retention in long term treatment associated with lower depression scores
Strain et al., 1991	N = 58 opiate dependent patients newly admitted to methadone maintenance (low dose)	Beck	19.6	14.8	12.5	13.0	13.8	Most patients continued to have opiate and cocaine positive urines, although likely some reduction due to methadone treatment

terized by reductions in serotonergic, dopaminergic, and GABAergic functioning and increases in corticotropin-releasing factor (CRF) activity, and withdrawal from cocaine and other stimulants, opiates, alcohol, and benzodiazepines had similar patterns. These data suggest the potential of viewing drug and alcohol withdrawal as model systems that might be useful to study as a means of elucidating the neurobiology of depression.

13.4

Effects of Mood on Response to Drugs and Alcohol

An emerging literature has begun to examine the effects of depressed mood on response to alcohol and other drugs, offering another window into the neurobiology of mood and drug use. These studies are summarized in Table 13.3. As can be seen, the studies have examined the effects of depression on responses to a range of substances, including alcohol, nicotine, cocaine, and amphetamine. The overall findings are strikingly similar, namely that depressed groups, defined and distinguished in various ways, have increased pleasurable or euphoric responses to drug challenges. In a study with cocaine users who were not seeking treatment, Uslaner and colleagues (1999) found that depressive symptoms were associated with an increased subjective high or euphoria in response to a laboratory administration of cocaine. This study was replicated and extended by Sofuoglu and colleagues (2001), who also studied cocaine users who were not seeking treatment and did not have major depression but were divided into groups with low, medium, or high Beck Depression Inventory scores; those with medium or high depression scores had increased subjective euphoria and stimulating drug effect compared to those in the low depression group. Interestingly, the effect appeared largest for the moderately depressed group. In a subsequent pair of studies, Sofuoglu and colleagues (2003) examined clinical characteristics distinguishing cocaine-using individuals seeking to participate in inpatient studies who did or did not meet DSM-IV criteria for cocaine withdrawal; those with withdrawal criteria had evidence of more severe histories of cocaine use and higher levels of depression and more history of severe depressive episodes and serious suicidal ideation. In a subsequent laboratory study, a subset of cocaine users with and without significant cocaine withdrawal were challenged with cocaine, and those with withdrawal symptoms had enhanced subjective euphoria and drug effects compared to those without withdrawal. In a naturalistic study, Rosenblum and colleagues (1999) found greater euphoria to cocaine among cocaine users with substance-induced depression than in those with primary depression.

Tremblay and colleagues (2002) compared response to a dose of dextroamphetamine in patients with major depression compared to non-depressed controls and found that rewarding effects in response to dextroamphetamine were significantly greater in those with a history of depression, particularly those with severely elevated severity of depressive symptoms as measured by the Hamilton depression scale.

Table 13.3 Effects of mood state on response to drugs or alcohol

Author, year	Participants	Substance Administered	Response Measures	Findings	Comment
Uslaner et al., 1999	N = 17 non-treatment seeking cocaine users; no other major Axis I disorder; 41% had baseline Beck Depression Inventory score > 10	Cocaine, 40 mg IV administered 4 days of abstinence on inpatient unit	Verbal rating of cocaine high on Likert scale	Positive correlation between Beck score and degree of cocaine high ($r = 0.56$, $p < .02$).	
Sufuoglu et al., 2001	N = 75 non-treatment seeking cocaine users, divided into 3 groups with low (0–7), medium (8–13), or high (14–23) Beck Depression Inventory (BDI)	Cocaine, 0.4 mg/kg, smoked	Cocaine Effects Questionnaire (CEQ), Vital signs (peak change scores)	CEQ Low BDI: 38 Medium BDI: 64* High BDI: 52 *signif. vs. low BDI group	High Desire 13 28* 25* As with High, vital signs and other CEQ subscales showed U-shaped curve with greatest response in medium BDI group.
Sufuoglu et al., 2003	N = 44 non-treatment seeking cocaine users either without (N = 10) or with (N = 34) DSM-IV cocaine withdrawal (depression plus ≥ 2 additional symptoms)	Cocaine, 0.4 mg/kg, smoked	Cocaine Effects Questionnaire (CEQ), Vital signs (peak change scores)	Cocaine Withdrawal: No: 30 Yes: 55* * signif. $p < .03$	CEQ "effect of last dose" also significantly greater with cocaine withdrawal; vital signs and other CEQ subscales not significant; withdrawal associated with history of more cocaine use and medical, psychological problems.
Rosenblum et al., 1999	Methadone maintenance patients with regular cocaine use: N = 18 with primary depression; N = 49 with substance-induced depress.	Cocaine (retrospective report of subjective effects during naturalistic cocaine use)	Retrospective ratings on Likert scales of cocaine effects during naturalistic use	Primary depression (vs. substance-induced) reported signif less cocaine use, less euphoria ($r = -.32$) and more dysphoria ($r = .26$) during cocaine use.	Limitation that cocaine response not directly observed in laboratory. Patients who received psychiatric medication were retained longer in treatment.

Table 13.3 (continued)

Author, year	Participants	Substance Administered	Response Measures	Findings	Comment
Tremblay et al., 2002	N = 21 patients with moderate MDD (HDS range 13–23); N = 19 patients with severe MDD (HDS range 24–32); N = 36 controls (mean BDI: 2.0); current substance use disorders excluded	Dextroamphetamine 30 mg oral, or placebo (between groups design)	ARCI rewarding effects composite (mean difference between Dex and placebo on peak change score), POMS, vital signs, plasma HVA	Depression Group: None; Moderate: 46.2 Severe: 156.4* * $p < .02$ drug by group interaction	Severe depression associated with greater rewarding effect of dextroamphetamine; similar trend for POMS; no effect of depression group for ARCI negative effects, vital signs, or HVA.
Spring et al., 2003	Cigarette smokers: N = 26 with MDD; N = 26 with schizophrenia; N = 26 controls	Nicotine (retrospective report of subjective effects during naturalistic smoking)	Decisional Balance Scale	Patients with MDD (vs. controls) reported more positive effects of smoking and greater preference for smoking over other rewards.	Same results for schizophrenia; no differences for negative effects of smoking; limitation that smoking not directly observed in laboratory.
Willner et al., 1998	N = 144 recreational drinkers, depressed mood induced with music	Low (< 1%) alcohol beer	Desires for Alcohol Questionnaire	Depressed mood increased craving score, decreased liking for alcohol	
Randall et al., 2001	N = 40 high risk alcohol drinkers (one or both parents problem drinkers); N = 40 low risk drinkers; Randomly assigned to positive or negative mood induction.	Placebo alcohol (non-alcoholic beer)	Positive and Negative Affect Scale	Mood induction: high risk drinkers > low risk on negative affect ($p < .07$) Beer consumption: high risk drinkers consumed more vs. low risk ($p < .05$)	Groups equivalent on current drinking; history of alcohol problems excluded. No difference between risk groups on positive affect to mood induction. Affect in response to beer consumption not reported as dependent measure.

Spring and colleagues (2003) surveyed three groups of nicotine-dependent patients: a group with schizophrenia, a group with major depression, and a group of non-psychiatric controls. Both the schizophrenic and depressed groups reported more positive attributes of cigarette smoking, preferred cigarette smoking more than other rewarding or pleasurable activities, and indicated that greater incentives were needed to quit smoking in comparison to the non-psychiatric controls. Like the studies with cocaine and dextroamphetamine, this study suggests greater subjective and rewarding effects of nicotine in individuals with depression.

Randall and Cox (2001) studied individuals at high and low risk for alcohol dependence based on family history and their response to an experimental depressive mood induction: the high-risk participants showed more severe dysphoria in response to the mood induction. When challenged with nonalcoholic beer shortly after the mood induction, individuals at high risk for alcoholism consumed more nonalcoholic beer than those at low risk. The effects of mood response to the mood induction were not significant when included in the same model as risk level. The increased consumption in the high-risk group suggests enhanced craving or enhanced subjective effects of alcohol (albeit placebo alcohol) and an association with vulnerability to depressive symptoms. A similar study found that a depressive mood induction increased craving, but decreased liking for low-alcohol beer (Willner et al. 1998).

In these studies depression was characterized in different ways, yet the findings are similar. Some studies identify patients with major depression, but others examined depressive symptoms in substance users in whom presence of major depression had been excluded, and another study examined an experimental mood induction in individuals at risk for alcoholism who had no current major depression but experienced greater negative affect during a mood induction. A related set of studies, not summarized in the table, examined responses to cocaine along the menstrual cycle, finding evidence for relief of dysphoria during the luteal phase (Evans et al. 2002). Thus, the effect of mood on substance response seems to depend on depressive symptoms or vulnerability to depressive symptoms rather than on a primary depressive disorder per se. If the depression represented purely a toxic effect of substances, as in the studies of acute substance effects and withdrawal effects reviewed in the previous section, one might expect depletion or desensitization of the brain-reward system and a blunted or diminished responsiveness to euphorogenic substances. However, the data show the opposite effect, suggesting that the presence of depressive symptoms marks an imbalance between the reward value of natural rewards in comparison to the reward value of the addictive substances, with a net effect that the reward value of the addictive substances is enhanced.

13.5

Shared Risk Factors

Having examined the acute effects of substances and substance withdrawal on mood and, conversely, the effects of mood on responses to substances, we now turn our attention to the interplay between substance use and depression over the course of development and its possible implications for neurobiology.

Table 13.4 summarizes possible and probable risk factors that have been identified for the development of depression and substance-dependence disorder over the course of the lifetime. The most salient risk factors for the development of major depression are a family history of depression, other psychiatric disorders such as anxiety disorders, and stressful life circumstances. Risk factors for a substance-use disorder include a family history of substance dependence, early onset of a disruptive disorder particularly conduct disorder, and exposure to or ready availability of addictive substances.

Table 13.4 Comparison of risk factors associated with development of depression or substance dependence

<i>Depression</i>	<i>Substance Dependence</i>
1. Family history of mood disorder (likely reflects in part unique genetic factors as well as shared genetic factors conveying risk for both depression and addiction).	1. Family history of alcoholism or other drug dependence (again, likely reflects unique as well as shared genetic factors and family environment).
2. Early-onset internalizing (anxious–depressive) symptoms.	2. Early-onset disruptive disorders, especially conduct disorder; early impulsive–aggressive temperament.
3. Other psychiatric disorders (especially anxiety disorders, also including substance-use disorders).	3. Exposure to addictive substances (availability in the environment, peer group influence).
4. Childhood adversity, including adverse family environment (lacking cohesiveness or violent).	4. Other psychiatric disorders (including depression).
5. Stress and trauma.	5. Family environment (including lack of parental monitoring).
	6. School failure.
	7. Stress and trauma.

Thus, although some risk factors are distinct, it is striking, in examining Table 13.4 how much overlap there appears to be in the risk factors between the two sets of disorders. In particular, other psychiatric disorders, stress, trauma, and adverse childhood environment are risk factors that are common to both depression and substance-dependence disorder. The sections below evaluate some of these various risk factors and their implications for etiology and neurobiology.

13.5.1

Substance Abuse as a Risk Factor for Development of Depression

In utero exposure to drugs or alcohol has been associated with subsequent development of drug or alcohol dependence in offspring, as well as, to some extent,

disruptive disorders and cognitive impairment. For example, maternal smoking during pregnancy has been associated with development of tobacco dependence (Buka et al. 2003) and attention deficit disorder (Thapar et al. 2003) in offspring. Maternal drinking during pregnancy has been associated with subsequent development of alcohol dependency in young adults (Baer et al. 2003). Maternal smoking also has been associated with neurocognitive deficits and attention deficit disorder, as well as nicotine dependence (for review see Niaura et al. 2001). Depression as a consequence of in utero drug or alcohol exposure has received less attention but should be a focus of future inquiry. The noted effects of in utero substance exposure could simply result from an association between substance use during pregnancy and a higher level of both genetic loading and subsequent familial disruption, increasing the ultimate risk for substance use among offspring. It is also possible that these associations represent a toxic effect of drug or alcohol upon the developing fetus. This possibility seems particularly likely, given emerging evidence from animal studies of the sensitivity of brain development to early substance exposure and the relatively permanent changes that may result from such exposure (Malanga and Kosofsky 2003).

Recent data has implicated the early onset of nicotine (Breslau et al. 1993) or marijuana use (Brook et al. 2002; Fergusson et al. 2002; Patton et al. 2002) as increasing the risk for later development of either depressive disorders or anxiety disorders. Other studies (e.g., Hanna et al. 2001) found no direct association between early-onset smoking and depression but rather found early-onset smoking to be associated with subsequent school problems and other problem behaviors, consistent with the well known link between substance-use disorders and disruptive disorders. Longitudinal studies in adults (e.g., Gilman and Abraham 2001) have found substance dependence to increase the risk of subsequent development of major depression, as well as the opposite relationship, namely, previous depression increasing the subsequent risk of substance abuse.

There has been longstanding interest in the potential neurotoxic effects of chronic exposure to drugs and alcohol, and there are potential links with depression. For example, chronic alcohol and cocaine exposure has been associated with brain atrophy (Bjork et al. 2003). Similarly, depression also has been associated with atrophy of cerebral grey matter (Lambe et al. 2003). Chronic drug and alcohol use have been associated with changes in the brain dopamine system in neuroimaging studies (Goldstein and Volkow 2002). Abuse of methamphetamine has been associated with reduced levels of dopamine transporters (Sekine et al. 2003), dopamine D1 receptor function (Tong et al. 2003), and striatal glucose metabolism (Wang et al. 2004), and some of these deficits have been associated with psychiatric symptoms or impaired neuropsychological functioning (Sekine et al. 2003; Wang et al. 2004). Years of heavy alcohol consumption has been found to be correlated with reduced CNS response to serotonergic (*D*-fenfluramine) challenge, although the latter was not in turn associated with mood symptoms (Berggren et al. 2002). The serotonergic stimulant, (+/)-3,4-methylenedioxymethamphetamine (MDMA, or 'ecstasy'), has been associated with neurochemical changes consistent with reduced serotonin functioning, and there is some evidence that this may relate to

toxic effects on serotonergic neurons, particularly dendritic atrophy (Hrometz et al. 2004). The long-lasting nature of these effects further raises concern that such patients may ultimately be at greater risk for developing depressive disorders, although evidence to support this hypothesis has yet to emerge. Drug and alcohol abuse have been associated with reduced brain metabolism in the frontal lobes, as has depression (Goldstein and Volkow 2002). It is difficult to know whether, in these neurochemical and neuroimaging studies, deficits represented preexisting conditions, as opposed to toxic effects of drugs and alcohol (Pope et al. 2003), although they certainly raise a high index of suspicion for the latter.

13.5.2

Depression as a Risk Factor for Substance Abuse

The role of early-onset depression as a risk factor for subsequent substance abuse is less clearly delineated. Strong evidence exists for a link between other psychiatric disorders, particularly early-onset conduct and other disruptive disorders and associated temperament and neuropsychological deficits, and development of substance abuse during adolescence (Kellam et al. 1983; Brook et al. 1990; Kuperman et al. 2001; Costello et al. 2003; Tarter et al. 2003). With respect to internalizing disorders, early-onset anxiety and anxiety disorders have been more clearly associated with subsequent development of substance-use disorders than depression (Brook et al. 1990; Kellam et al. 1991; Kushner et al. 1999; Costello et al. 2003). Some studies do support an association between prior depression and subsequent development of alcohol- or drug-use disorders (Kellam et al. 1991; Klein et al. 2000; Gilman and Abraham 2001). Such a link might be indirect, given associations between anxiety and depression and between externalizing and internalizing disorders, a notion consistent with evidence that the shared genetic risk factors for depression and substance-use disorders may be related to disruptive disorders (Fu et al. 2002).

13.5.3

Shared Genetic Risks and Endophenotypes

Depression and alcohol and other drug dependencies are well known to be heritable, based on results of twin and adoption studies, with distinct genetic contributions for internalizing and externalizing disorders (Kendler et al. 2003). However, evidence from twin studies also suggests that there are common genetic factors that predispose to both depressive and addictive disorders (Kendler et al. 1993a, 1993b). This raises the further question of what genes or gene products or associated endophenotypes might predispose to both sets of disorders.

Data from the Collaborative Study on the Genetics of Alcoholism (COGA) support linkage between a locus on chromosome 1 and the phenotype 'alcoholism or depression'; this region has also been linked to bipolar disorder and to low responsiveness to alcohol (Nurnberger et al. 2001). No specific gene in this region has as yet been implicated, although low responsiveness to alcohol is a trait marker

that has been associated with familial alcoholism. One analysis of twin data suggested that the common genetic factor is conduct–antisocial–personality disorder, which then predisposes to major depression, alcohol dependence, and marijuana dependence (Fu et al. 2002). Related to this, early-onset depression has been associated with increased risk for subsequent development of antisocial personality (Kasen et al. 2001).

Early-onset aggressivity and impulsivity are temperamental traits that are fundamental to conduct–antisocial–personality disorder and are strong risk factors for substance abuse. Aggressivity has been consistently linked, in both animal models and humans, to serotonin system deficits (e.g., decreased CSF 5-HIAA or abnormal response to serotonergic pharmacologic challenge), a relationship that may be mediated by dysphoric mood states (Heinz et al. 2001). Serotonin dysfunction is implicated in anxiety and depressive disorders and may also influence responsivity to alcohol (Heinz et al. 2001). Related to this, alcoholism has been classified into subtypes based partly on temperamental features, and one subtype (captured in the overlapping typologies as Cloninger's Type 2 or Babor's Type B) involves early onset of alcoholism along with externalizing behavior problems and temperamental traits of high novelty seeking and low harm avoidance. Alcoholics falling into Babor's Type B display moderately elevated levels of depressive symptoms and poor response to serotonin-reuptake inhibitor (SRI) antidepressants (Kranzler et al. 1996; Pettinati et al. 2000). Similar poor response to an SRI has also been observed in Cloninger's Type 2 alcoholics (Chick et al. 2004). There has been considerable interest in the role of functional polymorphisms in the promoter region of the serotonin transporter gene with respect to personality (particularly trait neuroticism), anxiety, depression, response to antidepressant medication (Gelernter et al. 1998; Kelsoe 1998; Jacob et al. 2004), opiate dependence (Gerra et al. 2004), early-onset alcoholism, and responsivity to alcohol (Johnson 2000), although findings remain conflicting.

13.5.4

Stress and the Neuroendocrine System

Environmental stress is a well established risk factor for the development of both addictive disorders and depression. Animal models of depression (e.g., forced swimming or inescapable shock) that are used to screen medications for antidepressant efficacy are similar to animal models that have demonstrated relationships between stress and increased propensity to drug self-administration. Significant loss, adversity, trauma, or abuse during childhood is associated with subsequent development of depressive and anxiety disorders (Gilman et al. 2003; Reinherz et al. 2003), as are abuse, trauma, or chronic stress during adulthood (Kendler et al. 2003). Exposure to trauma is also implicated in the development of substance dependence, an effect that may be mediated or marked by the development of post-traumatic stress disorder (Breslau et al. 2003). Several lines of evidence suggest that the association observed between depression and substance dependence may be attributable in part to physical or sexual abuse during childhood or other adverse

childhood experiences, such as violence between parents in the home or parental separation or divorce (Anda et al. 2002; Clark et al. 2003).

The underlying neurobiology of stress is complex and involves both the hypothalamic–pituitary adrenal axis and a variety of related systems (e.g., locus coeruleus norepinephrine system, meso–cortico–limbic dopamine system, serotonin system) (Koob 1999; Heinz et al. 2001; Charney 2004). These systems regulate phenomena relevant to depression and addiction, including sensitivity to reward, learned helplessness, and responsiveness to fear. Further, it is likely that individuals vary in their resiliency or in susceptibility of these systems to stress (Charney 2004), so that not all those who are exposed to severe stress develop depression or post-traumatic stress disorder. The development of symptoms in response to trauma (Breslau et al. 2003) or sensitivity to stress (Zvolensky et al. 2001; Brown et al. 2002) have been found to be predictive of risk for substance-use disorder. Different sensitivity to stress likely relates in part to genetic factors (possibly some of those implicated in the above discussion of genetics of depression and substance abuse) and to prior experience or conditioning wherein early or chronic stressful experiences gradually sensitized an individual to effects of stress. Chronic stress and resultant glucocorticoid excess have also been implicated in cortical atrophy and neuropsychological impairment (Sapolsky 2000), which are implicated in both mood- and substance-use disorders.

Ultimately, greater understanding of mechanisms linking stress to psychopathology and to addiction should help to guide advances in treatment development. For example, stress management techniques play a role in cognitive–behavioral treatments for both sets of disorders. Medications that antagonize aspects of the stress response (e.g., CRF antagonists, adrenergic antagonists, glucocorticoid receptor antagonists) are under consideration as treatments for depression or addiction. Stress and stress responsiveness may also play a role in mediating the impact of pharmacotherapies. For example the efficacy of the SRI antidepressant sertraline in opiate-dependent patients with depressive disorders was found to depend upon environmental context: sertraline was effective for patients with more rewarding or less aversive environments and ineffective for those in less rewarding and more aversive circumstances (Carpenter et al. 2004). A similar effect might explain the detrimental effects of serotonin reuptake inhibitors in early-onset (Type 2, or Type B) alcoholics (Kranzler et al. 1996; Pettinati et al. 2000; Chick et al. 2004), who might either experience more environmental stress or be constitutionally more susceptible to it.

13.6

Conclusions and Future Directions

The field has entered an exciting time in the study of psychopathology, when powerful tools of epidemiology, genetics, and neurobiology are beginning to converge in elucidating the pathoetiology of disorders such as depression and addiction. A traditional and still popular line of reasoning among clinicians holds

that depressive and substance-use disorders are relatively independent phenomena and should be approached as such in treatment planning. An analogous scientific approach suggests that the pathophysiology of a disorder can best be understood by studying the disorder in its pure form, rather than in patients whose symptoms are complicated by the presence of multiple disorders. We hope that this chapter, by outlining some of the areas of convergence between mood symptoms, mood disorders, and substance-use disorders, illustrates the promise of studying comorbidity as a way of better understanding the component disorders. Specifically, we have reviewed findings on the increased prevalence of addictive disorders among depressed persons, adverse prognostic effects when both disorders are combined, benefits of joint treatment for depression and addiction, depressogenic effects of chronic substance exposure and withdrawal, effects of depressed mood in heightening the euphoric response to and reward value of addictive substances, the interplay of both sets of disorders over the course of development, common genetic underpinnings and potential related endophenotypes, and the role of stress and response to stress in promoting both depression and addictions.

It seems clear that both addictive and depressive disorders are complex, heterogeneous disorders and that identification of more homogenous subtypes with distinct underlying neurobiology would advance our understanding of these disorders. In future research, a productive strategy may be to contrast addicted patients with and without depressive symptoms or disorders, and, conversely, to contrast depressed patients with and without histories of addiction in a range of behavioral, genetic, and biological measures. Such cross-disorder, cross-disciplinary research is consistent with the new guiding vision of translational research articulated at the National Institutes of Health.

Ultimately, we hope that greater understanding of depressed patients who are addicted to nicotine, alcohol, or other drugs will improve diagnosis, treatment, and relief of suffering in patients who have comorbid disorders. When nicotine, alcohol, and other drugs are all considered, a large proportion of depressed patients suffer from an addiction. To date, there has been some research on treatment of comorbid psychopathology among addicted patients and little research on the treatment of addictions among patients with depressive disorders. More research on the treatment of patients with such comorbidity is needed. The association of combined depression and addiction with poor treatment outcome and the high rates of treatment failure for both disorders illustrate the magnitude of the problem. Preliminary findings such as those on efficacy of antidepressant medication in substance abusers with depressive disorders (Nunes and Levin 2004) and the relevance of alcoholic subtypes for antidepressant efficacy (Kranzler et al. 1996; Pettinati et al. 2000; Chick et al. 2004) suggest the promise for more precisely targeted treatments based on greater fundamental understanding of subtypes defined by comorbidity.

References

- AMERICAN PSYCHIATRIC ASSOCIATION, *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edit. American Psychiatric Association, Washington, DC, 1994.
- ANDA, R. F., WHITFIELD, C. L., FELITTI, V. J., CHAPMAN, D., EDWARDS, V. J., DUBE, S. R., WILLIAMSON, D. F., Adverse childhood experiences, alcoholic parents, and later risk of alcoholism and depression. *Psychiatr. Serv.* **2002**, *53*, 1001–1009.
- ARMSTRONG, T. D., COSTELLO, E. J., Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity: a literature review. *J. Consult. Clin. Psychol.* **2002**, *70*, 1224–1239.
- BAER, J. S., SAMPSON, P. D., BARR, H. M., CONNOR, P. D., STREISSGUTH, A. P., A 21-year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking. *Arch. Gen. Psychiatry* **2003**, *60*, 377–385.
- BERGGREN, U., ERIKSSON, M., FAHLKE, C., BALLDIN, J., Is long-term heavy alcohol consumption toxic for brain serotonergic neurons? Relationship between years of excessive alcohol consumption and serotonergic neurotransmission. *Drug Alcohol Depend.* **2002**, *65*, 159–165.
- BJORK, J. M., GRANT, S. J., HOMMER, D. W., Cross-sectional volumetric analysis of brain atrophy in alcohol dependence: effects of drinking history and comorbid substance use disorder. *Am. J. Psychiatry* **2003**, *160*, 2038–2045.
- BRESLAU, N., KILBEY, M. M., Andreski P: Nicotine dependence and major depression: new evidence from a prospective investigation. *Arch. Gen. Psychiatry* **1993**, *50*, 31–35.
- BROOK, J. S., BROOK, D. W., GORDON, A. S., et al., The psychosocial etiology of adolescent drug use: a family interactional approach. *Genet. Soc. Gen. Psychol. Monogr.* **1990**, *116*, 111–267.
- BROOK, D. W., BROOK, J. S., ZHANG, C., COHEN, P., WHITEMAN, M., Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. *Arch. Gen. Psychiatry* **2002**, *59*, 1039–1044.
- BROWN, R. A., LEJUEZ, C. W., KAHLER, C. W., STRONG, D. R., Distress tolerance and duration of past smoking cessation attempts. *J. Abnorm. Psychol.* **2002**, *111*, 180–185.
- BROWN, S. A., SCHUCKIT, M. A., Changes in depression among abstinent alcoholics. *J. Stud. Alcohol* **1988**, *49*, 412–417.
- BROWN, S. A., INABA, R. K., GILLIN, J. C., SCHUCKIT, M. A., STEWART, M. A., IRWIN, M. R., Alcoholism and affective disorder: clinical course of depressive symptoms. *Am. J. Psychiatry* **1995**, *152*, 45–52.
- BUKA, S. L., SHENASSA, E. D., NIAURA, R., Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am. J. Psychiatry* **2003**, *160*, 1978–1984.
- CARROLL, K. M., NICH, C., ROUNSAVILLE, B. J., Differential symptom reduction in depressed cocaine abusers treated with psychotherapy or pharmacotherapy. *J. Nerv. Ment. Dis.* **1995**, *183*, 251–259.
- CHARNEY, D. S., Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am. J. Psychiatry* **2004**, *161*, 195–216.
- CHICK, J., ASCHAUER, H., HORNIK, K., Investigators Group. Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology. *Drug Alcohol Depend.* **2004**, *74*, 61–70.
- CLARK, D. B., DE BELLIS, M. D., LYNCH, K. G., CORNELIUS, J. R., MARTIN, C. S., Physical and sexual abuse, depression and alcohol use disorders in adolescents: onsets and outcomes. *Drug Alcohol Depend.* **2003**, *69*, 51–60.
- COSTELLO, E. J., MUSTILLO, S., ERKANLI, A., KEELER, G., ANGOLD, A., Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch. Gen. Psychiatry* **2003**, *60*, 837–844.
- COVEY, L. S., GLASSMAN, A. H., STETNER, F., Major depression following smoking cessation. *Am. J. Psychiatry* **1997**, *154*, 263–265.
- DELEON, G., SKODOL, A., ROSENTHAL, M. S., Phoenix House: changes in psychopathological signs of resident drug

- addicts. *Arch. Gen. Psychiatry* **1973**, *28*, 131–135.
- DRAKE, R. E., MCHUGO, G. J., CLARK, R. E., TEAGUE, G. B., XIE, H., MILES, K., ACKERSON, T. H., Assertive community treatment for patients with co-occurring severe mental illness and substance use disorder: a clinical trial. *Am. J. Orthopsychiatry* **1998**, *68*, 201–215.
- EVANS, S. M., HANEY, M., FOLTIN, R. W., The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. *Psychopharmacology (Berl.)* **2002**, *159*, 397–406.
- FERGUSON, D. M., HORWOOD, L. J., Swain-Campbell N: Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* **2002**, *97*, 1123–1135.
- FU, Q., HEATH, A. C., BUCHOLZ, K. K., NELSON, E., GOLDBERG, J., LYONS, M. J., TRUE, W. R., JACOB, T., TSUANG, M. T., EISEN, S. A., Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men. *Arch. Gen. Psychiatry* **2002**, *59*, 1125–1132.
- GELEERTER, J., KRANZLER, H., COCCARO, E. F., SIEVER, L. J., NEW, A. S., Serotonin transporter protein gene polymorphism and personality measures in African American and European American subjects. *Am. J. Psychiatry* **1998**, *155*, 1332–1338.
- GERRA, G., GAROFANO, L., SANTORO, G., BOSARI, S., PELLEGRINI, C., ZAIMOVIC, A., MOI, G., BUSSANDRI, M., MOI, A., BRAMBILLA, F., DONNINI, C., Association between low-activity serotonin transporter genotype and heroin dependence: behavioral and personality correlates. *Am. J. Med. Genet.* **2004**, *126B*, 37–42.
- GILMAN, S. E., ABRAHAM, H. D., A longitudinal study of the order of onset of alcohol dependence and major depression. *Drug Alcohol Depend.* **2001**, *63*, 277–286.
- GLASSMAN, A. H., Cigarette smoking: implications for psychiatric illness. *Am. J. Psychiatry* **1993**, *150*, 546–553.
- GLASSMAN, A. H., HELZER, J. E., COVEY, L. S., COTTLER, L. B., STETNER, F., TIPP, J. E., JOHNSON, J., Smoking, smoking cessation, and major depression. *JAMA* **1990**, *264*, 1546–1549.
- GOLDSTEIN, R. Z., Volkow ND: Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychiatry* **2002**, *159*, 1642–1652.
- GRANT, B. F., Comorbidity between DSM-IV drug use disorders and major depression: results of a national survey. *J. Subst. Abuse* **1995**, *7*, 481–497.
- GRANT, B. F., Harford TC: Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. *Drug Alcohol Depend.* **1995**, *39*, 197–206.
- GRANT, B. F., STINSON, F. S., DAWSON, D. A., CHOU, S. P., DUFOUR, M. C., COMPTON, W., PICKERING, R. P., KAPLAN, K., Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the national epidemiologic survey on alcohol and related conditions. *Arch. Gen. Psychiatry* **2004**, *61*, 807–816.
- HALL, S. M., REUS, V. I., MUNOZ, R. F., et al., Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Arch. Gen. Psychiatry* **1998**, *55*, 683–690.
- HANNA, E. Z., YI, H. Y., DUFOUR, M. C., WHITMORE, C. C., The relationship of early-onset regular smoking to alcohol use, depression, illicit drug use, and other risky behaviors during early adolescence: results from the youth supplement to the third national health and nutrition examination survey. *J. Subst. Abuse* **2001**, *13*, 265–282.
- HASIN, D., LIU, X., NUNES, E., et al., Effects of major depression on remission and relapse of substance dependence. *Arch. Gen. Psychiatry* **2002**, *59*, 375–380.
- HASIN, D., NUNES, E., MEYDAN, J., Comorbidity of alcohol, drug and psychiatric disorders: epidemiology. In: KRANZLER, H. R., TINSLEY, J. A. (Eds.), *Dual Diagnosis and Treatment: Substance Abuse and Comorbid Disorders*. New York: Dekker; **2004**.
- HAVASSY, B. E., ALVIDREZ, J., OWEN, K. K., Comparisons of patients with comorbid psychiatric and substance use disorders: implications for treatment and service delivery. *Am. J. Psychiatry* **2004**, *161*, 139–145.

- HEINZ, A., MANN, K., WEINBERGER, D. R., GOLDMAN, D., Serotonergic dysfunction, negative mood states, and response to alcohol. *Alcohol Clin. Exp. Res.* **2001**, *25*, 487–495.
- HELLERSTEIN, D. J., ROSENTHAL, R. N., MINER, C. R., Integrating services for schizophrenia and substance abuse. *Psychiatr. Q* **2001**, *72*, 291–306.
- HIGGINS, S. T., BUDNEY, A. J., BICKEL, W. K., HUGHES, J. R., FOERG, F., BADGER, G., Achieving cocaine abstinence with a behavioral approach. *Am. J. Psychiatry* **1993**, *150*, 763–769.
- HITSMAN, B., BORRELLI, B., MCCARGUE, D. E., SPRING, B., NIAURRA, R., History of depression and smoking cessation outcome: a meta-analysis. *J. Consult. Clin. Psychol.* **2003**, *71*, 657–663.
- HROMETZ, S. L., BROWN, A. W., NICHOLS, D. W., SPRAGUE, J. E., 3,4-methylene-dioxymethamphetamine (MDMA, ecstasy)-mediated production of hydrogen peroxide in an in vitro model: the role of dopamine, the serotonin-reuptake transporter, and monoamine oxidase-B. *Neurosci. Lett.* **2004**, *367*, 56–59.
- JACOB, C. P., STROBEL, A., HOHENBERGER, K., RINGEL, T., GUTKNECHT, L., REIF, A., BROCKE, B., LESCH, K. P., Association between allelic variation of serotonin transporter function and neuroticism in anxious cluster C personality disorders. *Am. J. Psychiatry* **2004**, *161*, 569–572.
- JOHNSON, B. A., Serotonergic agents and alcoholism treatment: rebirth of the subtype concept – an hypothesis. *Alcohol Clin. Exp. Res.* **2000**, *24*, 1597–1601.
- KASEN, S., COHEN, P., SKODOL, A. E., JOHNSON, J. G., SMAILES, E., BROOK, J. S., Childhood depression and adult personality disorder: alternative pathways of continuity. *Arch. Gen. Psychiatry* **2001**, *58*, 231–236.
- KELLAM, S. G., BROWN, C. H., RUBIN, B. R., et al., Paths leading to teenage psychiatric symptoms and substance use: developmental epidemiological studies in Woodlawn. In: GUZE, S. B., EARLS, F. J., BARRETT, J. E. (Eds.), *Childhood Psychopathology and Development*. New York: Raven Press; **1983**, pp 17–51.
- KELLAM, S. G., WERTHAMER-LARSSON, L., DOLAN, L. J., et al., Developmental epidemiologically based preventive trials; baseline modeling of early target behaviors and depressive symptoms. *Am. J. Commun. Psychol.* **1991**, *19*, 563–584.
- KELSOE, J. R., Promoter prognostication: the serotonin transporter gene and antidepressant response. *Mol. Psychiatry* **1998**, *3*, 475–476.
- KENDLER, K. S., NEALE, M. C., MACLEAN, C. J., et al., Smoking and major depression: a causal analysis. *Arch. Gen. Psychiatry* **1993a**, *50*, 3643.
- KENDLER, K. S., HEATH, A. C., NEALE, M. C., et al., Alcoholism and major depression in women: a twin study of the causes of comorbidity. *Arch. Gen. Psychiatry* **1993b**, *50*, 690–698.
- KENDLER, K. S., PRESCOTT, C. A., MYERS, J. K., et al., The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch. Gen. Psychiatry* **2003**, *60*, 929–937.
- KENFORD, S. L., SMITH, S. S., WETTER, D. W., JORENBY, D. E., FIORE, M. C., BAKER, T. B., Predicting relapse back to smoking: contrasting affective and physical models of dependence. *J. Consult. Clin. Psychol.* **2002**, *70*, 216–227.
- KESSLER RC: EPIDEMIOLOGY OF PSYCHIATRIC COMORBIDITY. In: TSUANG, M. T., TOHEN, M., Zahner, G. E. P. (Eds.), *Textbook in Psychiatric Epidemiology*. New York: Wiley; **1995**, pp 179–197.
- KHANTZIAN, E. J., The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am. J. Psychiatry* **1985**, *142*, 1259–1264.
- KLEIN, D. N., SCHWARTZ, J. E., ROSE, S., LEADER, J. B., Five-year course and outcome of dysthymic disorder: a prospective, naturalistic follow-up study. *Am. J. Psychiatry* **2000**, *157*, 931–939.
- KOOB, G. F., Stress, corticotropin-releasing factor, and drug addiction. *Ann. NY Acad. Sci.* **1999**, *897*, 27–45.
- KRANZLER, H. R., BURLESON, J. A., BROWN, J., BABOR, T. F., Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. *Alcohol Clin. Exp. Res.* **1996**, *20*, 1534–1541.
- KUPERMAN, S., SCHLOSSER, S. S., KRAMER, J. R., BUCHOLZ, K., HESSELBROCK, V., REICH, T., REICH, W., Developmental

- sequence from disruptive behavior diagnosis to adolescent alcohol dependence. *Am. J. Psychiatry* **2001**, *158*, 2022–2026.
- KUSHNER, M. G., SHER, K. J., ERICKSON, D. J., Prospective analysis of the relation between DSM-III anxiety disorders and alcohol use disorders. *Am. J. Psychiatry* **1999**, *156*, 723–732.
- LAMPE, I. K., HULSHOFF POL, H. E., JANSSEN, J., SCHNACK, H. G., KAHN, R. S., HEEREN, T. J., Association of depression duration with reduction of global cerebral gray matter volume in female patients with recurrent major depressive disorder. *Am. J. Psychiatry* **2003**, *160*, 2052–2054.
- LIAPPAS, J., PAPARRIGOPoulos, T., TZAVELLAS, E., CHRISTODOULOU, G., Impact of alcohol detoxification on anxiety and depressive symptoms. *Drug Alcohol Depend.* **2002**, *68*, 215–220.
- MALANGA, C. J., KOSOFSKY, B. E., Does drug abuse beget drug abuse? Behavioral analysis of addiction liability in animal models of prenatal drug exposure. *Brain Res. Dev. Brain Res.* **2003**, *147*, 47–57.
- MARKOU, A., KOSTEN, T. R., KOOB, G. F., Neurobiologic similarities in depression and drug dependence: a self-medication hypothesis. *Neuropsychopharmacology* **1998**, *18*, 135–174.
- NIAURA, R., BOCK, B., LLOYD, E. E., BROWN, R., LIPSITT, L. P., BUKA, S., Maternal transmission of nicotine dependence: psychiatric, neurocognitive and prenatal factors. *Am. J. Addict.* **2001**, *10*, 16–29.
- NUNES, E. V., LEVIN, F. R., Treatment of depression in patients with alcohol or drug dependence: a meta-analysis. *JAMA* **2004**, *291*, 1887–1896.
- NURNBERGER, J. I. JR., FOROUD, T., FLURY, L., SU, J., MEYER, E. T., HU, K., CROWE, R., EDENBERG, H., GOATE, A., BIERUT, L., REICH, T., SCHUCKIT, M., REICH, W., Evidence for a locus on chromosome 1 that influences vulnerability to alcoholism and affective disorder. *Am. J. Psychiatry* **2001**, *158*, 718–724.
- PATTON, G. C., COFFEY, C., CARLIN, J. B., et al., Cannabis use and mental health in young people: cohort study. *BMJ* **2002**, *325*, 1195–1198.
- PETTINATI, H. M., VOLPICELLI, J. R., KRANZLER, H. R., LUCK, G., RUKSTALIS, M. R., CNAAN, A., Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. *Alcohol Clin. Exp. Res.* **2000**, *24*, 1041–1049.
- POPE, H. G. JR., GRUBER, A. J., HUDSON, J. I., COHANE, G., HUESTIS, M. A., YURGELUN-TODD, D., Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend.* **2003**, *69*, 303–310.
- RACHBEISEL, J., SCOTT, J., DIXON, L., Co-occurring severe mental illness and substance use disorders: a review of recent research. *Psychiatr. Serv.* **1999**, *50*, 1427–1434.
- RANDALL, D. M., COX, W. M., Experimental mood inductions in persons at high and low risk for alcohol problems. *Am. J. Drug Alcohol Abuse* **2001**, *27*, 183–187.
- REGIER, D. A., FARMER, M. E., RAE, D. S., LOCKE, B. Z., KEITH, S. J., JUDD, L. L., GOODWIN, F. K., Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* **1990**, *264*, 2511–2518.
- ROSENBLUM, A., FALLON, B., MAGURA, S., HANDELSMAN, L., FOOTE, J., BERNSTEIN, D., The autonomy of mood disorders among cocaine-using methadone patients. *Am. J. Drug Alcohol Abuse* **1999**, *25*, 67–80.
- RUSH, A. J., FAVA, M., WISNIEWSKI, S. R., LAVORI, P. W., TRIVEDI, M. H., SACKEIM, H. A., THASE, M. E., NIERENBERG, A. A., QUITKIN, F. M., KASHNER, T. M., KUPFER, D. J., ROSENBAUM, J. F., ALPERT, J., STEWART, J. W., McGRATH, P. J., BIGGS, M. M., SHORES-WILSON, K., LEBOWITZ, B. D., RITZ, L., Niederehe G; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D), rationale and design. *Control Clin. Trials* **2004**, *25*, 119–142.
- SALLOUM, I. M., THASE, M. E., Impact of substance abuse on the course and treatment of bipolar disorder. *Bipolar Disord.* **2000**, *2*, 269–280.
- SAPOLSKY, R. M., Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch. Gen. Psychiatry* **2000**, *57*, 925–935.
- SATEL, S. L., PRICE, L. H., PALUMBO, J. M., MCDUGLE, C. J., KRYSTAL, J. H., GAWIN,

- F., CHARNEY, D. S., HENINGER, G. R., KLEBER, H. D., Clinical phenomenology and neurobiology of cocaine abstinence: a prospective inpatient study. *Am. J. Psychiatry* **1991**, *148*, 1712–1716.
- SCHUCKIT, M. A., The clinical implications of primary diagnostic groups among alcoholics. *Arch. Gen. Psychiatry* **1985**, *42*, 1043–1049.
- SCHUCKIT, M. A., Genetic and clinical implications of alcoholics and affective disorder. *Am. J. Psychiatry* **1986**, *143*, 140–147.
- SEKINE, Y., MINABE, Y., OUCHI, Y., TAKEI, N., IYO, M., NAKAMURA, K., SUZUKI, K., TSUKADA, H., OKADA, H., YOSHIKAWA, E., FUTATSUBASHI, M., MORI, N., Association of dopamine transporter loss in the orbitofrontal and dorsolateral prefrontal cortices with methamphetamine-related psychiatric symptoms. *Am. J. Psychiatry* **2003**, *160*, 1699–1701.
- SOFUOGLU, M., BROWN, S., BABB, D. A., HATSUKAMI, D. K., Depressive symptoms modulate the subjective and physiological response to cocaine in humans. *Drug Alcohol Depend.* **2001**, *63*, 131–137.
- SOFUOGLU, M., DUDISH-POULSEN, S., BROWN, S. B., HATSUKAMI, D. K., Association of cocaine withdrawal symptoms with more severe dependence and enhanced subjective response to cocaine. *Drug Alcohol Depend.* **2003**, *69*, 273–282.
- SPRING, B., PINGITORE, R., MCCHARGUE, D. E., Reward value of cigarette smoking for comparably heavy smoking schizophrenic, depressed, and nonpatient smokers. *Am. J. Psychiatry* **2003**, *160*, 316–322.
- STRAIN, E. C., STITZER, M. L., BIGELOW, G. E., Early treatment time course of depressive symptoms in opiate addicts. *J. Nerv. Ment. Dis.* **1991**, *179*, 215–221.
- TARTER, R. E., KIRISCI, L., MEZZICH, A., CORNELIUS, J. R., PAJER, K., VANYUKOV, M., GARDNER, W., BLACKSON, T., CLARK, D., Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *Am. J. Psychiatry* **2003**, *160*, 1078–1085.
- THAPAR, A., FOWLER, T. A., RICE, F., SCOURFIELD, J., VAN DEN BREE, M., THOMAS, H., HAROLD, G., HAY, D., Maternal smoking in pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *Am. J. Psychiatry* **2003**, *160*, 1985–1989.
- TIDEY, J. W., MEHL-MADRONA, L., HIGGINS, S. T., BADGER, G. J., Psychiatric symptom severity in cocaine-dependent outpatients: demographics, drug use characteristics and treatment outcome. *Drug Alcohol Depend.* **1998**, *50*, 9–17.
- TONG, J., ROSS, B. M., SCHMUNK, G. A., PERETTI, F. J., KALASINSKY, K. S., FURUKAWA, Y., ANG, L. C., AIKEN, S. S., WICKHAM, D. J., KISH, S. J., Decreased striatal dopamine D1 receptor-stimulated adenylyl cyclase activity in human methamphetamine users. *Am. J. Psychiatry* **2003**, *160*, 896–903.
- TREMBLAY, L. K., NARANJO, C. A., CARDENAS, L., HERRMANN, N., BUSTO, U. E., Probing brain reward system function in major depressive disorder: altered response to dextroamphetamine. *Arch. Gen. Psychiatry* **2002**, *59*, 409–416.
- USLANER, J., KALECHSTEIN, A., RICHTER, T., LING, W., NEWTON, T., Association of depressive symptoms during abstinence with the subjective high produced by cocaine. *Am. J. Psychiatry* **1999**, *156*, 1444–1446.
- WANG, G. J., VOLKOW, N. D., CHANG, L., MILLER, E., SEDLER, M., HITZEMANN, R., ZHU, W., LOGAN, J., MA, Y., FOWLER, J. S., Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. *Am. J. Psychiatry* **2004**, *161*, 242–248.
- WEDDINGTON, W. W., BROWN, B. S., HAERTZEN, C. A., CONE, E. J., DAX, E. M., HERNING, R. I., MICHAELSON, B. S., Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts: a controlled, residential study. *Arch. Gen. Psychiatry* **1990**, *47*, 861–868.
- WILLNER, P., FIELD, M., PITTS, K., REEVE, G., Mood, cue and gender influences on motivation, craving and liking for alcohol in recreational drinkers. *Behav. Pharmacol.* **1998**, *9*, 631–642.
- ZVOLENSKY, M. J., FELDNER, M. T., EIFERT, G. H., BROWN, R. A., Affective style among smokers: understanding anxiety sensitivity, emotional reactivity, and distress tolerance using biological challenge. *Addict. Behav.* **2001**, *26*, 901–915.

14

Depression in the Context of Cancer

Elliot J. Coups, Jeremy Winell and Jimmie C. Holland

Abstract

This chapter presents an up-to-date overview of depression in the context of cancer. Topics we examine include the measurement and diagnosis of depression, prevalence, biological markers and underpinnings, and the management of depression. The assessment of depression in cancer patients is complex. We discuss multiple conceptual approaches to the diagnosis of depression in cancer patients, and also examine available diagnostic measures and tools. Prevalence estimates of depression among cancer patients vary widely. We consider reasons for such diverse estimates and provide suggestions for improved reporting of prevalence estimates. On a biological level, we examine five biological markers of depression: serotonergic neurotransmission changes, sleep architecture changes, brain structure abnormalities, neuroendocrine changes, and cytokines. We conclude with an analysis of the management of depression in cancer patients. Available treatment modalities include antidepressant medications (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, atypical antidepressants, and psychostimulants), psychotherapy, and electroconvulsive therapy. In examining these inter-related topics regarding depression in the context of cancer, our review spans conceptual, methodological, physiological, and clinical issues.

14.1

Introduction

It is normal that sadness is a response to a diagnosis of cancer, since the implication of potential losses is the usual perception of cancer. But how much is “normal” and when does it become “abnormal”? Is there a continuum of severity of depressed mood from sadness to major depression, or are there discrete entities with their own differing etiologies? What is the difference between the depression that is a psychological response to cancer and depression that occurs with pancreatic cancer,

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or with high-dose interferon? These are some of the important and challenging conundrums related to depression in the context of cancer and its treatment.

14.2

Measurement and Diagnosis of Depression in Cancer Patients

The effective management and treatment of depression relies on timely and appropriate assessment. Ideally, a diagnosis of depression represents the initial step in an integrated and comprehensive approach to treatment and follow-up assessment. In cancer patients (and individuals with other debilitating illnesses), the assessment of depression is a difficult (and often-debated) matter. The primary presenting symptoms of depression are depressed mood and anhedonia (a marked loss of pleasure or interest in daily activities), but the key issue regarding assessment is the interpretation of neurovegetative symptoms of depression among cancer patients: loss of appetite, weight loss, fatigue, sleep disturbances, and impaired concentration. These may represent genuine symptoms of depression, or they may relate directly to the underlying cancer and/or its treatment. As presented in Table 14.1, four conceptual approaches are available to handle this issue: inclusive, exclusive, etiological, and substitutive [6].

There are merits and drawbacks – particularly with regard to sensitivity and specificity – associated with each conceptual approach [6], and no single approach is inherently superior to the others. One important distinction to consider is whether a diagnosis of depression is being made for clinical or research purposes. The high sensitivity associated with the inclusive approach makes it appropriate for the clinical setting, resulting in a relatively low number of missed cases of depression, but with an increased risk of false-positive diagnoses [6]. However, this is tempered by the low likelihood of complications from treatment for misdiagnosed depression, and suggestive evidence that treatment may ameliorate symptoms of depression, regardless of their etiology [7, 8]. The substitutive approach (which, for example,

Table 14.1 Conceptual approaches to the diagnosis of depression in cancer patients

Conceptual approach	Description	Representative reference(s)
Inclusive	All symptoms of depression are counted, regardless of their (suspected) etiology	[1]
Exclusive	Neurovegetative symptoms of depression are not considered	[2]
Etiological	A judgment is made as to the etiology of neurovegetative symptoms: symptoms judged to be depression-related are included, those judged to be cancer- or treatment-related are not counted	[3]
Substitutive	Other symptoms of depression are substituted for neurovegetative symptoms with an unclear etiology (e.g. replacing fatigue with brooding)	[4, 5]

recommends replacing the symptom of fatigue with brooding), suggested initially by Endicott [4], is an intuitively appealing alternative to the inclusive approach in clinical settings, but there is little evidence for its superiority (e.g. [9]). Future research that utilizes an empirically-confirmed theoretical basis for symptom substitution is needed, and may provide an improvement over the inclusive approach. The rationale behind the etiological approach is sound, but it is hard to apply in clinical practice. However, in certain circumstances, clinicians with in-depth knowledge and significant clinical experience in a particular setting (e.g. working with pancreatic cancer patients) may gainfully use the etiological approach to minimize false-positive diagnoses. The high specificity associated with the exclusive approach makes it highly-suited for research purposes.

14.2.1

DSM-IV Diagnoses of Depression in Cancer Patients

Several subcategories of DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [10]) depression diagnoses are found in the context of cancer. A diagnosis of “mood disorder with depressive features due to cancer” is the appropriate diagnosis when it is felt that the depressive disorder is due to an underlying cancer, such as pancreatic cancer, lymphoma, or a tumor of the central nervous system (CNS). It is also used when the depression appears to be directly related to the presence of disabling or troublesome physical symptoms. When a medication (such as interferon or tamoxifen) is judged to be the underlying cause of a depressive disorder, the diagnosis of “substance-induced mood disorder” is used. As noted above, establishing the etiology of symptoms of depression in cancer patients is difficult.

A diagnosis of “adjustment disorder with depressed mood” is used in the case of patients who have emotional or behavioral symptoms that significantly impair role (e.g. job, academic, social) functioning, or that are accompanied by a level of distress in excess of that which would normally be expected in the situation at hand. In the context of cancer diagnosis and treatment, one can reasonably expect many patients to experience some level of sadness and other minor depressive symptoms. Thus, the clinician must use his or her clinical experience to make a judgment as to when these symptoms exceed a “normal reaction”. The level of distress and depressive feelings associated with an adjustment disorder diagnosis are below the level required for a diagnosis of a “major depressive episode” (or major depression), which is the primary focus of this chapter.

Major depression refers to an episode of clinically significant persistent and pervasive depressed mood and/or anhedonia, which is accompanied by additional cognitive and behavioral symptoms. The DSM-IV presents the specific symptoms of depression (depressed mood and/or diminished interest or pleasure in daily activities, as well as additional cognitive and behavioral symptoms), the timing and frequency of symptoms (present during the same 2-week period, most of the day, nearly every day), and the effects of symptoms (causing clinically significant distress or functional impairment) that are necessary for the diagnosis of major depression.

(For a detailed analysis of the DSM-IV criteria, see Chapter 2 in this volume). These criteria are consistent with the etiological approach to depression diagnosis, since symptoms that are deemed to be due to a medical condition or medication do not count towards the diagnosis. As necessary, these criteria can be adapted in line with the other conceptual approaches to depression diagnosis which were outlined earlier.

14.2.2

Diagnostic Measures and Tools

The DSM-IV [10] (and the less-often utilized Research Diagnostic Criteria; RDC [11]) provides an overarching criterion-based framework for the assessment of depression. A number of structured and semi-structured interviews are available to assess the criteria outlined by this framework (see Table 14.2), including the Structured Clinical Interview for DSM-IV (SCID), which has both clinician and research versions [12, 13], the Schedule for Affective Disorders and Schizophrenia (SADS, [14]), the Primary Care Evaluation of Mental Disorders (PRIME-MD [15]), and the Diagnostic Interview Schedule (DIS [16]). The SCID, SADS, and PRIME-MD are semi-structured interviews that involve clinical judgments regarding symptoms, whereas the fully-structured DIS does not require such judgments and can thus be used by non-clinicians (as may be necessary in large epidemiological studies). The PRIME-MD was developed specifically for the primary care setting, but can also be utilized in oncology settings. It combines an initial self-report symptom checklist followed by structured clinician-delivered questions that query an endorsed symptom. In their entirety, each of these measures also assesses non-depression-related disorders, although these sections can be omitted, as necessary.

A second approach to the assessment of depression focuses on self-report measures (see Table 14.2). These measures are screening, rather than diagnostic tools *per se*, although clinical cut-off scores can be used with each measure to identify likely major depression. Self-report measures can also be useful for tracking changes

Table 14.2 Common measures of depression in cancer patients

Measures	Notes
Diagnostic interviews	
Structured Clinical Interview for DSM-IV (SCID)	Semi-structured
Schedule for Affective Disorders and Schizophrenia (SADS)	Semi-structured
Diagnostic Interview Schedule (DIS)	Fully structured
Primary Care Evaluation of Mental Disorders (Prime-MD)	Self-report checklist and semi-structured questions
Self-report	
Hospital Anxiety and Depression (HADS)	Seven depression items
Carroll Depression Rating Scale (CDRS)	Also available in short form
Beck Depression Inventory (BDI)	Also available in short form and fast screen for medical patients

in symptom severity (for clinical or research purposes), for example to assess the efficacy of a treatment regimen. Appropriate measures for oncology settings, and medical settings more generally, include the Beck Depression Inventory (BDI [17]), the Hospital Anxiety and Depression Scale (HADS [18]), and the Carroll Depression Rating Scale (CDRS [19]). These measures vary in length (note that the BDI and the CDRS are also available in a short form), question content and format, and have differing levels of sensitivity and specificity for detecting major depression (compared to the benchmark of clinician-administered interviews; see [20]). Issues to consider when selecting a self-report measure include the available time, the type of patient (e.g. age, level of disability), and the setting (e.g. palliative care versus outpatient oncology clinic).

There are also less formal tools and guidelines available for assessing depression in the context of cancer. For example, both Roth and Holland [21] and Potash and Breitbart [22] provide a list of questions that clinicians can use to assess depression in a relatively brief encounter. Questions regarding psychological symptoms include “How are your spirits?” and “How does the future look to you?” Questions about physical symptoms include “Do you fatigue easily?” and “How is your appetite?”. There is also evidence that, in certain circumstances, a single-item assessment can screen effectively for depression. For example, in a sample of 197 terminally-ill cancer patients receiving palliative care, a single depressed mood item from the SADS interview (“Have you been depressed most of the time for the past 2 weeks?”) exhibited perfect sensitivity and specificity compared to the full interview [23]. The short form of the BDI had a lower sensitivity and specificity in this study.

In clinical settings, use of diagnostic tools for depression should be complemented by a consideration of broader cognitive and psychosocial factors. An assessment of cognitive functioning (with neuropsychological testing, as necessary) should be used to identify potential dementia or delirium, both of which have overlapping symptoms with depressive disorders. Additionally, attention should be paid to each individual's personal and family history of depression, suicidal ideation, suicide attempts, and actual suicides.

14.3

Prevalence of Depression in Cancer Patients

Many studies have documented the prevalence of depression in cancer patients. The prevalence estimates of current major depression from these studies have varied widely, from a low of 1% to a high of 50% [2, 24, 25]. As a comparison, the current (30-day) prevalence of major depression in the general United States population is estimated to be 4.9% [26]. Prevalence estimates for depressive syndromes among cancer patients (such as adjustment disorder with depressed mood) have reached as high as 58% [24], with higher estimates usually found among patients with more advanced illness or more debilitation [2].

A range of factors likely account for a considerable portion of the large variability in prevalence estimates of depression among cancer patients. Given the earlier

discussion regarding the diagnosis of depression among cancer patients, it is no surprise that the use of different diagnostic measures and cut-off criteria impact prevalence estimates. For example, in a study of terminally-ill cancer patients, a symptom threshold consistent with DSM-IV criteria was associated with a depression diagnosis in 13.0% of patients [9]. A relatively minor reduction in the symptom severity threshold elevated the depression diagnosis to 26.1% of patients. In a recent study, use of DSM criteria was associated with a depression diagnosis in 49% of a sample of cancer outpatients (recruited from a pain therapy and palliative care unit) [27]. Use of the Endicott [4] substitution criteria decreased the depression diagnosis rate to 29%. Importantly, the site of cancer, the physical symptoms it causes, and the stage of cancer also contribute to the wide difference in prevalence estimates across research studies.

We have two recommendations that may permit easier comparison of prevalence rates among future studies. First, we encourage researchers to include confidence intervals around the point prevalence estimates of depression. Many studies have low sample sizes that will give rise to large confidence intervals. For example, in a study of 100 patients, the 95% confidence interval for a point estimate of depression of 30% is 21–39%. Use of such confidence intervals will allow easy examination of *statistically significant* differences in depression prevalence estimates across studies.

Our second recommendation concerns the use of terminology, which currently varies considerably across studies. It is important for researchers to distinguish appropriately and carefully before any depression-related term is used, so that clarification exists between major depression, mood disorder with depressive features due to cancer, depressive symptoms, and adjustment disorder with depressed mood. When these terms are used loosely and interchangeably, it presents difficulties in making comparisons and drawing conclusions across studies.

14.3.1

Risk Factors for Depression in Cancer Patients

A number of risk factors for depression have been identified among cancer patients. Knowledge of these risk factors can alert clinicians to the likelihood of depression, allowing for early intervention, or in certain specific circumstances, even prophylactic treatment (an issue we return to in the later discussion of the role of cytokines in depression among cancer patients). Risk factors that are specific to cancer patients are the site of cancer and treatment by certain chemotherapy regimens and other anticancer drugs (particularly corticosteroids, vinblastine, vincristine, interferon, procarbazine, asparaginase, tamoxifen, and cyproterone [28]). With regard to the site of cancer, a higher prevalence of depression has been found among patients with pancreatic, oropharyngeal, breast, and lung cancer, with lower rates observed among those with lymphoma, colon, and gynecological cancers [24, 25, 29]. The high prevalence of depression among pancreatic cancer patients is of particular note, since there may be several potential underlying causes, including tumor-related neuroendocrine changes, pain, and awareness of the poor prognosis [30]. Neuroendocrine changes may be a major contributing factor, as evidenced by

data suggesting a link between diagnosis of pancreatic cancer and a preceding episode of depression [31, 32].

Other risk factors for depression that are not specific to cancer patients (that is, they are also risk factors for depression in the context of other illnesses or among healthy individuals) include advanced disease stage and physical disability [2], various medications [33], a previous history of depression [34], uncontrolled pain [35], younger age [36], low social support [37], low self-esteem [37], and high levels of neuroticism [38]. It is noteworthy that the causal relationship between depression and pain (and conceivably other risk factors, such as social support) is likely of a bidirectional nature. One risk factor that is notably absent from this list is gender. Although it is well established that depression is more prevalent among women than men in the general population [39], this gender difference is not evident among cancer patients [40].

Future research is needed to clarify the relative predictive utility of depression risk factors among cancer patients. Such research should also consider the (potentially complex) interplay of depression risk factors, as represented, for example, by statistical mediation and moderation [41].

14.4

Biological Markers and Underpinnings

Biological markers represent potential diagnostic tools for depression in cancer patients, particularly when it is unclear whether neurovegetative symptoms should be interpreted as symptomatic of depression or alternatively, due to disease- or treatment-related factors. Biological markers for depression can also be used to track treatment effectiveness [25, 42].

There are five key biological markers of depression among cancer patients which are described below. McDaniel and colleagues [25, 42] defined four biological markers of depression: serotonergic neurotransmission changes; sleep architecture changes; brain structure abnormalities; and neuroendocrine changes. We add, as the fifth, the role of cytokines in depression among cancer patients. There have been relevant studies among cancer patients regarding hypothalamic–pituitary–adrenal (HPA) axis changes and cytokines.

14.4.1

Serotonergic Neurotransmission Changes

Synaptic deficits in serotonin were first proposed as contributors to mood disorders around 30 years ago. Since that time, considerable research has confirmed that antidepressant-free depressed physically healthy individuals have a reduction in the number of platelet [³H]-imipramine binding sites, indicating its potential use as a biomarker of depression (e.g. [43–46]). However, studies of [³H]-imipramine binding among depressed or non-depressed cancer patients have not been conducted. Serotonin-induced platelet calcium mobilization has been suggested

as another serotonin-related biological marker of depression [47]. In a recent study, enhancements of serotonin-induced platelet calcium mobilization levels were found only among cancer patients diagnosed with major depression according to the exclusive, and not the inclusive or substitutive criteria [48].

The role of serotonin in depression has been confirmed by the results of studies of antidepressant drugs [49–51]. This is most evident with the selective serotonin reuptake inhibitors (SSRIs) (although preliminary support was found with tricyclic antidepressants). SSRIs block serotonin reuptake transporters and thus stimulate an increase in synaptic levels of serotonin. As noted earlier, the prevalence of depression is particularly high among individuals with pancreatic cancer. It has been suggested that this may, in part, be due to an interaction between tumor proteins and CNS serotonin receptors [52].

14.4.2

Sleep Architecture Changes

A number of sleep architecture changes have been linked with depression. These include an extended first REM sleep period, reduced rapid eye movement (REM) latency, diminished delta (slow) wave production (especially during the first period of non-rapid eye movement [NREM] sleep), and decreased sleep continuity (for a review, see [53]). The extent of sleep architecture changes varies according to demographic and clinical characteristics. For example, such changes are more pronounced with increases in age [54] and severity of depression [55]. We are not aware of any studies of changes in sleep architecture among depressed cancer patients.

14.4.3

Brain Structure Abnormalities

Several CNS structural abnormalities have been identified among depressed individuals (for a review, see [56]), including reduced volume in the frontal cortex, temporal lobe, putamen, and caudate, and enlarged lateral and third ventricles (e.g. [57, 58]). There are likely differences in brain abnormalities according to depression typology, but these remain to be elucidated in future research. Additionally, the current data are not sufficient to permit use of brain structure abnormalities as biological markers of depression, but this remains an important area for future investigation. Further, it remains to be seen whether brain abnormalities associated with depression can be reversed or modulated using antidepressants [59]. We are not aware of any studies of structural brain abnormalities among cancer patients.

14.4.4

Neuroendocrine Changes

There is consistent evidence that depressed individuals show alterations in neuroendocrine activity. Primarily, research has focused on HPA axis hyperactivity

among those with depression, but attention has also been directed at alterations in the hypothalamic–pituitary–thyroid (HPT) axis. Manifestations of HPA axis hyperactivity include increased urinary free cortisol, hypercortisolemia, non-suppression of cortisol by dexamethasone administration, blunted adrenocorticotrophic hormone (ACTH) response to corticotropin-releasing factor (CRF), insufficient glucocorticoid signaling, and hypersecretion of CRF [42, 60, 61]. It has been suggested that HPA hyperactivity associated with major depression may largely be due to alterations in CRF neurons both within and outside of the hypothalamus [29].

A small number of studies have examined the link between depression and HPA axis alterations among cancer patients. For example, Evans and colleagues [62] examined the prevalence of depression and dexamethasone non-suppression among 83 women with gynecological cancer. Of the 19 women (23%) diagnosed with major depression, eight (40%) showed dexamethasone non-suppression. This is comparable to (i.e. not statistically different than) the rate of dexamethasone non-suppression among depressed psychiatric inpatients without cancer, which has been reported to be 60% or more [63, 64]. Dexamethasone non-suppression has also been found in a study of pancreatic and gastric cancer patients [65]. However, the results of this study are hard to interpret, given the sample size of only 12 patients, of whom only one had major depression, and 11 of whom showed dexamethasone non-suppression. Given the current available data, the dexamethasone suppression test is not a suitable biomarker for depression among cancer patients.

14.4.5

Cytokines

In recent years, considerable attention has been directed at the potential pathophysiological role of increased proinflammatory cytokine activity in depression (for reviews, see [66–68]). Attention has focused predominantly on the cytokines interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). Overall, the data are suggestive of an underlying role of cytokines in depression. However, this conclusion is mitigated by the fact that most of the data are from correlational studies (that do not permit causal inferences), and that studies of immunotherapy (that show effects on depression) use cytokine doses that are greater than circulating cytokine levels [66].

There are multiple pathways through which cytokines may influence depression [7]. These include effects of cytokines on: disruption of monoamine metabolism in the CNS; induction of CRF; disruption of glucocorticoid receptor-mediated feedback inhibition of inflammation and CRF; induction of L-tryptophan; and development of euthyroid sick syndrome. These pathways illustrate the complex interplay among the cytokine, neuroendocrine, and serotonergic pathophysiological bases of depression (see [69]).

In the context of cancer, there are many potential triggers of proinflammatory cytokine activity among cancer patients. These include tumor cells themselves [70],

cells of the immune and nervous systems (see [71]), as well as the cancer treatments of surgery, radiation, and chemotherapy (which commonly involves the administration of cytokines) [67, 72, 73]. Knowledge of treatment-induced heightened cytokine activity raises the possibility that prophylactic use of antidepressants prior to treatment among cancer patients may protect against subsequent depression. Musselman and colleagues tested this notion in a recent prospective, double-blind study [74]. Patients with malignant melanoma were randomly assigned to receive either a placebo or the SSRI paroxetine prior to and during the first 12 weeks of a therapeutic regimen of the cytokine interferon alfa-2b. Of the patients in the placebo group, 44% were diagnosed with major depression during the course of the study, compared to 11% in the paroxetine group. Additionally, patients in the placebo group were significantly more likely to discontinue interferon alfa-2b therapy due to severe depression or other neurotoxic effects. These results indicate considerable benefits of the prophylactic use of antidepressants among cancer patients receiving cytokine-based chemotherapy. It remains to be determined whether these benefits extend to other treatment regimens.

There is evidence that depressed cancer patients have elevated cytokine levels (of a similar magnitude to depressed individuals without cancer) compared to non-depressed patients [75], although more research is needed in this area. A number of recent papers have called for the use of a broader investigative approach regarding the role of proinflammatory cytokines in producing a constellation of symptoms – including depressive symptoms – among cancer patients [7, 68]. These symptoms, that include anhedonia, depressed mood, fatigue, anorexia, decreased psychomotor activity, impairments in concentration, and decreased interest in social activities, have been referred to collectively as “sickness behavior” [76]. Sickness behavior symptoms such as these are commonly seen among cancer patients. Accordingly, it is conceivable that depression may be one component of a broader cytokine-related sickness behavior syndrome among cancer patients. Recognition, as well as further conceptual and empirical elaboration, of such a sickness behavior syndrome has significant implications for the prevention and treatment of a host of symptoms (including depression) among cancer patients [77].

Given the lack of relevant data, it is currently not possible to pinpoint a cytokine biomarker of depression among cancer patients. Thus, although it is valuable to examine biological markers of depression among cancer patients for research purposes, we are unable to recommend a specific definitive biological marker of depression for use in clinical settings. However, further research on the pathophysiology of depression, and sickness behavior more generally, among cancer patients may identify such a marker, and will undoubtedly also have broader benefits for cancer care and control.

14.5

Management of Depression in Cancer Patients

Managing depression in cancer patients requires a comprehensive approach that can address the evaluation (with special consideration given to possible cancer- and treatment-related causes), treatment, and follow-up of patients. The American Psychiatric Association has created practice guidelines for the treatment of depressive disorders in physically healthy individuals [78]. These guidelines have been modified by the National Comprehensive Cancer Network (NCCN) to include the salient issues unique to cancer (NCCN [79]). The NCCN accomplished this modification through a multidisciplinary panel focusing on distress management. The term “distress” was carefully chosen to avoid stigma, which prevents many patients from seeking help, and to normalize “distress” as a response to cancer ranging from normal feelings of sadness and fear to psychiatric disorders including major depression. The NCCN guidelines include the management of mood disorders and five additional common psychiatric disorders encountered in patients with cancer. The NCCN guidelines for the management of mood disorders (including major depression) in cancer, presented in Figure 14.1, are evidence- and consensus-based, with recommendations for antidepressant medications (which have the highest level of evidence – Category 1 – suggesting their use), psychotherapy, suicidal precautions, and the use of social work and pastoral counseling services.

Once a diagnosis of depression has been made, the challenge is to choose the modality or combination of modalities that will best help the patient. There are several pharmacologic and psychotherapeutic strategies available to treat depression in cancer patients. Prior to selecting an appropriate treatment, attention should be paid to the type of cancer a patient has, current cancer treatment, comorbid medical conditions (including certain neurological, endocrine, and metabolic disorders), and medications, any of which may underlie the depression (see Table 14.3).

Figure 14.1 National Comprehensive Cancer Network (NCCN) guidelines for the evaluation, treatment, and follow-up of mood disorders. All recommendations are category 2A unless otherwise indicated. NCCN Categories of Consensus: Category 1 – There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate; Category 2A – There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate. These Guidelines [79] are a work in progress that will be refined as often as new significant data becomes available. The NCCN Guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. These Guidelines are copyrighted by the National Comprehensive Cancer Network. All rights reserved. These Guidelines and illustration herein may not be reproduced in any form for any purpose without the express written permission of the NCCN.

Table 14.3 Medical conditions and medications that cause depression

Uncontrolled pain
Metabolic abnormalities
Hypercalcemia
Sodium–potassium imbalance
Anemia
Vitamin B ₁₂ or folate deficiency
Endocrine abnormalities
Hyperthyroidism or hypothyroidism
Adrenal insufficiency
Medications
Steroids
Interferon and interleukin-2
Methyldopa
Reserpine
Barbituates
Benzodiazepines
Propranolol
Some antibiotics (e.g. amphotericin B)
Some chemotherapeutic agents:
– Vincristine
– Vinblastine
– Procarbazine
– Asparaginase
– Tamoxifen
– Cyproterone

Adapted from Roth and Holland [21].

This may reveal reversible causes of depression, such as thyroid function abnormalities, vitamin B₁₂ or folate deficiency, or medications that can be eliminated or substituted. When present, these reversible causes should be the focus of the first course of treatment, which can be followed by other treatments, as necessary.

14.5.1

Pharmacologic Treatments

Pharmacologic intervention is the primary treatment for depression in cancer patients. However, the use of antidepressant medications in cancer patients poses unique challenges. For example, a patient with a poor prognosis may not be able to wait the 4–8 weeks it can take for some of the medications to work. An appropriate antidepressant should be selected based on matching the potential side-effects of each antidepressant (some of which, such as weight gain, may be beneficial to some patients) and a consideration of each patient's prognosis, primary symptoms of depression, and any comorbid symptoms and conditions. There are five categories of antidepressants (see Table 14.4): selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), atypical antidepressants, and psychostimulants.

Table 14.4 Pharmacologic treatments for depression in cancer patients

Medication	Starting dose/ Therapeutic range	Common side-effects/Comments
Selective Serotonin Reuptake Inhibitors		
Fluoxetine (Prozac)	10–20 mg/20–60 mg	Varying degrees of gastrointestinal distress, nausea, headache, insomnia, increased anxiety, sexual dysfunction. (Side-effects are seen with all of these agents, although, reportedly, less anxiety and fewer sexual problems occur with citalopram. Sertraline, citalopram and escitalopram produce the least interaction with the P450 system)
Sertraline (Zoloft)	25–50 mg/50–200 mg	
Paroxetine (Paxil, Paxil CR)	10–20 mg/20–50 mg	
Fluvoxamine (Luvox)	50 mg/100–300 mg	
Citalopram (Celexa)	20 mg/20–60 mg	
Escitalopram (Lexapro)	10 mg/10–20 mg	
Tricyclic antidepressants		
Amitriptyline (Elavil)	10–25 mg/50–100 mg	Sedation; anticholinergic effects, orthostasis
Imipramine (Tofranil)	10–25 mg/50–300 mg	
Desipramine (Norpramin)	25 mg/75–200 mg	Minimal sedation or orthostasis; moderate anticholinergic effects
Nortriptyline (Pamelor)	10–25 mg/50–150 mg	Sedation; minimal anticholinergic effects or orthostasis
Doxepin (Sinequan)	25 mg/75–300 mg	Very sedating; anticholinergic effects; orthostasis; may be useful as sleep aid or for pruritis
Monoamine Oxidase Inhibitors		
Phenylzine (Nardil)	15 mg/30–60 mg	Orthostasis; drug interactions and food interactions requiring avoidance of certain foods; can cause hypertensive crisis
Tranylcypromine (Parnate)	10 mg/20–40 mg	
Atypical antidepressants		
Bupropion (Wellbutrin, Wellbutrin SR and XL)	75 mg/150–450 mg	Risk of seizures if predisposed; no sexual dysfunction, no weight gain
Trazodone (Desyrel)	50 mg/150–200 mg	Sedation; useful as a sleep aid; priapism; may be the only antidepressant compatible with procarbazine
Nefazodone (Serzone)	100 mg/150–300 mg	Risk of liver failure; sedation; dizziness; constipation; less sexual dysfunction
Venlafaxine (Effexor, Effexor XR)	37.5 mg BID/75–225 mg	Increased blood pressure; nausea; anxiety; sedation; sweating
Mirtazapine (Remeron)	15 mg/15–45 mg	Sedation; useful as sleep aid; weight gain; fewer gastrointestinal side-effects and less sexual dysfunction. Rare agranulocytosis. Available as a soluble tablet (Soltab form)

Table 14.4 (continued)

Medication	Starting dose/ Therapeutic range	Common side-effects/Comments
Psychostimulants		
Dextroamphetamine (Dexedrine)	2.5 mg/5–30 mg	Possible cardiac complications; agitation
Methylphenidate (Ritalin)	2.5 mg/5–30 mg	Possible cardiac complications; agitation
Pemoline (Cylert)	18.75 mg/37.5–112.5 mg	Liver and renal insufficiency
Modafinil (Provigil)	50 mg/100–300 mg	Possible cardiac complications

Adapted from Pirl and Roth [80].

14.5.1.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs have become the first line of treatment for depression (as well as some anxiety disorders). They are efficacious, generally well tolerated, and are not as toxic in overdose as tricyclic antidepressants. The main side-effects of SSRIs are gastrointestinal distress (constipation or diarrhea), nausea, headache, insomnia or hypersomnia, increased anxiety, diminished libido, and sexual dysfunction. Some SSRIs, such as fluoxetine and fluvoxamine, are inhibitors of cytochrome P450 (CYP) isoenzymes. It is therefore important to monitor for the possibility of drug–drug interactions between the SSRIs and other medications. Sertraline and citalopram (and escitalopram) are less protein-bound and may have a lower risk of drug interactions with the CYP system [81]. This may make them better choices for patients taking numerous other medications. Many of the SSRIs now come in liquid forms, making it easier for patients who cannot swallow pills. SSRIs with a short half-life, such as paroxetine, have occasionally been associated with flu-like withdrawal symptoms if stopped abruptly.

14.5.1.2 Tricyclic Antidepressants

These medications have been around for many years and are therefore less expensive than many of the SSRIs. The tricyclics are also used as adjunct pain medications, especially for neuropathic pain. However, their side-effect profile and potential for toxicity have reduced their use as first line agents for depression, particularly in patients with cancer. Side-effects of tricyclics are the anticholinergic symptoms of urinary retention, constipation, blurred vision and dry mouth, as well as orthostatic hypotension and arrhythmias. Tricyclic antidepressants are highly cardiotoxic in overdose.

14.5.1.3 Monoamine Oxidase Inhibitors (MAOIs)

MAOIs are rarely used as treatment for cancer patients with depression. Patients must adhere to a strict diet while on these medications, as concurrent intake of foods rich in tyramine or the use of sympathomimetic drugs can cause a poten-

tially fatal hypertensive crisis. In addition, there are numerous other potentially severe drug–drug interactions, such as the interaction between MAOIs and meperidine.

14.5.1.4 Atypical Antidepressants

This category of antidepressants includes medications with a range of therapeutic mechanisms. We consider five atypical antidepressants: bupropion (Wellbutrin), nefazodone (Serzone), trazodone (Desyrel), venlafaxine (Effexor), and mirtazapine (Remeron).

Bupropion acts primarily on the dopamine system and can have a mild stimulant effect, which can be beneficial for individuals with fatigue or psychomotor retardation. It is generally not associated with weight gain and has an additional application as a first-line pharmacotherapy for smoking cessation. It is often the drug of choice when sexual function must not be impaired, since it has little to no effect on libido or sexual function. Bupropion is associated with an increased risk of seizures and should not be used in individuals with central nervous system or seizure disorders. Newer extended release forms of bupropion allow for dosing once or twice daily.

Both nefazodone and trazodone block postsynaptic serotonin 5-HT₂ receptors. Nefazodone has been associated with less sexual dysfunction than the SSRIs, although it has recently received a black box warning concerning cases of hepatic failure. It must therefore be used with caution in patients with liver disease, and liver functions must be monitored for a patient on this medication. Trazodone is often used as a non-addictive sleep aid, rather than a primary antidepressant because of its main side-effect of sedation. Other rare side-effects include priapism and cardiac arrhythmias.

Venlafaxine works as a reuptake inhibitor of serotonin and norepinephrine. It is recommended that patients receiving venlafaxine have their blood pressure monitored due to the potential side-effect of hypertension. Venlafaxine can be useful for patients who fail to respond to other antidepressants. The extended release form of venlafaxine (Effexor XR) allows it to be dosed once or twice daily.

Mirtazapine acts by blocking the 5-HT₂, 5-HT₃, and α 2 adrenergic receptor sites. There are several advantages to the use of this medication in cancer patients. Its side-effects of sedation and weight gain are beneficial for many cancer patients with insomnia and weight loss. It is also available in a dissolvable tablet form (Remeron SolTab), which is particularly useful for patients who cannot swallow or who have difficulty with nausea and vomiting.

14.5.1.5 Psychostimulants

Low doses of psychostimulants are helpful to treat depressed cancer patients' symptoms of fatigue and poor concentration. They also combat the sedating side-effects of opioid medications. Side-effects are anorexia, insomnia, euphoria, irritability, and mood lability. Psychostimulants used in cancer patients include dextroamphetamine (Dexedrine), methylphenidate (Ritalin), pemoline (Cylert), and the recently-approved modafinil (Provigil).

14.5.2

Psychotherapy

Several different psychotherapeutic techniques have been successfully employed with depressed cancer patients, and psychotherapy is often combined with a pharmacologic intervention. The most commonly utilized forms of psychotherapy are supportive psychotherapy and cognitive-behavioral therapy. In supportive psychotherapy, the clinician adopts an empathic approach, and there is typically a psychoeducational component to the therapy, including a focus on adaptive coping strategies. Cognitive-behavioral therapy aims to alter patients' maladaptive thoughts and behaviors that adversely impact mood. Psychotherapies that are used less frequently include existential psychotherapy and the therapeutic life narrative [82]. Group therapy can be helpful to improve social networks and decrease a patient's sense of isolation. For example, cognitive-existential group psychotherapy has been used for women with breast cancer [83].

14.5.3

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is an extremely effective strategy to treat depression (see Chapter 3 in this volume). The use of unilateral ECT has decreased the risk of cognitive deficits, which was the main adverse side-effect of bilateral ECT. ECT should be considered in patients who do not respond to pharmacologic treatment, have severe weight loss secondary to depression, exhibit acute psychosis or high suicidal risk [84]. Although there are no absolute contraindications to ECT, it should be used with caution among individuals with central nervous system tumors or cardiac problems.

14.6

Conclusions

There are challenges inherent to the measurement and diagnosis of depression in the context of cancer. This contributes to the difficulty in identifying an overall prevalence of depression among cancer patients. Clearly, the prevalence varies widely according to the clinical variables of disease site, stage, and physical symptoms. Greater clinician awareness of risk factors for depression, and careful attention to the signs and symptoms of depression, will lead to improved recognition and management of depressive disorders among cancer patients. Further research into biological markers and underpinnings of depression in the context of cancer may reveal one or more highly sensitive and specific depression biomarkers and improved pharmacologic interventions. Additionally, continued research on cytokines, depression, and sickness behavior bears the promise of future theoretical and empirical advances that may further improve the diagnosis and management of depression in cancer patients.

References

- 1 RIFKIN, A., REARDON, G., SIRIS, S., et al., Trimipramine in physical illness with depression. *J. Clin. Psychiatry* **1985**, 46, 4–8.
- 2 BUKBERG, J., PENMAN, D., HOLLAND, J. C., Depression in hospitalized cancer patients. *Psychosom. Med.* **1984**, 46, 199–212.
- 3 SPITZER, R. L., WILLIAMS, J., GIBBONS, M., FIRST, M. B., *Structured Clinical Interview for DSM-III-R (SCID). Users Guide for the Structured Clinical Interview for DSM-III-R*. Washington, DC: American Psychiatric Press, **1990**.
- 4 ENDICOTT, J., Measurement of depression in patients with cancer. *Cancer* **1984**, 53, 2243–2248.
- 5 RAPP, S. R., VRANA, S., Substituting nonsomatic for somatic symptoms in the diagnosis of depression in elderly male medical patients. *Am. J. Psychiatry* **1989**, 146, 1197–1200.
- 6 COHEN-COLE, S. A., BROWN, F. W., MCDANIEL, J. S., Diagnostic assessment of depression in the medically ill. In: STOUDEMIRE, A., FOGEL, B. S. (Eds.), *Psychiatric Care of the Medical Patient*. New York: Oxford University Press, **1993**, 53–70.
- 7 RAISON, C. L., MILLER, A. H., Depression in cancer: New developments regarding diagnosis and treatment. *Biol. Psychiatry* **2003**, 54, 283–294.
- 8 YIRMIYA, R., WEIDENFELD, J., POLLAK, Y., et al., Cytokines, “depression due to a medical condition,” and antidepressant drugs. *Adv. Exp. Med. Biol.* **1999**, 461, 283–316.
- 9 CHOCHINOV, H. M., WILSON, K. G., ENNS, M., LANDER, S., Prevalence of depression in the terminally ill: Effects of diagnostic criteria and symptom threshold judgments. *Am. J. Psychiatry* **1994**, 151, 537–540.
- 10 AMERICAN PSYCHIATRIC ASSOCIATION, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association, **1994**.
- 11 SPITZER, R. L., ENDICOTT, J., ROBINS, E., Research Diagnostic Criteria: Rationale and reliability. *Arch. Gen. Psychiatry* **1978**, 35, 773–782.
- 12 FIRST, M. B., SPITZER, R. L., GIBBON, M., WILLIAMS, J. B. W., *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. New York: Biometrics Research, New York State Psychiatric Institute, **2002**.
- 13 FIRST, M. B., SPITZER, R. L., GIBBON, M., WILLIAMS, J. B. W., *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press, Inc., **1996**.
- 14 ENDICOTT, J., SPITZER, R. L., A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Arch. Gen. Psychiatry* **1978**, 35, 837–844.
- 15 SPITZER, R. L., WILLIAMS JBW, KROENKE, K., et al., Utility of a new procedure for diagnosing mental disorders in primary care: The PRIME-MD 1000 study. *JAMA* **1994**, 272, 1749–1756.
- 16 ROBINS, L. N., HELZER, J. E., CROUGHAN, J., RATCLIFF, K. F., National Institute of Mental Health Diagnostic Interview Schedule: Its history, characteristics, and validity. *Arch. Gen. Psychiatry* **1981**, 38, 381–389.
- 17 BECK, A. T., BROWN, G., STEER, R. A., *Beck Depression Inventory II Manual*. San Antonio, TX: The Psychological Corporation, **1996**.
- 18 ZIGMOND, A. S., SNAITH, R. P., The Hospital Anxiety and Depression Scale. *Acta Psychiatr. Scand.* **1983**, 67, 361–370.
- 19 CARROLL, B. J., FEINBERG, M., SMOUSE, P. E., RAWSON, S. G., GREDEN, J. F., The Carroll rating scale for depression I, Development, reliability, and validation. *Br. J. Psychiatry* **1981**, 138, 194–200.
- 20 WILSON, K. G., CHOCHINOV, H. M., DE FAYE, B. J., BREITBART, W., Diagnosis and management of depression in palliative care. In: CHOCHINOV, H. M., BREITBART, W. (Eds.), *Handbook of Psychiatry in Palliative Medicine*. New York: Oxford University Press, **2000**, 25–49.
- 21 ROTH, A. J., HOLLAND, J. C., Treatment of depression in cancer patients. *Prim. Care Cancer* **1994**, 14, 23–29.
- 22 POTASH, M., BREITBART, W., Affective disorders in advanced cancer. *Hematol. Oncol. Clin. North Am.* **2002**, 16, 671–700.

- 23 CHOCHINOV, H. M., WILSON, K. G., ENNS, M., LANDER, S., "Are you depressed?" Screening for depression in the terminally ill. *Am. J. Psychiatry* **1997**, *154*, 674–676.
- 24 MASSIE, M. J., Prevalence of depression in patients with cancer. *J. Natl. Cancer Inst. Monogr.* **2004**, *32*, 57–71.
- 25 MCDANIEL, J. S., MUSSELMAN, D. L., PORTER, M. R., REED, D. A., NEMEROFF, C. B., Depression in patients with cancer: Diagnosis, biology, and treatment. *Arch. Gen. Psychiatry* **1995**, *52*, 89–99.
- 26 BLAZER, D. G., KESSLER, R. C., MCGONAGLE, K. A., SWARTZ, M. S., The prevalence and distribution of major depression in a national community sample: The National Comorbidity Survey. *Am. J. Psychiatry* **1994**, *151*, 979–986.
- 27 CIARAMELLA, A., POLI, P., Assessment of depression among cancer patients: The role of pain, cancer type and treatment. *Psycho-Oncology* **2001**, *10*, 156–165.
- 28 MEDICAL LETTER, Drugs of choice for cancer chemotherapy. *Med Lett* **1993**, *35*, 43–50.
- 29 NEWPORT, D. J., NEMEROFF, C. B., Assessment and treatment of depression in the cancer patient. *J. Psychosom. Res.* **1998**, *45*, 215–237.
- 30 PASSIK, S. D., BREITBART, W. S., Depression in patients with pancreatic carcinoma. Diagnostic and treatment issues. *Cancer* **1996**, *8*, 615–626.
- 31 CARNEY, C. P., JONES, L., WOOLSON, R. F., NOYES, R. JR., DOEBBELING, B. N., Relationship between depression and pancreatic cancer in the general population. *Psychosom. Med.* **2003**, *65*, 884–888.
- 32 FRAS, I., LITIN, E. M., PEARSON, J. S., Comparison of psychiatric symptoms in carcinoma of the pancreas with those in some other intra-abdominal neoplasms. *Am. J. Psychiatry* **1967**, *123*, 1553–1562.
- 33 MEDICAL LETTER, Drugs that cause psychiatric symptoms. *Med. Lett.* **1993**, *35*, 65–70.
- 34 PLUMB, M. M., HOLLAND, J. C., Comparative studies of psychological function in patients with advanced cancer – II, Interviewer-rated current and past psychological symptoms. *Psychosom. Med.* **1981**, *43*, 243–254.
- 35 SPIEGEL, D., SAND, S., KOOPMAN, C., Pain and depression in patients with cancer. *Cancer* **1994**, *74*, 2570–2578.
- 36 KATHOL, R. G., MUTGI, A., WILLIAMS, J., CLAMON, G., NOYES, R. JR., Diagnosis of major depression in cancer patients according to four sets of criteria. *Am. J. Psychiatry* **1990**, *147*, 1021–1024.
- 37 SCHROEVERS, M. J., RANCHOR, A. V., SANDERMAN, R., The role of social support and self-esteem in the presence and course of depressive symptoms: A comparison of cancer patients and individuals from the general population. *Soc. Sci. Med.* **2003**, *57*, 375–385.
- 38 MORRIS, T., GREER, H. S., WHITE, P., Psychological and social adjustment to mastectomy: A two-year follow-up study. *Cancer* **1977**, *40*, 2381–2387.
- 39 KESSLER, R. C., MCGONAGLE, K. A., SWARTZ, M., BLAZER, D. G., NELSON, C. B., Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J. Affect Disord.* **1993**, *29*, 85–96.
- 40 DEFLORIO, M. L., MASSIE, M. J., Review of depression in cancer: Gender differences. *Depression* **1995**, *3*, 66–80.
- 41 BARON, R. M., KENNY, D. A., The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* **1986**, *51*, 1173–1182.
- 42 MCDANIEL, J. S., NEMEROFF, C. B., Depression in the cancer patient: Diagnostic, biological, and treatment aspects. In: CHAPMAN, C. R., FOLEY, K. M. (Eds.), *Current and Emerging Issues in Cancer Pain: Research and Practice*. New York: Raven Press, **1993**, 1–19.
- 43 LANGER, S. Z., GALZIN, A. M., POIRIER, M. F., LOO, H., SECHTER, D., ZARIFIAN, E., Association of [³H]imipramine and [³H]paroxetine binding with the 5-HT transporter in brain and platelets: Relevance to studies in depression. *J. Recept. Res.* **1987**, *7*, 499–521.
- 44 NANKAI, M., JOSHIMOTO, S., NARITA, K., TAKAHASHI, R., Platelet [³H]imipramine binding in depressed patients and its circadian variations in healthy controls. *J. Affect Disord.* **1986**, *11*, 207–212.

- 45 ROSEL, P., ARRANZ, B., VALLEJO, J., et al., Altered [³H]imipramine and 5-HT₂ but not [³H]paroxetine binding sites in platelets from depressed patients. *J. Affect Disord.* **1999**, 52, 225–233.
- 46 SURANYI-CADOTE, B., QUIRION, R., MCQUADE, P., et al., Platelet [³H]imipramine binding: A state-dependent marker in depression. *Neur. Psychopharmacol.* **1984**, 8, 737–741.
- 47 KAGAYA, A., MIKUNI, M., KUSUMI, I., YAMAMOTO, H., TAKAHASHI, K., Serotonin-induced acute desensitization of serotonin₂ receptors in human platelets via a mechanism involving protein kinase C. *J. Pharmacol. Exp. Ther.* **1990**, 255, 305–311.
- 48 UCHITOMI, Y., KUGAYA, A., AKECHI, T., et al., Three sets of diagnostic criteria for major depression and correlations with serotonin-induced platelet calcium mobilization in cancer patients. *Psychopharmacology* **2001**, 153, 244–248.
- 49 KEEGAN, D., BOWEN, R. C., BLACKSHAW, S., et al., A comparison of fluoxetine and amitriptyline in the treatment of major depression. *Int. Clin. Psychopharmacol.* **1991**, 6, 117–124.
- 50 NIELSEN, B. M., BEHNKE, K., ARUP, P., et al., A comparison of fluoxetine and imipramine in the treatment of outpatients with major depressive disorder. *Acta Psychiatr. Scand.* **1993**, 87, 269–272.
- 51 STARK, P., HARDISON, C. D., A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. *J. Clin. Psychiatry* **1985**, 46, 53–58.
- 52 GREEN, A. I., AUSTIN, C. P., Psychopathology of pancreatic cancer. A psychobiologic probe. *Psychosomatics* **1993**, 34, 208–221.
- 53 KUPFER, D. J., Sleep research in depressive illness: Clinical implications – a tasting menu. *Biol. Psychiatry* **1995**, 38, 391–403.
- 54 LAUER, C. J., RIEMANN, D., WIEGAND, M., BERGER, M., From early to late adulthood changes in EEG sleep of depressed patients and healthy volunteers. *Biol. Psychiatry* **1991**, 29, 979–993.
- 55 SPIKER, D. G., COBLE, P., COFSKY, J., FOSTER, F. G., KUPFER, D. J., EEG sleep and severity of depression. *Biol. Psychiatry* **1978**, 13, 485–488.
- 56 SHELINE, Y. I., Neuroimaging studies of mood disorder effects on the brain. *Biol. Psychiatry* **2003**, 54, 338–352.
- 57 DREVETS, W. C., PRICE, J. L., SIMPSON, J. R. JR., et al., Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **1997**, 386, 824–827.
- 58 KRISHNAN, K. R., McDONALD, W. M., ESCALONA, P. R., et al., Magnetic resonance imaging of the caudate nuclei in depression: Preliminary observations. *Arch. Gen. Psychiatry* **1992**, 49, 553–557.
- 59 MIGUEL-HIDALGO, J. J., RAJKOWSKA, G., Morphological brain changes in depression: Can antidepressants reverse them? *CNS Drugs* **2002**, 16, 361–372.
- 60 PLOTSKY, P. M., OWENS, M. J., NEMEROFF, C. B., Psychoneuroendocrinology of depression: Hypothalamic-pituitary-adrenal axis. *Psychiatr. Clin. North Am.* **1998**, 21, 293–307.
- 61 RAISON, C. L., MILLER, A. H., When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am. J. Psychiatry* **2003**, 160, 1554–1565.
- 62 EVANS, D. L., MCCARTNEY, C. F., NEMEROFF, C. B., et al., Depression in women treated for gynecological cancer: Clinical and neuroendocrine assessment. *Am. J. Psychiatry* **1986**, 143, 447–452.
- 63 EVANS, D. L., BURNETT, G. B., NEMEROFF, C. B., The dexamethasone suppression test in the clinical setting. *Am. J. Psychiatry* **1983**, 140, 586–589.
- 64 EVANS, E. L., NEMEROFF, C. B., The clinical use of the dexamethasone suppression test in DSM-III affective disorders: Correlation with the severe depressive subtypes of melancholia and psychosis. *J. Psychiatr. Res.* **1987**, 21, 185–194.
- 65 JOFFE, R. T., RUBINOW, D. R., DENICOFF, K. D., MAHER, M., SINDELAU, W. F., Depression and carcinoma of the pancreas. *Gen. Hosp. Psychiatry* **1986**, 8, 241–245.
- 66 ANISMAN, H., MERALI, Z., Cytokines, stress, and depressive illness. *Brain Behav. Immun.* **2002**, 16, 513–524.
- 67 CAPURON, L., DANTZER, R., Cytokines and depression: The need for a new paradigm. *Brain Behav. Immun.* **2003**, 17, S119–S124.

- 68 CLEELAND, C. S., BENNETT, G. J., DANTZER, R., et al., Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer* **2003**, 97, 2919–2925.
- 69 BESEDOVSKY, H. O., DEL REY, A., Immune–neuro–endocrine interactions: Facts and hypotheses. *Endocr. Rev.* **1996**, 17, 64–102.
- 70 ZAKS-ZILBERMAN, M., ZAKS, T. Z., VOGEL, S. N., Induction of proinflammatory and chemokine genes by lipopolysaccharide and paclitaxel (Taxol) in murine and human breast cancer cell lines. *Cytokine* **2001**, 15, 156–165.
- 71 DANTZER, R., Cytokine-induced sickness behavior: Where do we stand? *Brain Behav. Immun.* **2001**, 15, 7–24.
- 72 CAPURON, L., RAVAUD, A., GUALDE, N., et al., Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. *Psychoneuroendocrinology* **2001**, 26, 797–808.
- 73 KRISTIANSSON, M., SARASTE, L., SOOP, M., SUNDQVIST, K. G., THORNE, A., Diminished interleukin-6 and C-reactive protein responses to laparoscopic versus open cholecystectomy. *Acta Anaesthesiol. Scand.* **1999**, 43, 146–152.
- 74 MUSSELMAN, D. L., LAWSON, D. H., GUMNICK, J. F., et al., Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med.* **2001**, 344, 961–966.
- 75 MUSSELMAN, D. L., MILLER, A. H., PORTER, M. R., Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: Preliminary findings. *Am. J. Psychiatry* **2001**, 158, 1252–1257.
- 76 KENT, S., BLUTHE, R. M., KELLEY, K. W., DANTZER, R., Sickness behavior as a new target for drug development. *Trends Pharmacol. Sci.* **1992**, 13, 24–28.
- 77 MILLER, A. H., Cytokines and sickness behavior: Implications for cancer care and control. *Brain Behav. Immun.* **2003**, 17, S132–S134.
- 78 AMERICAN PSYCHIATRIC ASSOCIATION, *Practice Guidelines for the Treatment of Patients with Major Depressive Disorder*, 2nd ed. Arlington, VA: American Psychiatric Publishing, Inc., **2000**.
- 79 THE NATIONAL COMPREHENSIVE CANCER NETWORK, Distress Management Clinical Practice Guidelines in Oncology, version 1.2003. (Accessed December 1, 2003, at http://www.nccn.org/physician_gls/index.html. To view the most recent and complete version of the Guideline, go to <http://www.nccn.org>.)
- 80 PIRL, W. F., ROTH, A. J., Diagnosis and treatment of depression in cancer patients. *Oncology* **1999**, 13, 1293–1301.
- 81 DEVANE, C. L., Differential pharmacology of newer antidepressants. *J. Clin. Psychiatry* **1998**, 59 (suppl 20), 85–93.
- 82 SCHWARTZ, L., LANDER, M., CHOCHINOV, H. M., Current management of depression in cancer patients. *Oncology* **2002**, 16, 1102–1115.
- 83 KISSANE, D. W., BLOCH, S., SMITH, G. C., et al., Cognitive-existential group psychotherapy for women with primary breast cancer: A randomized controlled trial. *Psycho-oncology* **2003**, 12, 532–546.
- 84 BEALE, M. D., KELLNER, C. H., PARSONS, P. J., ECT for the treatment of mood disorders in cancer patients. *Convuls. Ther.* **1997**, 13, 222–226.

15

Treatment of Refractory Depression

Michael Gitlin

Abstract

Depressions that have not responded to conventional treatment have long been a conundrum in psychopharmacology. The field has been hampered by a lack of consensus in defining treatment refractoriness or resistance. Central definitional problems concern the number of treatments, dose and time thresholds, questions about dichotomous vs. staging definitions, and others. Additional difficulties have been the overall lack of placebo-controlled double-blind studies and, even more, the lack of studies comparing different treatment approaches. Diagnostic issues in evaluating treatment-refractory depression include the potential presence of certain depressive subtypes and psychiatric and medical comorbidities. Adequacy of initial treatment in dose, length of treatment time, and treatment adherence must always be evaluated. For those patients who are treatment-refractory, first-line treatment options include switching antidepressants or adding a second medication. The most common adjunctive treatments are lithium, tri-iodothyronine, stimulants, and antidepressant combinations. Adding an atypical antipsychotic or lamotrigine are important second-line options. Electroconvulsive therapy should always be considered for treatment-refractory patients. Finally, transcranial magnetic stimulation, omega-3 fatty acids, and possibly vagal nerve stimulation are three experimental treatments currently being evaluated. In view of the current lack of sufficient data, clinicians choose varied treatment strategies, using multiple idiosyncratic algorithms reflecting the confusion in the field.

15.1

Introduction

Considerations surrounding the definition of, predictors of, and approaches to treatment-refractory (or treatment-resistant, as it is synonymously called) depression have been a central part of treating depression since the dawn of antidepressant psychopharmacology. Despite consistent advances in the range of available

antidepressant treatments (both biological and psychotherapeutic) however, a body of systematic knowledge and a data-based algorithmic approach to treating patients with difficult-to-treat depressions have yet to emerge. Difficulties preventing a more consensual approach mirror the methodological difficulties typical of research in all psychiatric disorders – inconsistent and shifting definitions, lack of similar patient populations across studies, variable methods of dealing with comorbid disorders, inconsistent outcome variables and definitions, a relative paucity of placebo-controlled studies and, even more, a rarity of studies comparing potential treatment approaches. As always, despite this lack of clarity, clinicians must treat patients whom they consider to be treatment-refractory on a daily basis, and not surprisingly, with markedly differing approaches. Core practical clinical questions in this area include: How do I treat a patient who has not fully responded to this first antidepressant? or: How do I decide when to switch medications or to add an adjunctive therapy? and: At what point of treatment failure should electroconvulsive therapy (ECT) be seriously considered? In reviewing treatment-resistant depression, this chapter highlights both current knowledge as well as areas of uncertainty.

15.2

Definitions of Treatment-refractory Depression

Despite a number of reasonable proposals of criteria for treatment refractoriness in depression, there is as yet no consensus as to the optimal definition. Table 15.1 lists the variables to be considered within the definition. Beyond the obvious criteria of the number of treatments previously utilized and the adequacy of each trial, another important factor in research settings is the adequacy of documentation of treatment resistance [1]. Options include retrospective data collection, prospective data collection (i.e., evaluating only patients who have failed a treatment trial within the current investigation), or a combination of the two.

The number of failed treatment trials is almost always the starting point for defining treatment refractoriness, with increasing numbers of failed trials constituting a higher level of treatment resistance. Some definitions dichotomize

Table 15.1 Considerations in defining treatment refractoriness

-
- Number of treatment trials
 - Number of treatment classes failed
 - Role of adjunctive treatments failed
 - Adequacy of each treatment trial
 - Dose
 - Duration
 - Definition of adequate treatment response
 - Response
 - Remission
-

treatment refractoriness, and others utilize a staging method. An example of a simpler approach is that of Soury et al. [2], who defined treatment refractoriness as a major depressive episode with poor response to two adequate trials of different classes of antidepressants. (These authors, however, also define chronic resistant depression for those patients who fail to respond to multiple trials lasting at least one year beyond the two adequate trials [2].) The most popular of the more complex staging methods is that of Thase and Rush [3]. Their scheme proposed staging treatment resistance along a continuum of five stages based on the number of treatment failures of diverse antidepressant categories. Using this method, treatment resistance ranges from Stage I (failure of at least one adequate trial of one major class of antidepressant) to Stage V (failure of adequate trials of two distinctly different classes of antidepressants plus failure of adequate trials of a tricyclic antidepressant, an monoamine oxidase inhibitor, and a course of bilateral ECT). Other definitions, such as those of Fava et al. [4] and Sackeim et al. [5], more clearly define treatment adequacy using either specific dose and duration criteria [5] or optimization of dose or duration and augmentation trials to define progressive levels of treatment resistance [4].

Most definitions consider failing antidepressants from two classes as reflecting a higher grade of treatment refractoriness than failing two antidepressants from the same class (typically, two SSRIs.). Few studies have examined this issue systematically, and current data are conflicting [6–8]. The lack of consistent data in this area creates an ‘upstream’ problem. Even though most definitions of treatment refractoriness do not include patients who simply fail one antidepressant, being able to predict response to a second trial from the same class vs. a different class would alter the prevalence of treatment resistance and is critical from a practical viewpoint.

Despite universal acknowledgement that adjunctive treatments and/or combination treatments are reasonable strategies for treating antidepressant nonresponse (discussed in detail later in this chapter), most definitions of treatment refractoriness (with the exception of Fava et al. [4]) ignore these two strategies in defining treatment refractoriness. Failure to address the role of adjunctive or combination treatments in the definition of treatment refractoriness limits the clinical utility of treatment strategies, since these two approaches are consistently among the most commonly used by clinicians [9–11].

Another consideration in defining treatment refractoriness reflects the need to confront the sizable percentage of depressed patients who have failed one of more inadequate medication trials or do not have a primary depressive disorder. This phenomenon has been referred to as pseudoresistance [12]. Causes of pseudoresistance are listed in Table 15.2. For researchers, these are potential subjects to exclude from systematic treatment trials of treatment-refractory patients. Paradoxically, however, for clinicians, these may be the more prevalent and difficult patients who are colloquially considered to be treatment-refractory. Some observers have suggested that misdiagnosed depression may account for a substantial proportion of those labeled treatment-refractory [13]. Studies from the tricyclic era [14, 15] and more recent studies [16, 17] consistently show that many depressed

Table 15.2 Causes of pseudoresistance in treatment-refractory depression

-
- Incorrect diagnosis
 - Inadequate antidepressant dose due to prescribing error
 - Inadequate dose due to partial noncompliance or to missed doses
 - Inadequate dose due to side effects precluding dose escalation
 - Inadequate plasma-level dose due to rapid metabolism
 - Inadequate plasma level due to concomitant use of medication with enzyme-inducing properties
 - Inadequate length of treatment time
-

patients who remain depressed in naturalistic treatment have received less-than-adequate doses of antidepressants. In the tricyclic era, it was estimated that up to 60% of patients defined as treatment-resistant and referred for alternative treatments may have been under-treated [18]. For any patient described as treatment-resistant, the clinician must consider the presence of pseudoresistance and consider strategies to combat it. At the least, it is imperative to recognize the conceptual differences between true treatment refractoriness and treatment pseudoresistance, since clinical approaches between these two differ markedly.

Adding to the difficulty is the lack of systematic data examining the threshold for adequate dosing, especially with the newer antidepressants. As an example, a prime unanswered question in this area is the marginal utility of very high doses of SSRIs (e.g., fluoxetine, paroxetine, or citalopram 100 mg; sertraline 300 mg), beyond that seen with high doses (e.g., fluoxetine, paroxetine, or citalopram 60 mg; sertraline 200 mg). Although SSRIs have flat dose-response curves in usually prescribed doses for non-treatment-refractory patients [19], these studies do not exclude a potentially different response curve for a smaller treatment-refractory group.

Remarkably, similar questions still arise as to the proper length of time for an adequate antidepressant trial [20, 21]. Definitions from papers and/or studies on treatment-refractory patients vary and include: (1) at least four weeks of treatment with at least three weeks at an adequate dose [3]; (2) maximum tolerated dose with at least four weeks at the optimal dose [2]; (3) nonresponse to six weeks of an adequate dose [4]; and (4) one treatment for four weeks at an effective dose and at least four weeks (or two weeks if a safety problem caused discontinuation) for the second failed treatment [7]. Yet, data from non-treatment-refractory patients demonstrate substantial improvement in some patients beyond four or even six weeks [22]. In the most recent study examining this issue, Quitkin et al. found that, among patients treated with fluoxetine 20 mg daily who were unimproved at week six, 41% remitted at week 12 [23]. Among patients unimproved at week eight, 23% had remissions at week 12. Evidence of similar late improvement has been seen with antidepressants from classes such as nefazodone and bupropion [24, 25]. Thus, proposed definitions of treatment resistance using 3–6-week duration

criteria may include substantial numbers of slowly responding patients as opposed to truly treatment-refractory ones.

The final issue in defining treatment refractoriness reflects the need to quantify the amount of clinical improvement that defines the goal of treatment. Although the degree of improvement is, of course, dimensional, and categorical systems of responses use inherently arbitrary criteria, delineating degrees of response is required for studies. The classic definition of response has been a 50% decrease in the symptoms as measured by a validated depression rating scale, such as the Hamilton Rating Scale for Depression [26] or the Montgomery Asberg Depression Rating Scale [27] plus a Clinical Global Impression–Improvement score of 1 or 2 (much improved or very much improved) [28]. Yet, this threshold for improvement leaves many patients still significantly symptomatic. Thus, the concept of remission – a Hamilton depression score of 7 or lower – has been proposed as the optimal goal of treatment. Some but not all definitions of treatment resistance have utilized these distinctions. As examples, one definition divides response by the degree of treatment resistance as: nonresponse (< 25% improvement), partial response (25%–50% improvement), and response without remission (> 50% improvement but without meeting remission criteria [29]. In contrast, other definitions do not distinguish between response and remission and simply include all patients who have not met response criteria, thereby excluding those who have improved but still suffer residual symptoms [5]. The clinical importance of a less-than-complete response is not only its possible link to poorer functional recovery but that residual symptoms predict earlier recurrence of a full depressive episode [30–32].

15.3

Extent of Treatment Refractoriness

Given the varying definitions of treatment refractoriness and the differing goals of treatment – especially the distinction between response and remission – it is impossible to accurately provide a single estimate of treatment resistance. The classic response rate to an antidepressant hovers between 60% and 70% [33]. However, this number typically reflects an analysis of completers, not an intent-to-treat analysis. Including dropouts (those who might be called pseudoresistant) would decrease the response rate to 50%–55%. Estimates of remission in antidepressant trials are 25%–50% [34]. Thus, a trial that defined treatment-refractory patients as those who do not meet remission criteria from a single adequate antidepressant trial (a very broad definition) would include more than half the patients evaluated in this definition. It has been estimated (but not studied systematically) that up to 10% of patients remain depressed despite multiple interventions [3]. Regardless of which definition is used, the number of patients who have a less-than-adequate response to antidepressants is substantial.

15.4

Risk Factors for Treatment-refractory Depression

Table 15.3 lists a number of factors that may contribute to the likelihood of treatment resistance.

Table 15.3 Factors associated with treatment-refractory depression

-
- Comorbid psychiatric disorders
 - Alcohol abuse
 - Personality disorders
 - Panic disorder
 - Specific subtypes of depression
 - Psychotic depression
 - Winter depression
 - Atypical depression
 - Comorbid medical disorders
 - Psychosocial factors
-

15.4.1

Psychiatric Comorbid Disorders

Comorbid psychiatric disorders are generally considered to be among the most important causes of antidepressant treatment resistance. However, not all studies find that comorbid disorders contribute to treatment resistance [35].

Among the psychiatric comorbid disorders that may contribute to treatment resistance, substance abuse, especially alcohol abuse, must always be considered. Substance abuse may be a primary cause of the depression (in which case the disorder should be described as substance-induced mood disorder) or may make the antidepressant treatment less effective. In the first instance – so-called secondary depression – simple sobriety would cause remission of the depression. The results of some [36] but not all studies [37] are consistent with this notion. In the second instance, patients can be conceptualized as having either two primary disorders or as having primary depression with secondary drug/alcohol abuse, which interferes with treatment efficacy [38]. Even moderate alcohol consumption may diminish antidepressant-treatment response [39].

Comorbid personality disorders have been shown in some [40, 41] but not all studies [42, 43] to diminish antidepressant-treatment response [44, 45]. Many studies examining this issue evaluated tricyclic antidepressant responsiveness. The effects of personality traits and disorders on the response to strongly serotonergic antidepressants may differ, since these medications may be useful in both Cluster B and potentially Cluster C personality disorders [46]. Clinically, when the two disorders coexist, both should be treated simultaneously by either pharmacotherapy or a combination of medication and psychotherapy.

Anxiety and anxiety disorders have also been associated with a less robust or slower response to antidepressant treatments in some but not all studies [35, 47–49]. Whether this reflects the effect of a comorbid disorder or of simply defining a subtype of a more severe depression is unclear.

15.4.2

Depressive Subtypes

Three depressive subtypes may show more selective responses to specific somatic treatment and may therefore be associated with lower response rates if these treatments are not selected. The most important of these is psychotic depression, which generally responds best to an antidepressant plus an antipsychotic or ECT [50, 51]. However, some recent studies have suggested that psychotic depression may respond to SSRIs without concomitant treatment with antipsychotics [52].

Atypical depression – characterized by mood reactivity, weight gain/hyperphagia, hypersomnia, leaden fatigue, and interpersonal rejection sensitivity – responds better to MAO inhibitors than to tricyclics [53]. Data on SSRIs are mixed [54], although anecdotal clinical experience is generally positive.

Seasonal/winter depression, typically emerging in October through December in the Northern hemisphere and remitting spontaneously in late winter or early spring, responds specifically to full-frequency light therapy [55]. The relative efficacy of winter depression to light therapy vs. antidepressants is as yet unknown. It is reasonable, however, to assume that at least a subset of those with winter depression need light therapy (with or without antidepressants) for optimal response.

15.4.3

Medical Comorbid Disorders

Medical illness in general has been considered to be a consistent cause of treatment refractoriness in depression, especially when the medical illness is irreversible [56, 57]. What is less clear is whether specific medical disorders (e.g., vascular disorders) show a specific association with treatment resistance.

15.4.4

Psychosocial Factors

Psychosocial stressors, such as low socioeconomic status, nonsupportive social environment, and chronic stressors have all been reported to be associated with poor antidepressant-treatment outcome [58–60]. Consistent with this, both developmental factors (e.g., early trauma, childhood adversity) and psychosocial stressors (e.g., death of a loved one, having an ill close relative) are associated with chronicity in depression [61].

15.5

Strategies for Treatment-refractory Depression

Once the diagnosis of depression has been confirmed, issues such as comorbidity have been addressed, and adequate dose and duration of at least one antidepressant trial has been evaluated, an algorithm for treating the nonresponding depression must be constructed. As noted above, although a handful of studies have addressed potential treatment approaches, the relative paucity of studies comparing one approach to another precludes a data-based algorithm. Even though most research definitions of treatment resistance require nonresponse to at least two antidepressants, there is no reason to consider the options differently after one vs. two vs. three trials, except that choosing a next-stage antidepressant may depend on whether multiple antidepressants from a single class or different classes have been ineffective. Additionally, even though many definitions of treatment resistance distinguish between degrees of resistance (e.g., response but not remission vs. complete nonresponse), no study has yet shown differential treatment responses between these two groups [62]. Therefore, the options for the two groups are identical.

Conceptually, options for treating refractory depression include optimization, switching, augmentation, and combination [63].

15.5.1

Optimization

Optimization refers to continuing the original antidepressant but either at unusually high dose or for an extended time period. As noted above, some antidepressants, such as SSRIs, demonstrate a flat dose–response curve in groups. Some individual patients, however, may require higher than typical doses for optimal response. Similarly, the recent studies of Quitkin et al. [23] and of Licht and Qvitzau [64], in which five weeks of adding placebo was as effective as adding mianserin for six-week sertraline nonresponders, demonstrate that a number of patients may require 11–12 weeks of treatment for full effect, far longer than is usually considered. Unfortunately, it is clinically difficult to convince treatment-nonresponsive depressed patients to continue on an antidepressant for six extra weeks after six weeks of treatment with little to no benefit. Often, clinicians make changes – adding an adjunct, switching medications – for compliance reasons and to generate therapeutic optimism.

15.5.2

Switch Strategies

Switching antidepressants is an obvious and common option for treatment-resistant depression. The question is whether to switch within a class (typically from one SSRI to another, since tricyclics are rarely used first-line) or across class. No carefully designed study has yet addressed this question. Response rates to a second SSRI

after failure to respond to a first agent in open studies approximate 50% [8]. A number of these studies are confounded by the inclusion of both medication-nonresponsive and medication-intolerant patients [65–67]. In the only SSRI-to-SSRI switch study in which only medication nonresponders were included, 50% of patients responded to the second agent [68].

Although a number of studies have examined response rates after switching agents across antidepressant classes, most of these are open trials with no comparison groups. Here too, response rates to the second agent average approximately 50%. Among controlled studies, Thase [69] crossed imipramine and sertraline nonresponders over to the other agent. Response rates were similar in the completer analysis (55% vs. 63%), with sertraline showing an advantage in the intent-to-treat analysis ($p < 0.03$), because of the higher dropout rate with imipramine. Poirier and Boyer [7] randomized assigned patients who had failed to respond to at least two antidepressants to treatment with either venlafaxine or paroxetine. Over two thirds of the patients had failed a previous trial with another SSRI. Venlafaxine was significantly more effective than paroxetine (52% vs. 33%, $p < 0.05$). A potential confounding factor in the study was the relatively higher daily dose of venlafaxine (mean = 269 mg) than paroxetine (mean = 36 mg). In a third controlled study, Thase [70] found a faster response to mirtazapine than to sertraline but similar response rates among SSRI (but not sertraline) nonresponders.

Overall, switch studies do not give compelling reasons to recommend either trying a second agent within the same class or switching antidepressant classes. At this point then, either approach would be reasonable. Most observers, however, recommend switching classes after the failure of two agents of the same class (almost always two SSRIs) [71].

15.5.3

Augmentation/Combination Strategies

Beyond optimization and switching, augmentation and combination treatments are the other commonly considered options for treatment-refractory depressions. By definition, augmentation is typically defined as an agent that, by itself, is not an antidepressant but which enhances the efficacy of an antidepressant. Combination strategies involve adding a second agent which itself is an antidepressant. In clinical work, these two strategies are considered together, since the core element is adding a medication to the current regimen (vs. switching medications). The evaluation of various augmentation and combination strategies comprise the majority of the data-based literature on treatment-refractory depression. As noted above, although there are some double-blind studies, many more are not, and studies comparing treatment approaches to each other are rare. Table 15.4 lists the most commonly considered augmentation/combination strategies.

Table 15.4 Adjunctive and combination strategies for treatment-refractory depression

	<i>Strength of Data</i>	<i>Utility/Popularity</i>	<i>Comments</i>
First Line			
Lithium	+++	**	Levels > 0.5–0.6 mEq L ⁻¹ typically suffice. Response typically seen within two weeks.
T3	+	**	25–50 µg. T3 > T4 in one study [80]; three weeks is adequate trial.
Combination	+	***	Typical combinations = serotonergic antidepressant plus dopaminergic/noradrenergic agent.
Stimulants	---	***	Rapid response.
Second Line			
Atypical antipsychotic	+	**	Probably rapid response. Relative efficacy across agents unknown.
Lamotrigine	---	**	Requires slow dose titration.
Buspirone	+	**	Well tolerated.
Pindolol	+	*	Rarely used: data more convincing for acceleration, not augmentation.
Other			
Electroconvulsive therapy (ECT)	+++	**	Typically used alone; negative publicity diminishes use.
Psychotherapy	++	***	Should be considered more often.

--- No controlled trials or negative controlled trials; + weak; ++ moderate; +++ strong;
 * rarely prescribed; ** occasionally prescribed; *** commonly prescribed.

15.5.3.1 First-line Augmentation/Combination Treatments

Lithium has been the most thoroughly investigated adjunctive antidepressant treatment, with 12 placebo-controlled published studies [72, 73] and a cumulative response rate over 50%. A meta-analysis showed clear evidence of efficacy [72]. The majority of these studies used tricyclics as the original failed antidepressant, with only two studies examining lithium augmentation to SSRIs [74, 75]. Response to adjunctive lithium typically occurs within two weeks. Doses and plasma levels of adjunctive lithium may be somewhat lower than those used in treating bipolar disorder. Current recommendations are to obtain a serum level ≥ 0.5 mEq L⁻¹ [72]. In the one controlled study examining the issue, placebo substitution for lithium after successful augmentation resulted in higher relapse rates than in patients who continued on adjunctive lithium [76].

The thyroid hormone tri-iodothyronine (T3) is one of the oldest adjunctive treatments. Overall, the data in support of its efficacy are mixed. Pooling results from all studies documented efficacy, but pooled results from the four double-

blind studies did not distinguish from placebo treatment [77], and two [78, 79] of the five systematic studies showed negative results (although one of these used historical controls) [79]. All the systematic studies on T3 as an adjunct have utilized tricyclic antidepressants, with no studies examining SSRI/T3 augmentation treatment. Typical daily doses of T3 are 25–50 µg. In the one controlled study evaluating two different thyroid hormones, T3 was superior to T4 (L-thyroxine) as an adjunctive antidepressant [80]. However, the relatively short length of this study (three weeks), combined with the markedly shorter half-life of T3 than of T4, is a significant limitation of this study.

Combination strategies, in which a second antidepressant is added to the first, is a strategy for treatment-refractory depression that is commonly used but rarely systematically investigated [81]. Virtually always, the second antidepressant prescribed is from a different antidepressant class than the first agent and usually has different neurotransmitter effects. The underlying theory, of course, is that if (for example) a strongly serotonergic antidepressant has not been effective, adding an agent with dopaminergic and/or noradrenergic effects might add what has been missing. Consistent with this, the most common combination strategy in clinical practice is that of supplementing a strongly serotonergic antidepressant (an SSRI or venlafaxine) with bupropion [82]. Many anecdotal reports and case series describe positive responses to the addition of a second antidepressant.

Despite the popularity of this approach, only a handful of recent controlled studies have evaluated combination treatment. In one study, fluoxetine and desipramine combination was superior to either treatment alone, although the patients treated were not specifically selected for treatment resistance [83]. The placebo-controlled addition of mirtazapine to 26 patients who had failed to respond to other antidepressants (primarily SSRIs) resulted in significantly higher response rates compared to placebo (64% vs. 20%, $p < 0.05$) [84]. This study cannot answer whether adding mirtazapine would have more effective than simply switching to mirtazapine. The combination of mianserin (unavailable in the United States) and fluoxetine resulted in a significantly higher response rate than treatment with fluoxetine alone (60% vs. 9%) in a small cohort of treatment-resistant patients [85]. In a larger study, depressed patients unresponsive to fluoxetine 20 mg for six weeks were randomly assigned to continued fluoxetine, switched to mianserin, or treated with fluoxetine 20 mg plus mianserin 60 mg [86]. Those treated with the combination had a significantly greater reduction in Ham-D scores and nonsignificantly higher response rates.

Fava and colleagues evaluated the efficacy of desipramine (mean plasma level of desipramine = 100 ng mL⁻¹ in only three patients in whom levels were obtained in the first study and desipramine level = 105 ng mL⁻¹ in the second study) added to fluoxetine in two studies [87, 88]. No placebo groups were used in either study. Adjunctive desipramine was somewhat less effective than raising the dose of fluoxetine in these studies (see section 15.5.4 for more details).

If combination strategies are utilized, care must be taken to consider potential pharmacokinetic interactions. The most important of these is between SSRIs and tricyclics, in which the former, especially fluoxetine and paroxetine, can markedly

raise the plasma levels of the latter, by inhibiting the cytochrome P450 2D6 pathway, potentially resulting in toxic levels. Fluvoxamine's ability to inhibit the cytochrome P450 1A2 pathway could also result in higher tricyclic levels if they are co-prescribed.

Like combinations, adding stimulants (or, more properly, dopamine agonists) is a commonly used adjunctive strategy with virtually no controlled research supporting its use. Only small open case series support the practice [89, 90]. Most commonly, methylphenidate and *D*-amphetamine are prescribed. When stimulants are prescribed adjunctively, they seem to be effective relatively rapidly, within a few days. Daily doses vary widely, from (for example) methylphenidate 5 to 60 mg. Other dopamine agonists that have been reported as effective in open case series are pramipexole, a D2, D3 agonist [91], and amantadine [92]. More recently, modafinil [93] has also been prescribed.

Two open case series describe the efficacy of stimulants when added to MAO inhibitors [93, 94]. Although this combination theoretically confers a risk of provoking a hypertensive episode, in practice and in the two case series, these occur rarely if the stimulant is slowly added to the MAOI, starting with very low doses.

15.5.3.2 Second-line Augmentation/Combination Treatments

A number of adjunctive treatments, listed in Table 15.4, can be described as second line, due to the availability of only preliminary data and general lack of clinical experience (atypical antipsychotics and lamotrigine) or mostly negative data (buspirone, pindolol).

Atypical antipsychotics as antidepressant adjuncts has become an increasingly popular option [95]. Anecdotal data describe the efficacy of risperidone [96–97]. Neither the presence of psychosis nor severe agitation seems necessary for efficacy. In the only published controlled study, Shelton [98] demonstrated the greater efficacy of olanzapine and fluoxetine compared to either fluoxetine or olanzapine alone in patients who had just failed a trial of fluoxetine and at least one other antidepressant. Efficacy was seen quickly, within one week, similar to general clinical observations. However, this study was relatively small ($n = 28$) and was biased by comparing the combination treatment to an antidepressant that patients had just failed. Whether the putative adjunctive antidepressant effect of olanzapine and possibly risperidone would be seen with all other atypical antipsychotics is as yet unclear.

Lamotrigine, an anticonvulsant with demonstrated efficacy in bipolar depression [99], has recently been explored as an adjunctive antidepressant. Open case series using mean daily doses of 113 mg and 155 mg, respectively, showed positive effects [100, 101]. In the only controlled study, lamotrigine plus fluoxetine 20 mg was somewhat more effective than fluoxetine alone in depressed patients who had failed to respond to one other antidepressant [102]. However, both unipolar ($n = 15$) and bipolar ($n = 8$) patients were included. Although unipolar and bipolar subjects had similar responses to treatment, the small number of subjects resulted in insufficient statistical power to meaningfully test the efficacy in unipolar patients.

Although open studies are positive, buspirone, a serotonin-1A partial agonist, has not been shown to be particularly effective in two controlled studies of treatment-

refractory depression [103, 104]. In the first study, buspirone did not distinguish from placebo when added to an ineffective four-week trial of an SSRI [103]. A high placebo response rate and the relatively short (four weeks) SSRI treatment were problematic in this study. In the other controlled study, buspirone was more effective than placebo after one week and in the more severely depressed subjects, but overall the responses did not differ from placebo after six weeks [104]. Buspirone daily doses in these studies were 30–60 mg.

Pindolol, a beta blocker with pro-serotonergic properties, has been evaluated both as an acceleration strategy and as an antidepressant-augmenting agent. Although the acceleration data provide some support, the two controlled studies comparing pindolol to placebo for treatment-resistant depression showed no evidence of efficacy [105, 106]. When prescribed, typical pindolol doses are 2.5 mg three times daily.

15.5.3.3 Switching vs. Adding: Advantages and Disadvantages

As noted above, few studies have compared the major options of switching antidepressants vs. adding augmentation/combination treatments. Clinically, each approach is associated with distinct advantages and disadvantages. Table 15.5 shows the advantages and disadvantages of the augmentation/combination approach. The most important advantage of adding a second medication is the possibility of maintaining whatever response (albeit partial) was seen with the primary antidepressant. Partial responses are common, and losing that improvement is both unfortunate by itself and very discouraging to patients. Of course, if there has been no response to the original agent, this factor is meaningless. The other advantage of adding a second agent reflects the theoretical underpinnings of the combinations prescribed. When adding, the clinician can construct combinations that target specific neurotransmitter systems. Thus, if enhancing the serotonergic system is the goal, buspirone or pindolol might be added. Conversely, noradrenergic influences can be heightened by adding a stimulant or bupropion. Unfortunately, no data whatsoever support the notion that the construction of medication combinations based on neurotransmitter effects yields more effective results than random combinations.

The negative effects of additive treatment reflect the usual criticisms of polypharmacy in general. Potential pharmacokinetic interactions are always relevant. The greater the number of medications prescribed, the more likely are interactions, many of which are unknown, and most of which are unremembered by clinicians.

Table 15.5 Advantages and disadvantages of adding (vs. switching) in treatment-refractory depression

Advantages	Disadvantages
<ul style="list-style-type: none"> • Minimize relapse • Provide specific neurotransmitter effect 	<ul style="list-style-type: none"> • Potential pharmacokinetic interactions • Additive side effects • Regimen complexity leading to poor compliance

With rare exception (e.g., neutralizing sedation by prescribing an activating medication), side effects are additive when multiple medications are prescribed. When multiple medications are prescribed, each of which may cause the same mild, subclinical side effect (e.g., sedation or weight gain), the result may be either overt dullness, sedation and cognitive disturbance, or marked weight gain that precipitates noncompliance. Finally, all compliance studies have shown that the more complex the regimen – number of medications, number of pills, number of doses administered on a daily basis – the lower the compliance rate.

15.5.4

Studies Comparing Different Approaches to Treatment-refractory Depression

Only a handful of studies have compared the efficacy of more than one of the approaches already discussed. In the first controlled study in this area, Joffe et al. [107] found lithium and T3 to be equivalently effective when added to tricyclic nonresponders. Both treatments were significantly more effective than placebo (respective response rates: 53%, 59%, 19%). Fava et al. [87] compared the double-blind efficacy of higher-dose fluoxetine (40–60 mg) vs. adding desipramine 25–50 mg vs. adding lithium 300–600 mg for four weeks to patients who had failed to respond to eight weeks of fluoxetine 20 mg daily. Patients receiving higher-dose fluoxetine showed higher response rates than the other two groups, although the small number of subjects studied made achieving statistical significance virtually impossible. These authors then replicated this study using a larger sample (101 subjects vs. 49 in the original report) [88]. Again, higher-dose fluoxetine was nonsignificantly superior to the other two groups (42% response rate vs. 29% vs. 24%). Similar results were found for both nonresponders and partial responders, although the latter showed generally better results. Here too, despite the larger sample size, the study was probably underpowered to detect significant differences.

In the largest controlled double-blind study to date comparing two or more strategies for treatment-refractory depression, Licht et al. [64] compared three treatment approaches in 295 patients who had failed to respond openly to sertraline 50 mg for four weeks and 100 mg for two additional weeks. Continued sertraline treatment at 100 mg and adding mianserin 30 mg daily were equivalently effective (70% and 67% response rates), and both were significantly superior to higher-dose (200 mg) sertraline (56% response rate). The results of continued sertraline at 100 mg again highlights the effect of longer trials at the same dose (an optimization strategy) as a viable strategy for patients not responding within the usual six-week time frame.

15.5.5

Electroconvulsive Therapy

As has been true for decades, electroconvulsive therapy (ECT) continues as the most important treatment modality for those depressed patients who have not responded to antidepressants. What varies across individual practitioners and

clinical communities is the place of ECT in the algorithm of treatment refractoriness. Some proponents of ECT recommend it relatively early in the course of treatment, after one or two failed antidepressant trials. For others, ECT is one of the last-line treatments. As an example, in Thase and Rush's staging of treatment resistance, ECT is the treatment of choice for Stage IV (of V) depression, with Stage V (the higher level of treatment resistance) defined by the failure of ECT along with previous treatments [3]. Of course, the timing of ECT also depends on clinical factors such as depressive severity, presence of psychosis, intensity of suicidal ideation, and urgency for rapid improvement.

Response rates to ECT for depression also vary, depending on the extent of pre-ECT antidepressant treatment resistance. As an example, in one study ECT response was 86% in those patients who had not had adequate pharmacotherapy, compared to 50% for those who had had adequate trials [108]. In a more recent study, ECT response rates were similar between those depressed patients who had adequate pharmacotherapy and those who had not [109]. However, remission rates with ECT were almost twice as high among those who had not had an adequate course of pharmacotherapy (50% vs. 28%). Thus, even though ECT has been and should continue to be considered for treatment-refractory depressed patients, response rates should not be quoted as the $\geq 80\%$ rates that are more typical of non-treatment-refractory patients.

Patients who have failed an adequate course of ECT remain among the most difficult-to-treat refractory patients. A number of small case series, though, have demonstrated that at least some ECT-refractory patients do respond to antidepressants, either alone or in combination [110, 111]. The possibility that ineffective ECT may sensitize neuronal systems, thereby making antidepressants potentially more effective, has been suggested but never evaluated.

15.5.6

Psychotherapy

Despite the dominance of somatic treatments in the discussion of treating refractory depression, psychotherapy may be a critical treatment option, usually but not always prescribed in concert with medication. From education on depression to issues regarding treatment adherence, psychotherapy may provide benefit beyond what is possible with pharmacotherapy. Additionally, a number of studies have shown that psychotherapy may enhance and extend treatment efficacy. Because they are easier to test, manual driven psychotherapies – cognitive behavioral (CBT) and interpersonal – are the best-validated antidepressant psychotherapies, with no compelling evidence suggesting the superiority of one over the other [112]. Nonetheless, it is as yet unclear what features of psychotherapy confer efficacy, and equivalent improvement may be found with other therapies not yet tested.

Psychotherapies have been shown to enhance the efficacy of medication in chronically depressed individuals [113] and in those with severe recurrent depressions [114]. Treatment-resistant patients have shown improvement with cognitive-behavioral therapy [115]. Finally, residual depressive symptoms may be

improved by CBT [116]. Thus, for patients who have been refractory to multiple somatic treatments, especially those with prominent personality pathology or psychosocial stresses, psychotherapy should always be considered.

15.6

Alternative/Experimental Approaches to Treatment-refractory Depression

A number of other treatments for treatment-refractory depressed patients have been more recently suggested. None of these can be considered mainstream yet, due to insufficient research and/or clinical experience. Among the most important of these are transcranial magnetic stimulation, vagal nerve stimulation, and the use of omega-3 fatty acids.

15.6.1

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) utilizes a rapidly alternating electrical current to produce fluctuating magnetic pulses. When the metal coil that produces the current is placed on the scalp, the magnetic pulses enter the brain unimpeded, causing neuronal depolarization and generating action potentials [117]. A number of controlled studies have compared TMS to sham TMS in which the coil is placed at an angle so that less magnetic stimulus penetrates the brain. This placement typically produces scalp tingling, which is also seen with real TMS, thereby providing an active placebo. Different coil placements may produce differing amounts of magnetic effects, suggesting that some 'sham' treatments may be active [118]. Nonetheless, TMS is consistently more effective than sham TMS [117], although not all studies find a difference between the two treatments [119]. As with any new treatment, technical issues such as dose and length of treatment must be established before efficacy can be meaningfully evaluated. For TMS, these parameters are pulse frequency, course duration, pulse intensity and quantity, and coil placement [117]. Although much remains to be investigated, high-frequency treatment with the coil placed over the left prefrontal cortex currently seems optimal.

Comparative treatment studies with TMS have understandably focused on its efficacy for patients typically considered for ECT. A meta-analysis of published studies suggests similar efficacy [120], with a more recent study also showing similar results [121]. Psychotically depressed patients, however, may still respond better to ECT [122], although the differential use of other psychotropic agents across the two groups limits the interpretation of the study. Given that TMS is administered without anesthesia and is associated with far fewer cognitive effects than ECT, with increasing evidence for its efficacy in treatment-refractory depression it may become a preferred treatment.

15.6.2

Vagal Nerve Stimulation

Vagal nerve stimulation (VNS), primarily used as a treatment for treatment-resistant epilepsy, has been evaluated for its antidepressant efficacy, with the rationale of the use of other antiepileptic treatments in mood disorders and the reports of enhanced mood in epilepsy patients receiving VNS [123]. In the one open, published study, VNS was added to the treatment regimen of 59 patients with nonpsychotic treatment-resistant depression [124]. Approximately one third responded. Response predictors were not having failed ECT and being somewhat less treatment-resistant. Responders who continued in treatment showed further improvement over an additional nine-month period [125]. Although these results are described as promising, the lack of a control group, the lack of efficacy of VNS for the most treatment-resistant patients, and the expense of the treatment cast some doubt on the viability of VNS as a strategy to commonly consider in treatment-refractory depression.

15.6.3

Omega-3 Fatty Acids

Omega-3 fatty acids have been evaluated as antidepressant treatments based on three rationales: (1) lipids play an important role in neuronal signal transduction processes; (2) omega-3 fatty acid levels, or the ratio of omega-3 to omega-6 fatty acids, have been shown to be abnormal in depressed patients; and (3) there is a strong inverse relationship between the consumption of omega-3 fatty acids in a population and the prevalence of depression [125, 126]. In the largest controlled study, Peet et al. [125] treated 70 patients who had failed to respond adequately to an antidepressant (a relatively loose definition of treatment-refractory depression) to treatment with three doses of ethyl-eicosapentaenoate (EPA) or placebo. The lowest dose, one gram daily, showed the best effect and significantly distinguished from placebo on all rating scales. Side effects were few.

In another, smaller controlled study, however, another omega-3 fatty acid, docosahexaenoic acid (DHA), did not distinguish from placebo in treating non-treatment-refractory depression [127]. Whether the difference between the two studies reflects the different populations studied, the different omega-3 fatty acids (EPA vs. DHA) evaluated, or dosing effects remains unclear.

15.7

Clinical Choices for Treatment-refractory Depression

Consistent findings in clinical research do not always translate into clinical practice by community clinicians or even by the academic clinicians who have participated in the research. Nowhere is this more true than in treatment-refractory depression. According to what has been reviewed above, the treatments for refractory depression

that are most supported by clinical research are waiting more time for efficacy, adjunctive lithium, and, to a much lesser extent, T3. Yet, in clinical surveys these strategies are not typically utilized as first-line. As an example, attendees at a large psychopharmacology course ($n = 432$ participants, 54% of the attendees) were surveyed as to their next-step strategies in clinical scenarios [11]. Increasing the dose was the most commonly endorsed strategy (82%) for a four-week SSRI nonresponse, with only 16% choosing to wait longer. Adjunctive treatments were chosen relatively infrequently for nonresponders or partial responders (12% and 14%). Among the adjunctive agents, adding bupropion (for which there are no controlled data) was more commonly recommended than was adding lithium or T3.

Similarly, in an earlier survey of 20 expert psychopharmacologists published in 1999, dopaminergic medications – bupropion, methylphenidate, and dextro-amphetamine – were perceived as the most effective adjunctive agents, with lithium and T3 rated as among the least likely to be effective [127]. An informal survey among expert psychopharmacologists at UCLA yielded similar results (personal experience). Here too, a dramatic disparity between the research literature and clinical experience and practice is evident.

Although no data currently shed light on the reasons for the disparity between clinical research and clinical practice, some factors are obvious. First, controlled studies do not take into account the difference between efficacy (positive effects seen in research studies) and effectiveness (a combination of perceived efficacy plus patient acceptance, side effect burden, and difficulty of administration). As an example, lithium may show efficacy, but its side-effect profile, including weight gain and the need for blood tests associated with its use, makes it less popular among clinicians and patients alike. Second, a number of the suggested adjuncts – especially bupropion and stimulants – have not been shown to be ineffective, they have simply not been tested in controlled studies. This is partly but not completely explained by proprietary concerns – stimulants are no longer patent-protected in the United States, and no manufacturer of an antidepressant (e.g., bupropion) wants it to be thought of as an adjunct rather than a primary agent. Therefore, financial support from manufacturers of these medications is absent. Third, waiting longer for the original antidepressant to be effective, as suggested by the results of a number of studies [23, 64], is difficult, given the typical urgency of depressed patients and those who treat them. Altering treatment in any way – whether it is increasing the dose or adding a second medication – is easier and, to the clinician, seems to maximize placebo effects beyond simply waiting longer.

15.8

Summary

Non-response to antidepressants continues to vex researchers and clinicians alike. Despite the ubiquity of nonresponsive patients, elements of a systematic approach have been lacking in the relevant studies. The initial step would be for the field to

define a typology of treatment resistance, whether as a dichotomous variable or by utilizing a staging schema, with different gradations of treatment resistance. Second, universal standards of the definitions of an adequate treatment trial must be agreed upon. Third, we must construct a consistent approach to the dimensional quality of response. Partial response must be distinguished from non-response, and the place of responders who are not remitters must also be considered. Fourth, more attention must be paid to those labeled pseudoresponders. Even though they are theoretically less interesting than non-responders to adequate treatments, they are exceedingly common in clinical practice and may be the most important subgroup of those who are clinically conceptualized as non-responders. Fifth, the population studied in any treatment trial must be carefully considered. Excluding those with comorbid psychiatric disorders may provide a more homogenous sample, but will sorely limit the generalizability of the study results. As an example, the majority of patients appropriately considered for antidepressant treatment are excluded from research studies [128]. Among the most common reasons for exclusion are comorbid psychiatric disorders. Sixth, more large-scale controlled studies evaluating strategies for treating resistant patients are sorely needed. One example would be more placebo-controlled trials, especially of those proposed treatments for which no current controlled data exist, such as treatment with bupropion or stimulants. Another type of needed study would be to compare some of the current approaches. As noted above, only a handful of these studies have been published. Additionally, because these studies would compare two or more active treatments, sufficient power to detect differences in outcome between groups would be impossible to obtain without large-scale studies that would inevitably require multiple study sites. An encouraging example of a multicenter algorithmic approach to treatment-refractory depression that is not controlled is STAR*D [129].

Until there are more consensual definitions regarding treatment-refractory patients and until results of more large-scale controlled studies are available, clinicians will continue to make prescribing decisions based more on clinical experience and intuition than on any other factor.

References

- 1 RUSH, J., THASE, M. E., DUBÉ, S., Research issues in the study of difficult-to-treat depression. *Biological Psychiatry* **2003**, 53, 743–753.
- 2 SOUERY, D., AMSTERDAM, J., DE MONTIGNY, C., LECRUBIER, Y., MONTGOMERY, S., LIPP, O., RACAGNI, G., ZOHAR, J., MENDLEWICZ, J., Treatment resistant depression: methodological overview and operational criteria. *European Neuropsychopharmacology* **1999**, 9, 83–91.
- 3 THASE, M. E., RUSH, A. J., Treatment-resistant depression. In: BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, New York, **1995**, 1081–1098.
- 4 FAVA, M., Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry* **2003**, 53, 649–659.
- 5 SACKEIM, H. A., The definition and meaning of treatment resistant depression. *Journal of Clinical Psychiatry* **2001**, 62 (suppl. 16), 10–16.

- 6 THASE, M. E., KREMER, C., RODRIGUES, H., Mirtazapine versus sertraline after SSRI nonresponse. *154th Annual Meeting of the American Psychiatric Association*. New Orleans, LA, 2001.
- 7 POIRIER, M.-F., BOYER, P., Venlafaxine and paroxetine in treatment-resistant depression. *British Journal of Psychiatry* 1999, 12–16.
- 8 FAVA, M., Management of nonresponse and intolerance: switching strategies. *Journal of Clinical Psychiatry* 2000, 61 (suppl. 2), 10–12.
- 9 FAVA, M., MISCHOULON, D., ROSENBAUM, J., Augmentation strategies for failed SSRI treatment. *American Society of Clinical Psychopharmacology Progress Notes*. 1998, 9, 7.
- 10 MISCHOULON, D., FAVA, M., ROSENBAUM, J. F., Strategies for augmentation of SSRI treatments: a survey of an academic psychopharmacology practice. *Harvard Review of Psychiatry* 1999, 6, 322–326.
- 11 FREDMAN, S. J., FAVA, M., KIENKE, A. S., WHITE, C. N., NIERENBERG, A. A., ROSENBAUM, J. F., Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current 'next-step' practices. *Journal of Clinical Psychiatry* 2000, 6, 403–407.
- 12 NIERENBERG, A., AMSTERDAM, J. D., Treatment-resistant depression: definition and treatment approaches. *Journal of Clinical Psychiatry* 1990, 51 (suppl. 6) 39–47.
- 13 GUSCOTT, R., GROF, P., The clinical meaning of refractory depression: a review for the clinician, *The American Journal of Psychiatry* 1991, 6, 695–704.
- 14 KELLER, M. B., LAVORI, P. W., KLERMAN, G. L., et al., Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. *Archives of General Psychiatry* 1986, 43, 458–466.
- 15 KELLER, M. B., KLERMAN, G. L., LAVORI, P. W., et al., Treatment received by depressed patients. *JAMA* 1982, 248, 1848–1855.
- 16 DAWSON, R., LAVORI, P. W., CORYELL, W. H., ENDICOTT, J., KELLER, M. B., Course of treatment received by depressed patients. *Journal of Psychiatric Research* 1999, 33, 233–242.
- 17 UNÜTZER, J., RUBENSTEIN, L., KATON, W. J., TANG, L., DUAN, N., LAGOMASINO, I. T., WELLS, K. B., Two-year effects of quality improvement programs on medication management for depression. *Archives General Psychiatry* 2001, 58, 935–942.
- 18 SCHATZBERG, F., COLE, J. O., COHEN, B. M., et al., Survey of depressed patients who have failed to respond to treatment. In: DAVIS, J. M., MAAS, J. W. (Eds.), *The Affective Disorders*, American Psychiatric Press, Washington DC, 1986, 73–85.
- 19 BEASLEY, C. M., BOSOMWORTH, J. C., WERNICKE, J. F., Fluoxetine: relationships among dose, response, adverse events, and plasma concentrations in the treatment of depression. *Psychopharmacology Bulletin* 1990, 26, 18–24.
- 20 SCHWEIZER, E., RICKELS, K., AMSTERDAM, J. D., FOX, I., PUZZUOLI, G., WEISE, C., What constitutes an adequate antidepressant trial for fluoxetine? *Journal of Clinical Psychiatry* 1990, 51, 8–11.
- 21 NIERENBERG, A., FARABAUGH, A. H., ALPERT, J. E., GORDON, J., WORTHINGTON, J. J., ROSENBAUM, J. F., FAVA, M., Timing of onset of antidepressant response with fluoxetine treatment. *American Journal of Psychiatry* 2000, 157, 1423–1428.
- 22 GELENBERG, J., CHESN, C. L., How fast are antidepressants? *Journal of Clinical Psychiatry* 2000, 61, 712–721.
- 23 QUITKIN, F. M., PETKOVA, E., MCGRATH, P. J., TAYLOR, B., BEASLEY, C., STEWART, J., AMSTERDAM, J., FAVA, M., ROSENBAUM, J., REIMHERR, F., FAWCETT, J., CHEN, Y., KLEIN, D., When should a trial of fluoxetine for major depression be declared failed? *American Journal of Psychiatry* 2003, 160, 734–740.
- 24 TRIVEDI, M. H., RUSH, A. J., PAN, J. Y., CARMODY, T. J., Which depressed patients respond to nefazodone and when? *Journal of Clinical Psychiatry* 2001, 62, 158–163.
- 25 RUSH, J., BATEY, S. R., DONAHUE, R. M., ASCHER, J. A., CARMODY, T., METZ, A., Does pretreatment anxiety predict response to either bupropion SR or sertraline? *Journal of Affective Disorders* 2001, 64, 81–87.
- 26 HAMILTON, M., A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 1960, 23, 56–62.

- 27 MONTGOMERY, S. A., ÅSBERG, M., A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 1979, 134, 382–389.
- 28 GUY, W., *ECDEU Assessment Manual of Psychopharmacology, Revised*, NIMH Psychopharmacology Branch, Division of Extramural Research Programs, Rockville, MD, 1976.
- 29 FAVA, M., DAVIDSON, K. G., Definition and epidemiology of treatment-resistant depression. *Psychiatric Clinics of North America* 1996, 19, 179–200.
- 30 PAYKEL, E. S., RAMANA, R., COOPER, Z., HAYHURST, H., KERR, J., BAROCKA, A., Residual symptoms after partial remission: an important outcome in depression. *Psychological Medicine* 1995, 25, 1171–1180.
- 31 JUDD, L. L., AKISKAL, H. S., MASER, J. D., et al., Major depressive disorder: a prospective study of residual sub-threshold depressive symptoms as predictor of rapid relapse. *Journal of Affective Disorders* 1998, 50, 97–108.
- 32 THASE, M. E., SIMONS, A. D., MCGEARY, J., et al., Relapse after cognitive behavioral therapy of depression: potential implications for longer courses of treatment. *American Journal of Psychiatry* 1992, 149, 1046–1052.
- 33 KLEIN, D. F., GITTELMAN, R., QUITKIN, F., RIFKIN, A., *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*, 2nd edit. Williams and Wilkins, Baltimore, MD, 1980.
- 34 NIERENBERG, A., DECECCO, L. M., Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *Journal of Clinical Psychiatry* 2001, 62 (suppl. 16), 5–9.
- 35 PETERSEN, T., GORDON, J. A., KANT, A., FAVA, M., ROSENBAUM, J. F., NIERENBERG, A. A., Treatment resistant depression and Axis I co-morbidity. *Psychological Medicine* 2001, 31, 1223–1229.
- 36 BROWN, S. A., INABA, R. K., GILLIN, J. C., SCHUCKIT, M. A., STEWARD, M. A., IRWIN, M. R., Alcoholism and affective disorder: clinical course of depressive symptom. *American Journal of Psychiatry* 1995, 152, 45–52.
- 37 MASON, B. J., KOCSIS, J. H., RITVO, C. E., CUTLER, R. B., A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *JAMA* 1996, 257, 761–767.
- 38 NUNES, E. V., DELIYANNIDES, D., DONAVAN, S., MCGRATH, P. J., The management of treatment resistance in depressed patients with substance use disorders. *Psychiatric Clinics of North America* 1996, 19, 311–327.
- 39 WORTHINGTON, J., FAVA, M., AGUSTIN, C., ALPERT, J., NIERENBERG, A. A., PAVA, J. A., ROSENBAUM, J. F., Consumption of alcohol, nicotine, and caffeine among depressed outpatients: relationship with response to treatment. *Psychosomatics* 1996, 37, 518–522.
- 40 REICH, J. H., Effect of DSM-III personality disorders on outcome of tricyclic antidepressant-treated nonpsychotic outpatients with major or minor depressive disorder. *Psychiatry Research* 1990, 32, 175–181.
- 41 SHEA, M. T., PILKONIS, P. A., BECKHAM, E., COLLINS, J. F., ELKIN, I., SOTSKY, S. M., et al., Personality disorders and treatment outcome in the NIMH Treatment of Depression Collaborative Research Program. *American Journal of Psychiatry* 1990, 147, 711–718.
- 42 HIRSCHFELD, R. M., RUSSELL, J. M., DELGADO, P. L., FAWCETT, J., FRIEDMAN, R. A., HARRISON, W. M., et al., Predictors of response to acute treatment of chronic and double depression with sertraline or imipramine. *Journal of Clinical Psychiatry* 1998, 59, 669–675.
- 43 RUSSELL, J. M., KORNSTEIN, S. G., SHEA, M. T., MCCULLOUGH, J. P., HARRISON, W. M., HIRSCHFELD, R. M. A., KELLER, M. B., Chronic depression and comorbid personality disorders: response to sertraline versus imipramine. *Journal of Clinical Psychiatry* 2003, 64, 554–561.
- 44 THASE, M. E., The role of Axis II comorbidity in the management of patients with treatment-resistant depression. *Psychiatric Clinics of North America* 1996, 19, 287–309.
- 45 SHEA, M. T., WIDIGER, T. A., KLEIN, M. H., Comorbidity of personality disorders and depression: implications

- for treatment. *Journal of Consulting and Clinical Psychology* 1992, 60, 857–868.
- 46 GITLIN, M. J., Pharmacotherapy for personality disorders. *Psychiatric Clinics of North America* 1995, 2, 151–185.
 - 47 ALPERT, J. E., LAGOMASINO, I. T., Psychiatric comorbidity in treatment-resistant depression. In: AMSTERDAM, J. D., HORNIG, M., NIERENBERG, A. A. (Eds.), *Treatment-resistant Mood Disorders*, Cambridge University Press, New York, 2001, 430–478.
 - 48 FRANK, E., SHEAR, M. K., RUCCI, P., CYRANOWSKI, J., ENDICOTT, J., FAGIOLINI, A., et al., Influence of pain–agoraphobic spectrum symptoms on treatment response in patients with recurrent major depression. *American Journal of Psychiatry* 2000, 157, 1101–1107.
 - 49 VAN VALKENBURG, C., AKISKAL, H. S., PUNZANTIAN, V., et al., Anxious depressions: clinical, family history and naturalistic outcome: comparisons with panic and major depressive disorders. *Journal of Affective Disorders* 1984, 6, 67–82.
 - 50 SPIKER, D. G., WEISS, J. C., DEALY, R. S., GRIFFIN, S. J., HANIN, I., NEIL, J. F., PEREL, J. M., ROSSI, A. J., SOLOFF, P. H., The pharmacological treatment of delusional depression. *American Journal of Psychiatry* 1983, 140, 318–322.
 - 51 KANTOR, S. J., GLASSMAN, A. H., Delusional depression: natural history and response to treatment. *British Journal of Psychiatry* 1977, 131, 351–360.
 - 52 WHEELER VEGA, J. A., MORTIMER, A. M., TYSON, P. J., Somatic treatment of psychotic depression: review and recommendations for practice. *Journal of Clinical Psychopharmacology* 2000, 20, 504–519.
 - 53 LIEBOWITZ, M. R., QUITKIN, F. M., STEWART, J. W., McGRATH, P. J., HARRISON, W. M., MARKOWITZ, J. S., RABKIN, J. G., TRICHINA, E., GOETZ, D. M., KLEIN, D. F., Antidepressant specificity in atypical depression. *Archives of General Psychiatry* 1988, 45, 129–137.
 - 54 McGRATH, P. J., STEWART, J. W., JANAL, M. N., PETKOVA, E., QUITKIN, F. M., KLEIN, D. F., A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. *American Journal of Psychiatry* 2000, 157, 344–350.
 - 55 EASTMAN, C. I., YOUNG, M. A., FOGG, L. F., LIU, L., MEADEN, P. M., Bright light treatment of winter depression: a placebo-controlled trial. *Archives of General Psychiatry* 1998, 55, 503–508.
 - 56 O'REARDON, J. P., AMSTERDAM, J. D., Medical disorders and treatment-resistant depression. In: AMSTERDAM, J. D., HORNIG, M., NIERENBERG, A. A. (Eds.), *Treatment-resistant Mood Disorders*, Cambridge University Press, New York, 2001, 405–429.
 - 57 KEITNER, G. I., RYAN, C. E., MILLER, I. W., KOHN, R., EPSTEIN, N. B., Twelve-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). *American Journal of Psychiatry* 1991, 148, 345–350.
 - 58 JOYCE, P. R., PAYKEL, E. S., Predictors of drug response in depression. *Archives of General Psychiatry* 1989, 46, 89–99.
 - 59 MILLER, W., KEITNER, G. I., WHISMAN, M. A., RYAN, C. E., EPSTEIN, N. B., BISHOP, D. S., Depressed patients with dysfunctional families: description and course of illness. *Journal of Abnormal Psychology* 1992, 101, 637–646.
 - 60 MOOS, R. H., Depressed outpatients' life contexts, amount of treatment, and treatment outcome. *Journal of Nervous and Mental Disorders* 1990, 178, 105–112.
 - 61 RISO, L. P., MIYATAKE, R. K., THASE, M. E., The search for determinants of chronic depression: a review of six factors. *Journal of Affective Disorders* 2002, 70, 103–115.
 - 62 JOFFE, R. T., LEVITT, A. J., Relationship between antidepressant partial and nonresponse and subsequent response to antidepressant augmentation. *Journal of Affective Disorders* 1999, 52, 257–259.
 - 63 PRICE, L. H., Pharmacological strategies in refractory depression. In: TASMAN, A., GOLDFINGER, S., KAUFMAN, C. (Eds.), *Review of Psychiatry*, American Psychiatric Press, Washington, DC, 1990, Vol. 9, pp. 116–131.
 - 64 LICHT, R. W., QVITZAU, S., Treatment strategies in patients with major depression not responding to first-line sertraline treatment: a randomized study of extended duration of treatment, dose increase or mianserin augmentation. *Psychopharmacology* 2002, 161, 143–151.

- 65 BROWN, W. A., HARRISON, W., Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *Journal of Clinical Psychiatry* **1995**, *56*, 30–34.
- 66 ZARATE, C. A., KANDO, J. C., TOHEN, M., WEISS, M. K., COLE, J. O., Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? *Journal of Clinical Psychiatry* **1996**, *57*, 67–71.
- 67 THASE, M. E., BLOMGREN, S. L., BIRKETT, M. A., APTER, J. T., TEPNER, R. G., Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. *Journal of Clinical Psychiatry* **1997**, *58*, 16–21.
- 68 JOFFE, R. T., LEVITT, A. J., SOKOLOV, S. T. H., YOUNG, L. T., Response to an open trial of a second SSRI in major depression. *Journal of Clinical Psychiatry* **1996**, *57*, 114–115.
- 69 THASE, M. E., RUSH, A. J., HOWLAND, R. H., KORNSTEIN, S. G., KOCSIS, J. H., GELENBERG, A. J., SCHATZBERG, A. F., KORAN, L. M., KELLER, M. B., RUSSELL, J. M., HIRSCHFELD, R. M. A., LAVANGE, L. M., KLEIN, D. N., FAWCETT, J., HARRISON, W., Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Archives of General Psychiatry* **2002**, *59*, 233–239.
- 70 THASE, M. E., KREMER, C., RODRIGUES, H. E., et al., Mirtazapine versus sertraline after SSRI non-response. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology, Dec 10–14, **2000**, San Juan, Puerto Rico.
- 71 MARANGELL, L. B., Switching antidepressants for treatment-resistant major depression. *Journal of Clinical Psychiatry* **2001**, *62* (suppl. 18), 12–17.
- 72 BAUER, M., BSCHOR, T., KUNZ, D., BERGHÖFER, A., STRÖHLE, A., MÜLLER-OERLINGHAUSEN, B., Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *American Journal of Psychiatry* **2000**, *157*, 1429–1435.
- 73 NIERENBERG, A., PAPAKOSTAS, G. I., PETERSON, T., MONTOYA, H. D., WORTHINGTON, J. J., TEDLOW, J. T., ALPERT, J. E., FAVA, M., Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. *Journal of Clinical Psychopharmacology* **2003**, *23*, 92–95.
- 74 KATONA, L. E., ABOU-SALEH, M. T., HARRISON, D. A., NAIRAC, B. A., EDWARDS, D. R. L., LOCK, T., BURNS, R. A., ROBERTSON, M. M., Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *British Journal of Psychiatry* **1995**, *166*, 80–86.
- 75 BAUMANN, P., NIL, R., SOUCHE, A., MONTALDI, S., BAETTIG, D., LAMBERT, S., UEHLINGER, C., KASAS, A., AMEY, M., Jonzier, M. -Perey, A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *Journal of Clinical Psychopharmacology* **1996**, *16*, 307–314.
- 76 BAUER, M., DÖPFMER, S., Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *Journal of Clinical Psychopharmacology* **1999**, *19*, 427–433.
- 77 ARONSON, R., OFFMAN, H. J., JOFFE, R. T., NAYLOR, C. D., Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Archives of General Psychiatry* **1996**, *53*, 842–848.
- 78 GITLIN, M. J., WEINER, H., FAIRBANKS, L., HERSHMAN, J. M., FRIEDFELD, N., Failure of T3 to potentiate tricyclic antidepressant response. *Journal of Affective Disorders* **1987**, *13*, 267–272.
- 79 THASE, M. E., KUPFER, D. J., JARRETT, D. B., Treatment of imipramine-resistant recurrent depression I, An open clinical trial of adjunctive L-triiodothyronine. *Journal of Clinical Psychiatry* **1989**, *50*, 385–388.
- 80 JOFFE, R. T., SINGER, W., A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Research* **1990**, *32*, 241–251.
- 81 LAM, R. W., WAN, D. D. C., COHEN, N. L., KENNEDY, S. H., Combining antidepressants for treatment-resistant depression: a review. *Journal of Clinical Psychiatry* **2002**, *63*, 685–693.

- 82 DeBattista, C., Solvason, H. B., Poirier, J., Kendrick, E., Shatzberg, A. F., A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. *Journal of Clinical Psychiatry* **2003**, *23*, 27–30.
- 83 Nelson, J. C., Mazure, C. M., Tatlow, P. I., Bowers, M. B., Price, L. H., Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind study. *Biological Psychiatry* **2004**, *55*, 296–300.
- 84 Carpenter, L. L., Yasmin, S., Price, L. H., A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biological Psychiatry* **2002**, *51*, 183–188.
- 85 Maes, M., Libbrecht, I., Van Hunsel, F., Campens, D., Meltzer, H. Y., Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. *Journal of Clinical Psychopharmacology* **1999**, *19*, 177–182.
- 86 Ferreri, M., Lavergne, F., Berlin, I., et al., Benefits from mianserin augmentation of fluoxetine in patients with major depression: non-responders to fluoxetine alone. *Acta Psychiatrica Scandinavica* **2001**, *103*, 66–72.
- 87 Fava, M., Rosenbaum, J. F., McGrath, P. J., Stewart, J. W., Amsterdam, J. D., Quitkin, F. M., Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *American Journal of Psychiatry* **1994**, *151*, 1372–1374.
- 88 Fava, M., Alpert, J., Nierenberg, A., Lagomasino, I., Sonawalla, S., Tedlow, J., Worthington, J., Baer, L., Rosenbaum, J. F., Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and non-responders to fluoxetine. *Journal of Clinical Psychopharmacology* **2002**, *22*, 379–387.
- 89 Mesand, P. S., Anand, V. S., Tanguary, J. F., Psychostimulant augmentation of second generation antidepressants: a case series. *Depression and Anxiety* **1998**, *7*, 89–91.
- 90 Stoll, L., Pillay, S. S., Diamond, L., Workum, S. B., Cole, J. O., Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *Journal of Clinical Psychiatry* **1996**, *57*, 72–76.
- 91 Lattanzi, L., Dell'Oso, L., Cassano, P., Pini, S., Rucci, P., Houck, P. R., Gemignani, A., Battisani, G., Bassi, A., Abelli, M., Cassano, G. B., Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disorders* **2002**, *4*, 307–314.
- 92 Stryjer, R., Strous, R. D., Shaked, G., Bar, F., Feldman, B., Kotler, M., Polak, L., Rosenczwaig, S., Weizman, A., Amantadine as augmentation therapy in the management of treatment-resistant depression. *International Clinical Psychopharmacology* **2003**, *18*, 93–96.
- 93 Markovitz, P. J., Wagner, S., An open-label trial of modafinil augmentation in patients with partial response to antidepressant therapy. *Journal of Clinical Psychopharmacology* **2003**, *23*, 207–209.
- 94 Fawcett, J., Kravitz, H. M., Zajecka, J. M., Schaff, M. R., CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. *Journal of Clinical Psychopharmacology* **1991**, *11*, 127–132.
- 95 Thase, M. E., What role do atypical antipsychotic drugs have in treatment-resistant depression? *Journal of Clinical Psychiatry* **2002**, *63*, 95–103.
- 96 Ostroff, R. B., Nelson, J. C., Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *Journal of Clinical Psychiatry* **1999**, *60*, 256–259.
- 97 Hirose, S., Ashby, Jr, C. R., An open pilot study combining risperidone and a selective serotonin reuptake inhibitor as initial antidepressant therapy. *Journal of Clinical Psychiatry* **2002**, *63*, 733–736.
- 98 Sheldon, R. C., Tollefson, G. D., Tohen, M., et al., A novel augmentation strategy for treating resistant major depression. *American Journal of Psychiatry* **2001**, *158*, 131–134.
- 99 Calabrese, J. R., Bowden, C. L., Sachs, G. S., Ascher, J. A., Monaghan, E., Rudd, G. D., A double-blind placebo-controlled study of lamotrigine mono-

- therapy in outpatients with bipolar I depression. *Journal of Clinical Psychiatry* 1999, 60, 79–88.
- 100 BARBEE, J. G., JAMHOUR, N. J., Lamotrigine as an augmentation agent in treatment-resistant depression. *Journal of Clinical Psychiatry* 2002, 63, 737–741.
 - 101 ROCHA, F. L., HARA, C., Lamotrigine augmentation in unipolar depression. *International Clinical Psychopharmacology* 2003, 18, 97–99.
 - 102 BARBOSA, L., BERK, M., VORSTER, M., A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *Journal of Clinical Psychiatry* 2003, 64, 403–407.
 - 103 LANDÉN, M., BJÖRTING, G., ÅGREN, H., FAHLÉN, T., A randomized, double-blind placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *Journal of Clinical Psychiatry* 1998, 59, 664–668.
 - 104 APPELBERG, B. G., SYVÄLAHTI, E. K., KOSHINEN, T. E., et al., Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in. *Journal of Clinical Psychiatry* 2001, 62, 448–452.
 - 105 MORENO, F. A., GELENBERG, A. J., BACHAR, K., DELGADO, P. L., Pindolol augmentation of treatment-resistant depressed patients. *Journal of Clinical Psychiatry* 1997, 58, 437–439.
 - 106 PÉREZ, V., SOLER, J., PUIGDEMONT, D., ALVAREZ, E., GRUP DE RECERCA EN TRASTORNS AFECTIUS, ARTIGAS, F., A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Archives of General Psychiatry* 1999, 56, 375–379.
 - 107 JOFFE, R. T., SINGER, W., LEVITT, A. J., MACDONALD, C., A placebo-controlled comparison of lithium and triiodothyronine augmentation in tricyclic antidepressants in unipolar refractory depression. *Archives of General Psychiatry* 1993, 50, 387–393.
 - 108 PRUDIC, J., SACKEIM, H. A., DEVANAND, D. P., Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research* 1990, 31, 287–296.
 - 109 PLUIJMS, E. M., BIRKENHAGER, T. K., HUIJBRECHTS, I. P., P., Moleman, Influence of resistance to antidepressant pharmacotherapy on short-term response to electroconvulsive therapy. *Journal of Affective Disorders* 2002, 69, 93–99.
 - 110 HALE, S., PROCTER, A. W., BRIDGES, P. K., Clomipramine, tryptophan and lithium in combination for resistant endogenous depression: seven case series. *British Journal of Psychiatry* 1987, 151, 213–217.
 - 111 SHAPIRA, KINDLER, S., LERER, B., Medication outcome in ECT-resistant depression. *Convulsive Therapy* 1988, 4, 192–198.
 - 112 DEPRESSION GUIDELINE PANEL. *Clinical Practice Guideline Number 5: Depression in Primary Care, Vol. 2, Treatment of Major Depression*. U.S. Dept Health Human Services, Agency for Health Care Policy and Research, Rockville, MD, 1993, 55, 23–28.
 - 113 KELLER, M. B., MCCULLOUGH, J. P., KLEIN, D. N., ARNOW, B., DUNNER, D. L., GELENBERG, A. J., MARKOWITZ, J. C., NEMEROFF, C. B., RUSSELL, J. M., THASE, M. E., TRIVEDI, M. H., ZAJECKA, J., Nefazodone, psychotherapy, and their combination for the treatment of chronic depression: a comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New England Journal of Medicine* 2000, 342, 1462–1470.
 - 114 THASE, M. E., GREENHOUSE, J. B., FRANK, E., et al., Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Archives of General Psychiatry* 1997, 54, 1009–1015.
 - 115 FAVA, G. A., SAVRON, G., GRANDI, S., et al., Cognitive-behavioral management of drug-resistant major depressive disorder. *Journal of Clinical Psychiatry* 1997, 58, 278–282.
 - 116 FAVA, G. A., GRANDI, S., ZIELEZNY, M., et al., Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. *American Journal of Psychiatry* 1994, 151, 1295–1299.

- 117 GERSON, A., DANNON, P. N., GRUNHAUS, L., Transcranial magnetic stimulation in the treatment of depression. *American Journal of Psychiatry* **2003**, *160*, 835–845.
- 118 LOO, K., TAYLOR, J. L., GANDEVIA, S. C., McDARMONT, B. M., MITCHELL, P. B., SACHDEV, P. S., Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some 'sham' forms active? *Biological Psychiatry* **2000**, *47*, 325–331.
- 119 LOO, K., MITCHELL, P. B., CROKER, V. M., MALHI, G. S., WEN, W., GANDEVIA, S. C., SACHDEV, P. S., Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychological Medicine* **2003**, *33*, 33–40.
- 120 BURT, T., LISANBY, S., SACKEIM, H., Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *International Journal of Neuropsychopharmacology* **2002**, *5*, 73–103.
- 121 GRUNHAUS, L., SCHREIBER, S., DOLBERG, O. T., POLAK, D., DANNON, P. N., A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biological Psychiatry* **2003**, *53*, 324–331.
- 122 GRUNHAUS, L., DANNON, P. N., SCHREIBER, S., DOLBERG, O. H., AMIAZ, R., ZIV, R., LEFKIFKER, E., Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biological Psychiatry* **2000**, *47*, 314–324.
- 123 ELGER, G., HOPPE, C., FALKAI, P., RUSH, A. J., ELGER, C. E., Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Research* **2000**, *42*, 203–210.
- 124 SACKEIM, H. A., RUSH, A. J., GEORGE, M. S., MARANGELL, L. B., HUSAIN, M. M., NAHAS, Z., JOHNSON, C. R., SEIDMAN, S., GILLER, C., HAINES, S., SIMPSON, R. K., GOODMAN, R. R., Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* **2001**, *25*, 713–728.
- 125 PEET, M., HORROBIN, D. F., A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Archives of General Psychiatry* **2002**, *59*, 913–919.
- 126 HIBBELN, J. R., Long-chain polyunsaturated fatty acids in depression and related conditions. In: PEET, M., GLEN, I., HORROBIN, D. F. (Eds.), *Phospholipid Spectrum Disorder in Psychiatry*, Marius Press, Carnforth, England, **1999**, 195–210.
- 127 MISCHOULON, D., FAVA, M., ROSENBAUM, J. F., Strategies for augmentation of SSRI treatment: a survey of an academic psychopharmacology practice. *Harvard Review of Psychiatry* **1999**, *6*, 322–326.
- 128 ZIMMERMAN, M., MATTIA, J. I., POSTERNAK, M. A., Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *American Journal of Psychiatry* **2002**, *153*, 469–473.
- 129 RUSH, J., TRIVEDI, M., FAVA, M., STAR*D treatment trial for depression. *American Journal of Psychiatry* **2003**, *160*, 237.

16

Clinical Pharmacology of New Classes of Antidepressant Drugs

Justine M. Kent

Abstract

Newer classes of antidepressant drugs, including norepinephrine-reuptake inhibitors, dual (serotonin–norepinephrine)-reuptake inhibitors, and norepinephrine and specific serotonin antidepressants, are challenging the position of the serotonin-reuptake inhibitors as first-line treatment for depression. These agents offer clinicians a broader range of effective treatments, through targeting neurotransmitter systems beyond serotonin. Selection of antidepressant treatment by identifying distinct therapeutic profiles matched to the patient's presentation of depression, while taking into consideration side-effect profile, improves efficacy and tolerability, along with patient compliance and satisfaction. Understanding the clinical pharmacology of the newer antidepressant agents is important in choosing among them. In this chapter, the mechanism of action and clinical pharmacology of duloxetine, venlafaxine, nefazodone, mirtazapine, and reboxetine are reviewed, followed by a discussion of adverse effects related to pharmacokinetic and receptor-binding properties. Potential drug interactions related to metabolism and protein binding are discussed as relevant to patients with multiple medical problems.

16.1

Introduction

Prior to the introduction of the serotonin-reuptake inhibitors (SSRIs) in the 1980s, the antidepressant classes available to clinicians to treat depression were limited to lithium, the tricyclic/heterocyclic antidepressants, and the monoamine oxidase inhibitors (MAOIs). The tricyclic class of antidepressants (TCAs) have significant side effects as a result of nonselective binding to receptors unrelated to their mechanism of action, which is believed to involve modulation of norepinephrine (NE) and serotonin (5-HT) neurotransmission. Binding to H₁-histaminic, α -1-adrenergic, and muscarinic cholinergic receptors correlates well with the tricyclics'

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side-effect profile of sedation, orthostatic hypotension, tachycardia, constipation, urinary retention, and dry mouth. These side effects cause considerable distress, leading to patient noncompliance or discontinuation.

With the introduction of the serotonin-reuptake inhibitors, clinicians had available a class of antidepressants with similar efficacy to the tricyclics and MAOIs, but with significantly better tolerability, safety, and ease of dosing. Despite the tremendous clinical success of the SSRIs in the treatment of depression, certain limitations in both efficacy in the most severely depressed patients and tolerance have led to the introduction of several new classes of antidepressants with pharmacological characteristics distinct from those of the SSRIs, including distinct side-effect profiles. SSRI side effects such as gastrointestinal complaints, nervousness and agitation, sexual dysfunction, and weight gain with long term use often lead to early discontinuation despite therapeutic effects.

Most of the newer classes of antidepressant drugs exploit the fact that several lines of evidence support the involvement of both serotonergic and noradrenergic systems in depression [1–3]. Modulation of at least one of these systems is thought to be critical to the therapeutic effects of most antidepressants. By modulating both of these monoaminergic systems, newer dual agents may extend greater benefits to more severely depressed patients and may reduce the time to antidepressant response, mimicking the effects of giving an SSRI and a NE-selective tricyclic antidepressant [4, 5].

Duloxetine, milnacipran, mirtazapine, nefazodone, reboxetine, and venlafaxine are significant departures from the earlier classes of antidepressants, with de-

Table 16.1 Newer antidepressants

Drug Name	Trade Name	Manufacturer	Class	Approved Uses
Duloxetine	Cymbalta	Eli Lilly	SNRI	depression
Milnacipran	Ixel	Pierre Fabre	SNRI	depression (limited Europe, Japan)
Venlafaxine IR, XR	Effexor, Effexor XR	Wyeth-Ayerst	SNRI	depression, generalized anxiety disorder, social anxiety disorder
Nefazodone	Serzone, Dutonin, Nefador, Nefirel, Rezeril	Bristol-Myers Squibb, others	SNRI, 5-HT ₂ antagonist	depression
Mirtazapine	Remeron, Zispin, Avanza, Norset Remergil	Organon, others	NSSA	depression
Reboxetine	Edronax, Vestra, Prolift, Integrex, Norebox	Pharmacia & Upjohn	NRI	depression (widely available outside the USA)

SNRI = serotonin norepinephrine-reuptake inhibitor, NSSA = norepinephrine-specific serotonin-reuptake antidepressant, NRI = norepinephrine-reuptake inhibitor.

monstrated equivalent or superior efficacy and often more favorable side-effect profiles than the earlier classes (Table 16.1). Duloxetine, milnacipran, venlafaxine, and nefazodone are serotonin- and norepinephrine- (dual) reuptake inhibitors (SNRIs). Milnacipran is not approved in the United States and is in limited use outside the U.S. and therefore is not covered in detail here. Nefazodone is a weaker dual-reuptake inhibitor than venlafaxine and duloxetine but has the additional action of antagonizing the 5-HT₂ receptor, resulting in greater serotonin binding at the 5-HT₁ receptor. Mirtazapine is a norepinephrine and specific serotonergic antidepressant (NSSA). It is a potent antagonist of central α -2-adrenergic autoreceptors, thereby increasing NE transmission. It is also an antagonist of serotonin 5-HT₂ and 5-HT₃ receptors, resulting in a net increase in 5-HT₁ serotonergic neurotransmission. Reboxetine is a norepinephrine-reuptake inhibitor (NRI) lacking significant serotonergic effects. Although the FDA declined reboxetine's approval as an antidepressant in the U.S. in 2001, it is widely available outside the U.S. for the treatment of depression.

16.2

Clinical Pharmacology

The structures of duloxetine (a phenethylamine), venlafaxine (a bicyclic phenylethylamine derivative), and reboxetine (an α -ariloxymethyl derivative of morpholine) differ significantly from earlier marketed antidepressants. Nefazodone (a phenylpiperazine compound) and mirtazapine (a tetracyclic piperazinoazepine) are structurally related to the earlier antidepressants trazodone and mianserin, respectively (Fig. 16.1).

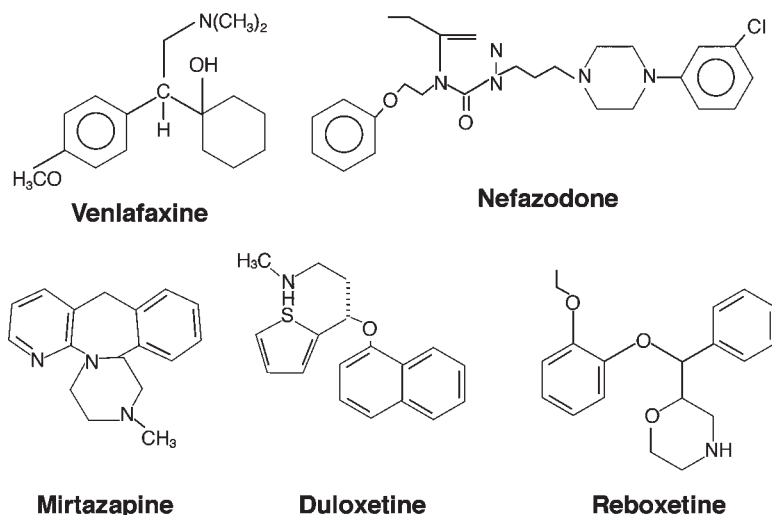


Figure 16.1 Structures of the newer antidepressants

The reuptake-inhibition properties and specific receptor affinities of duloxetine, venlafaxine, nefazodone, mirtazapine, and reboxetine are presented in Table 16.2, with the SSRIs also included for comparison. The pharmacokinetic parameters of the newer antidepressants are summarized in Table 16.3.

Duloxetine. Duloxetine [(+)-*N*-methyl-3-(1-naphthalenyloxy)-2 thiophenepropan-amine] has been shown to be a potent inhibitor of both 5-HT and NE reuptake, to weakly inhibit dopamine reuptake, and to have no significant affinity for other central receptors [6–8]. In preclinical studies, duloxetine inhibits [³H]5-HT and [³H]NE binding in vitro [6, 9] and ex vivo [7] at similar doses. Duloxetine inhibits binding of NE and 5-HT to their respective transporters with K_i values of 7.5 and 0.8 nM, respectively. The ratio (~9) of duloxetine's K_i values for inhibition of the NE and 5-HT transporters indicates its greater ability to block reuptake of 5-HT than of NE [10]. It is a more potent inhibitor of both the human 5-HT and NE transporters than is venlafaxine; however, similar to venlafaxine, duloxetine may act like an SSRI at lower doses, whereas at higher doses NE-reuptake blockade comes into effect.

Duloxetine is well absorbed and extensively metabolized. The numerous conjugates of its oxidative metabolites are inactive and are primarily excreted in the urine. Duloxetine exhibits linear pharmacokinetics over a therapeutic dose range of 60 to 120 mg per day.

Venlafaxine and its active metabolite, *O*-desmethylvenlafaxine (ODV), are both potent inhibitors of neuronal reuptake of serotonin, norepinephrine, and more weakly, of dopamine [11, 12]. The ratio (30) of venlafaxine's K_i values for NE vs. 5-HT blockade indicates its greater potency in blocking 5-HT reuptake sites [10]. Venlafaxine and

Table 16.2 In vitro reuptake inhibition and receptor-binding affinities of the newer antidepressants in comparison with the serotonin-reuptake inhibitors

Drug Name	Monamine Uptake, K_i [nM] ^{a)}			Receptor Affinity, K_i or K_d [nM] ^{b)}			
	5-HT Reuptake	NE Reuptake	DA Reuptake	α_1	α_2	H ₁	Mus
Duloxetine	5	16	369	8300 ^{c), d)}	8600 ^{c), d)}	2300 ^{c), d)}	3000 ^{c), d)}
Venlafaxine	77	538	6371	> 35 000	> 35 000	> 35 000	> 35 000
Nefazodone	68	110	470	42	1200	370	> 10 000
Mirtazapine	none	> 10 000	none	—	—	—	—
Reboxetine	1070	8	> 10 000	10 000 ^{d)}	43 000 ^{d)}	1400 ^{d)}	3900 ^{d)}
Fluoxetine	20	1230	2884	3800	13 900	5400	590
Sertraline	3	220	260	380	4100	24 000	630
Paroxetine	1	33	1700	4600	17 000	22 000	108
Citalopram	2	6100	> 10 000	4500	> 10 000	470	2900

— = Data not available.

a) In vitro inhibition of monoamine reuptake into rat synaptosomes.

b) Data from humans, except where noted.

c) Data in IC₅₀, nM units [20].

d) Data from rats.

Data from references 6, 10, 11, 13, 16, 19–25.

Table 16.3 Pharmacokinetic parameters of the newer antidepressants

Drug	Therapeutic Dose Range	Bio-availability	Biotransformation Pathways	Major Metabolites	Half-life	Elimination Routes	Protein Binding
Duloxetine	40–60 mg per day (single or divided dose)	–	Oxidation followed by methylation and/or conjugation, CYP2D6, 1A2	Glucuronide conjugate of 4-hydroxy-duloxetine (inactive) and numerous other inactive metabolites	12.5 h (parent)	urine (72%) feces (18%)	–
Venlafaxine IR Venlafaxine XR	75–225 mg per day (divided dose) 75–225 mg d ⁻¹ (single dose)	45%	CYP2D6 and others	O-desmethyl-venlafaxine (ODV) (active)	4 h (parent) 10 h (ODV)	urine (87%)	27% (parent) 30% (ODV)
Nefazodone	300–600 mg per day (divided dose)	20% (variable)	Dealkylation and hydroxylation, CYP3A4, 2D6	Hydroxynefazodone (active), triazolidione (active), mCPP (direct 5-HT agonist)	2–4 h (parent) 2–4 h (HO-Nef) 18–33 (TAD) 4–8 (mCPP)	urine (55%) feces (30%)	99% (parent)
Mirtazapine	15–45 mg per day (single dose)	50%	Demethylation and hydroxylation, CYP2D6, 1A2, 3A4	Demethyl-mirtazapine (weak activity)	20–40 h (parent)	urine (85%) feces (15%)	85% (parent)
Reboxetine	8–12 mg per day (divided dose)	60%	Dealkylation and hydroxylation, CYP3A4	O-desethyl reboxetine (inactive)	13 h (parent)	urine (78%) feces	97% (parent) α -1-acid glycoprotein > albumin

Data from references 26–30.

its main metabolite have very little affinity for muscarinic cholinergic, H_1 -histaminic, or α -adrenergic receptors in vitro; they also have no monoamine oxidase A or B inhibitory activity [12].

Venlafaxine and ODV exhibit linear kinetics over the normal dosing range. Venlafaxine is available in both immediate-release (IR) and extended-release (XR) formulations. The starting dose for the immediate-release product is generally 75 mg per day divided into two or three doses. The recommended maximum dose is 375 mg per day in three divided doses. Once-daily dosing with the XR formulation achieves bioavailability equivalent to that of twice-daily dosing with the IR formulation. Clearance of venlafaxine and its metabolites may be reduced in patients with hepatic cirrhosis and severe renal disease, requiring a reduction in dose. In healthy elderly patients, however, dosage adjustment does not appear necessary.

Nefazodone is a $5-HT_2$ receptor antagonist with some degree of inhibition of serotonin and norepinephrine reuptake, which is less than that of the more potent dual-uptake inhibitors venlafaxine and duloxetine [11, 13]. Nefazodone acts to produce a net effect of increasing serotonin neurotransmission; preclinical studies suggest that nefazodone increases $5-HT_{1A}$ receptor binding [13]. The development of nefazodone aimed at improving the pharmacologic characteristics of the earlier antidepressant trazodone, which is sedating and tends to cause postural hypotension. By differences in comparison to the structure of trazodone, nefazodone has significantly less affinity for the α -1-adrenergic receptor, resulting in less postural hypotension and sedation. Nefazodone possesses a weak affinity for α -2, β -adrenergic, and $5-HT_2$ receptors, but does not bind most other receptor sites, including H_1 -histaminic, muscarinic cholinergic, and dopamine sites [13, 14].

Due to its nonlinear kinetics, mean plasma concentrations of nefazodone and its pharmacologically similar metabolite hydroxynefazodone are greater than expected at higher doses. The recommended starting dose of nefazodone is 200 mg per day (100 mg BID). The therapeutic dose range is 300–600 mg per day in divided doses. Because plasma levels of nefazodone and hydroxynefazodone have been noted to be twice as high in patients with cirrhosis than in healthy subjects, dosage reduction is warranted in this population. Likewise, caution should be used in elderly patients, and the initial starting dose should be reduced to 100 mg per day in divided doses.

Mirtazapine is considered to be unique in its pharmacological profile, with a configuration of effects including potent antagonism of central α -2-adrenergic auto- and heteroreceptors and antagonism of both serotonin $5-HT_2$ and $5-HT_3$ receptors. Unlike duloxetine, venlafaxine, and nefazodone, it has minimal effects on monoamine reuptake [15]. Although mirtazapine has a low affinity for muscarinic cholinergic and dopaminergic receptors, it has a high affinity for H_1 -histaminic receptors, resulting in sedation as one of its more prominent side effects. Pharmacologic effects from mirtazapine's antagonism of the α -2-adrenergic receptors are twofold: blockade of presynaptic autoreceptors results in enhanced norepinephrine release [16], while blockade of heteroreceptors on serotonergic neurons increases serotonin release. In combination with $5-HT_2$ and $5-HT_3$ receptor blockade, the

enhancement of serotonin release results in a net increase in 5-HT₁-mediated neurotransmission [17].

Mirtazapine exhibits linear kinetics across the typical dosing range. The recommended initial dose is 15 mg per day administered as a single bedtime dose. Clinical trials suggest the effective dose range is between 15 and 45 mg per day; however, a definitive dose–response relationship has not been determined. Due to mirtazapine’s unique pharmacology, antihistaminergic effects predominate at lower doses (drowsiness, sedation), but noradrenergic neurotransmission increases with increasing doses, counteracting at least some of the antihistaminergic effects. Because of this unique pharmacology, doses below 15 mg are not recommended, to avoid excessive sedation. Clearance of mirtazapine has been shown to be significantly reduced in patients with liver (up to 30%) or kidney (30%–50%) disease and in the elderly. Therefore, dosage reductions should be considered in these populations.

Reboxetine is a selective inhibitor of NE reuptake, with minimal effect on 5-HT and no effect on DA uptake. It has no MAO-A inhibitory properties and has minimal affinity for α -adrenergic and muscarinic cholinergic receptors [18].

Reboxetine demonstrates linear kinetics across the normal dosing range. The recommended therapeutic dose of reboxetine is 8 mg per day in two divided doses. The full therapeutic dose of 8 mg per day can be given upon initiating treatment, with the dose increased to a maximum of 12 mg per day. For patients with renal or hepatic insufficiency, the clearance of reboxetine is reduced and therefore the dose should be reduced by half. For the elderly, the recommended starting dose is 4 mg per day in two divided doses.

16.3

Adverse Effects Related to Pharmacokinetics and Receptor Binding

Side effects are a major reason for noncompliance and early discontinuation of antidepressant use. The side-effect profile for any antidepressant can be predicted by what is known about its pharmacokinetics and receptor binding. Compared with previous classes of antidepressants, the newer antidepressants discussed here have similar or superior efficacy but differing side-effect profiles.

Duloxetine. In comparison to the tricyclic antidepressants, duloxetine has a low affinity for the adrenergic, histaminic, and muscarinic cholinergic receptors associated with the major side effects of those drugs. Treatment-emergent side effects that were reported in a large 52-week trial by more than 10% of patients with major depression included nausea, insomnia, headache, somnolence, dry mouth, dizziness, constipation, increased sweating, anxiety, diarrhea, and fatigue [31]. Mean changes in pulse over the course of the study were less than 2 b.p.m., while mean changes in blood pressure (< 1.0 mm Hg), corrected QT interval (< 1 ms), and body weight (2.4 kg) were not clinically significant [31].

Venlafaxine. Venlafaxine's low affinity for muscarinic cholinergic, histaminic, and α -adrenergic receptors accounts for its minimal anticholinergic side effects and lack of orthostatic hypotensive or sedative effects. The most commonly reported adverse effect associated with venlafaxine XR is nausea, reported by 31% of depressed patients in short-term trials, versus 12% taking placebo. Other frequently reported side effects in depressed patients (> 10% of subjects, occurring at an incidence at least twice that of the placebo group), include dizziness, somnolence, insomnia, ejaculatory abnormalities, sweating, and dry mouth. Some patients on venlafaxine have a sustained increase in blood pressure. This drug-associated hypertension (supine diastolic blood pressure > 90 mm Hg and > 10 mm Hg above baseline over three consecutive visits) is dose-related. In clinical studies with the immediate-release formulation, the incidence of sustained hypertension increased from 3%–7% at doses of 100–300 mg per day up to 13% at doses greater than 300 mg per day. For the extended-release formulation, the incidence of sustained hypertension in depressed patients is 3% for doses of 75–375 mg per day. All patients receiving venlafaxine should have their blood pressure regularly monitored [26].

Nefazodone is a 5-HT₂ receptor antagonist and weak inhibitor of serotonin and norepinephrine reuptake. Its low affinity for muscarinic cholinergic receptors accounts for its lesser anticholinergic effects (dry mouth, constipation, blurred vision) when compared with the TCAs. Nefazodone and its major metabolite have weak affinity for histamine H₁ receptors, resulting in a mild sedative effect in some patients. The most commonly reported adverse events associated with nefazodone are nausea, somnolence, dry mouth, dizziness, constipation, asthenia, light-headedness, and blurred vision [32]. Side effects occur at significantly higher rates at doses greater than 300 mg per day [27], and therefore the minimum effective dose should be used.

In rare instances, life-threatening hepatic failure has been associated with nefazodone administration. The rate of liver failure in the U.S. is about 1 instance per 250 000–300 000 patient-years of nefazodone treatment. Nefazodone should not be used in patients with active liver disease or elevated baseline serum transaminases. Patients on nefazodone should be advised to be alert for clinical signs of liver failure and should be withdrawn immediately from the drug if signs or symptoms suggest liver failure or if serum liver enzymes reach a level three times the upper limit of normal [27].

Effects of nefazodone on the cardiovascular system seen with significantly greater frequency than with placebo include a reduction in systolic blood pressure (< 90 mm Hg; > 20 mm Hg change) and asymptomatic bradycardia (< 50 b.p.m. and a decrease of 15 b.p.m. from baseline). Orthostatic hypotension, tachycardia, and prolonged QT_c interval occur less frequently with nefazodone than imipramine [32]. Nefazodone has no effect on seizure threshold. Priapism has been reported in a small number of nefazodone-treated men during post-marketing surveillance and is considered a rare event. The incidence of sexual dysfunction with nefazodone is low [33].

Mirtazapine. Although mirtazapine has a low affinity for muscarinic cholinergic and dopaminergic receptors, its high affinity for histamine H₁ receptors makes it sedating at low doses. At higher doses, the activating effect of increased noradrenergic neurotransmission appears to counteract some of the sedating antihistaminic effect, resulting in less sedation at higher doses. Somnolence, increased appetite, and weight gain were the most commonly observed adverse events in controlled clinical trials (incidence > 10% and at least twice that of placebo). Other side effects include dry mouth, constipation, and dizziness [28]. Like nefazodone, mirtazapine is not associated with sexual dysfunction [34]. Mirtazapine appears to have no clinically significant effects on the cardiovascular system or on seizure threshold [34].

Mirtazapine has been associated with particular abnormalities of laboratory values in small numbers of patients. These include transient elevations in liver alanine aminotransferase (ALT) (2% of patients) and increases in random total cholesterol levels (3%–4% of patients) [35]. Mirtazapine has been associated with severe neutropenia in rare cases (absolute neutrophil count 500 per mm³). Of the three reported cases of neutropenia (incidence = 1.1 per thousand patients), two developed agranulocytosis with associated symptoms of infection [28]. All patients recovered upon discontinuation of mirtazapine. Because of this concern, it is recommended that mirtazapine treatment be stopped in any patient developing signs of infection along with a low white blood cell count and that close clinical monitoring be instituted.

Reboxetine. Reboxetine is generally well tolerated and has minimal side effects, reflecting its low affinity for muscarinic cholinergic, histaminic, and α -adrenergic receptors. Dry mouth, constipation, insomnia, increased sweating, tachycardia, vertigo, urinary hesitancy/retention, and impotence are the most commonly reported adverse events reported. Genitourinary effects may be clinically significant and lead to discontinuation. Male patients reported rates of impotence at 5% for reboxetine versus 0% for placebo and were more likely to complain of urinary hesitancy and/or retention than female patients (14% for males versus 1% for females on long-term treatment) [36]. Reboxetine has been associated with an increase in heart rate (> 20% or > 100 b.p.m.) in patients involved in both short- (20% versus 6% on placebo) and long-term treatment trials (23% versus 17% on placebo) [36]. The clinical significance of this finding is unknown. Reboxetine is not associated with any electrocardiogram abnormalities.

16.4

Drug Interactions Related to Metabolism and Protein Binding

Venlafaxine, mirtazapine, duloxetine, and reboxetine are associated with very low frequencies of drug–drug interactions compared with the SSRIs, which all have the potential for CYP-isoenzyme-based interactions. Of the newer antidepressants discussed here, only nefazodone is a potent inhibitor of any of these

isoenzymes. Nefazodone is a substrate of, and a potent inhibitor of, the CYP3A4 isoenzyme both in vitro and in vivo [37]. Because nefazodone can inhibit the metabolism of any medication metabolized by CYP3A4, it can result in increased plasma levels of that drug. Before administering any drug metabolized by CYP3A4 along with nefazodone, the risks of increased plasma levels of the parent drug, including the risk of cardiotoxicity, should be considered and the dosage adjusted accordingly, or an alternative medication should be administered. Cisapride, terfenadine, astemizole, and pimozide are contraindicated for use in combination with nefazodone for this reason [27]. Nefazodone has also been shown to increase levels of those benzodiazepines that are substrates for CYP3A4. In particular, triazolam and alprazolam require significant dose reductions when administered with nefazodone (75% dose reduction for triazolam, 50% for alprazolam) [38]. Because lorazepam is not metabolized by CYP3A4, it is not affected by co-administration with nefazodone and can be safely used without dosage adjustment [39].

Venlafaxine is extensively metabolized by the hepatic cytochrome P450 (CYP) enzyme system, primarily by the CYP2D6 isoenzyme. The metabolism of venlafaxine varies between patients due to genetic polymorphisms of CYP2D6. However, the total amount of active compounds (venlafaxine and its major active metabolite, ODV) has been shown to be comparable in CYP2D6-poor and CYP2D6-extensive metabolizers, suggesting that dosage adjustment is unnecessary when venlafaxine is administered with a CYP2D6 inhibitor [26].

Despite being metabolized by several of the P450 isoenzymes, mirtazapine is not a potent inhibitor of any of these enzymes and is thus unlikely to have clinically significant effects on the metabolism of other drugs. However, the data regarding the concomitant use of mirtazapine with other drugs that are substrates for the CYP450 enzymes is limited. When taken in combination with alcohol or diazepam, mirtazapine has been shown to have additive effects on cognitive and motor performance [40, 41]; therefore, patients should be advised to avoid alcohol and diazepam when taking mirtazapine.

In vitro studies indicate that reboxetine is mainly metabolized by the CYP3A4 isoenzyme and is not metabolized by CYP2D6. Drugs that inhibit the activity of CYP3A4, such as the azole antifungals, are expected to increase levels of reboxetine. For instance, ketoconazole, a potent inhibitor of CYP3A4, increased plasma levels of reboxetine by about 50% [42]. Reboxetine itself is only a weak inhibitor of CYP3A4 in vitro, and at high concentrations it inhibits CYP2D6 [43]. Because the clinical significance of these effects is not known, caution should be used when co-administering reboxetine with any drug having a narrow therapeutic margin and metabolized by CYP2D6 or CYP3A4.

Venlafaxine, nefazodone, mirtazapine, duloxetine, and reboxetine are all contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), due to their potential for serious reactions, in some instances progressing to delirium, coma, and death. These drugs should not be used within two weeks of discontinuing a MAOI, and new treatment with a MAOI should not be begun within seven days of discontinuation of any of these drugs.

In summary, venlafaxine, mirtazapine, and reboxetine are associated with very low frequencies of drug–drug interactions compared with the serotonin-reuptake inhibitors. Although drug–drug interactions based on protein binding are rare, venlafaxine is the least likely of these newer drugs to cause an interaction with a highly protein-bound, displaceable medication.

16.5 Conclusions

Major drawbacks of the older classes of antidepressants (TCAs and MAOIs) are their poor safety profiles and their nonselective interaction with a range of receptors not involved in their antidepressant effects. The newer classes of drugs presented here have low affinity for receptors irrelevant to their antidepressant efficacy, thus reducing side-effect potential. Compared with the SSRIs, the dual-reuptake inhibitors in particular exhibit a similar or superior range of antidepressant efficacy, with a differing side-effect profile.

Clinically significant side effects associated with the SSRIs that affect patients' satisfaction and compliance include sexual dysfunction and weight gain with long-term use. Among the newer antidepressants, nefazodone and mirtazapine have the lowest incidence of associated sexual dysfunction and are alternatives for patients experiencing treatment-related sexual side effects with the SSRIs. If weight gain is an issue, nefazodone, venlafaxine, and reboxetine have not been associated with significant weight changes. Of the newer agents, weight gain is a common side effect of mirtazapine, so it is therefore most appropriate for patients in which depression-associated weight loss and/or anorexia is significant.

For those patients with depression-associated insomnia, nefazodone and mirtazapine may best alleviate sleep disturbances without the use of an additional sleep agent. However, these drugs can also cause excessive daytime sedation, and dose adjustments may be necessary to minimize this effect. On the other hand, reboxetine's noradrenergic effects, which tend to be activating, may be particularly useful in targeting depression-associated fatigue and anergia. Several of these newer agents, including venlafaxine, nefazodone, and mirtazapine, have shown promise in alleviating symptoms of anxiety associated with depression.

Overall, the development of these newer agents increases the range of antidepressants available with varying mechanisms of action. Selection of antidepressant treatment by identifying distinct therapeutic profiles matched to the patient's presentation of depression while taking into consideration side-effect profile, improves efficacy and tolerability as well as patient compliance and satisfaction.

References

- 1 BLIER, P., DE MONTIGNY, C., Current advances and trends in the treatment of depression. *Trends Pharmacol. Sci.* **1994**, *15*, 220–226.
- 2 DELGADO, P. L., CHARNEY, D. S., PRICE, L. H., AGHAJANIAN, G. K., LANDIS, H., HENINGER, G. R., Serotonin function and the mechanism of antidepressant action: reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch. Gen. Psychiatry* **1990**, *47*, 411–418.
- 3 DELGADO, P. L., MILLER, H. L., SALOMON, R. M., LICINIO, J., HENINGER, G. R., GELENBERG, A. J., CHARNEY, D. S., Monoamines and the mechanism of antidepressant action: effects of catecholamine depletion on mood of patients treated with antidepressants. *Psychopharmacol. Bull.* **1993**, *29*, 389–396.2 and WONG, D. T., BYMASTER, F. P., REID, L. R., MAYLE, D. A., KRUSHINSKI, J. H., ROBERTSON, D. W., Norfluoxetine enantiomers as inhibitors of serotonin uptake in rat brain. *Neuropsychopharmacology* **1993**, *8*, 337–344.
- 4 NELSON, J. C., MAZURE, C. M., BOWERS, M. B., JATLOW, P. I., A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Arch. Gen. Psychiatry* **1991**, *48*, 303–307.
- 5 SETH, R., JENNINGS, A. L., BINDMAN, J., PHILLIPS, J., BERGMAN, K., Combination treatment with noradrenaline and serotonin reuptake inhibitors in resistant depression. *Br. J. Psychiatry* **1992**, *161*, 562–265.
- 6 WONG, D. T., BYMASTER, F. P., MAYLE, D. A., REID, L. R., KRUSHINSKI, J. H., ROBERTSON, D. W., LY248686, a new inhibitor of serotonin and norepinephrine uptake. *Neuropsychopharmacology* **1993**, *8*, 23–33.
- 7 KASAMO, K., BLIER, P., DE MONTIGNY, C., Blockade of the serotonin and norepinephrine uptake processes by duloxetine: in vitro and in vivo studies in the rat brain. *J. Pharmacol. Exp. Therapeutics* **1996**, *288*, 278–286.
- 8 PITSIKAS, N., Duloxetine Eli Lilly & Co. *Curr. Opin. Investig. Drugs* **2000**, *1*, 116–121.
- 9 ENGLEMAN, E. S., PERRY, K. W., MAYLE, D. A., WONG, D. T., Simultaneous increases of extracellular monoamines in microdialysates from hypothalamus of conscious rats by duloxetine, a dual serotonin and norepinephrine uptake inhibitor. *Neuropsychopharmacology* **1995**, *12*, 287–295.
- 10 BYMASTER, F. P., DRESHFIELD-AHMAD, L. J., THRELKELD, P. G., SHAW, J. L., THOMPSON, L., NELSON, D. L., HEMRICK-LUECKE, S. K., WONG, D. T., Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* **2001**, *25*, 871–880.
- 11 BOLDEN-WATSON, C., RICHELSON, E., Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci.* **1993**, *52*, 1023.
- 12 MUTH, E. A., HASKINS, J. T., MOYER, J. A., et al., Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ethyl cyclohexanol derivative. *Biochem. Pharmacol.* **1986**, *35*, 4493–4497.
- 13 EISON, A. S., EISON, M. S., TORRENTE, J. R., et al., Nefazodone: preclinical pharmacology of a new antidepressant. *Psychopharmacol. Bull.* **1990**, *26*, 311–315.
- 14 TAYLOR, D. P., SMITH, D. W., HYSLOP, D. K., et al., Receptor binding and atypical antidepressant drug discovery. In O'BRIEN, R. A. (Ed.), *Receptor Binding in Drug Research*. New York: Dekker, **1986**, pp. 151–165.
- 15 DE BOER, T., The pharmacological profile of mirtazapine. *J. Clin. Psychiatry* **1996**, *57* (Suppl. 4), 19–25.
- 16 DE BOER, T., MAURA, G., RAITERI, M., et al., Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, mirtazapine and its enantiomers. *Neuropharmacology* **1988**, *27*, 399–408.
- 17 DE BOER, T., The effects of mirtazapine on central noradrenergic and serotonergic neurotransmission. *Int. Clin. Psychopharmacol.* **1995**, *10* (Suppl. 4), 19–23.

- 18 RIVA, M., BRUNELLO, N., ROVESCALLI, A. C., et al., Effect of reboxetine, a new antidepressant drug, on the central noradrenergic system: behavioural and biochemical studies. *J. Drug Dev.* **1989**, *1*, 243–253.
- 19 SANCHEZ, C., HYTTTEL, J., Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. *Cell Mol. Neurobiol.* **1999**, *19*, 467–489.
- 20 WONG, E. H., SONNERS, M. S., AMARA, S. G., TINHOLT, P. M., PIERCEY, M. F., HOFFMANN, W. P., HYSLOP, D. K., FRANKLIN, S., PORSOLT, R. D., BONSIGNORI, A., CARFAGNA, N., McARTHUR, R. A., Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. *Biol. Psychiatry* **2000**, *47*, 818–829.
- 21 TAYLOR, D. P., CARTER, R. B., EISON, A. S., et al., Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. *J. Clin. Psychiatry* **1995**, *56*, 3–11.
- 22 HYTTTEL, J., Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). *Int. Clin. Psychopharmacol.* **1994**, *9* (Suppl. 1), 19–26.
- 23 HALL, H., OGREN, S.-O., Effects of antidepressant drugs on different receptors in the brain. *Eur. J. Pharmacol.* **1981**, *70*, 393–407.
- 24 FEIGHNER, J. P., BOYER, W. F., Selective serotonin reuptake inhibitors: the clinical use of citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. In *Perspectives in Psychiatry*, Vol. 1. Chichester: Wiley, **1993**.
- 25 WONG, D. T., BYMASTER, F. P., REID, L. R., MAYLE, D. A., KRUSHINSKI, J. H., ROBERTSON, D. W., Norfluoxetine enantiomers as inhibitors of serotonin uptake in rat brain. *Neuropsychopharmacology* **1993**, *8*, 337–344.
- 26 Venlafaxine U.S.A. Package Insert, Wyeth Ayerst 12/03.
- 27 Nefazodone U.S.A. Package Insert, Bristol Myers Squibb 12/03.
- 28 Mirtazapine U.S.A. Package Insert, Organon 12/03.
- 29 Reboxetine European Package Insert, Pharmacia & Upjohn 12/97.
- 30 LANTZ, R. J., GILLESPIE, T. A., RASH, T. J., KUO, F., SKINNER, M., KUAN, H. Y., KNADLER, M. P., Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. *Drug Met. Disposition* **2003**, *31*, 1142–1150.
- 31 RASKIN, J., GOLDSTEIN, D. J., MALLINCKRODT, C. H., FERGUSON, M. B., Duloxetine in the long-term treatment of major depressive disorder. *J. Clin. Psychiatry* **2003**, *64*, 1237–1244.
- 32 ROBINSON, D. S., ROBERTS, D. L., SMITH, J. M., et al., The safety profile of nefazodone. *J. Clin. Psychiatry* **1996**, *57* (Suppl. 2), 31–38.
- 33 FEIGER, A., KIEV, A., SHRIVASTAVA, R. K., et al., Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J. Clin. Psychiatry* **1996**, *57* (Suppl. 2), 53–62.
- 34 MONGOMERY, S. A., Safety of mirtazapine: a review. *Int. Clin. Psychopharmacol.* **1995**, *10* (Suppl. 4), 37–45.
- 35 DAVIS, R., WILDE, M. I., Mirtazapine: a review of its pharmacology and therapeutic potential in the management of major depression. *CNS Drugs* **1996**, *5*, 389–402.
- 36 MUCCI, M., Reboxetine: a review of antidepressant tolerability. *J. Psychopharmacol.* **1997**, *11* (Suppl. 4), S33–S37.
- 37 DAVIS, R., WHITTINGTON, R., BRYSON, H. M., Nefazodone, A review of its pharmacology and clinical efficacy in the management of major depression. *Drugs* **1997**, *53*, 608–636.
- 38 KROBOTH, P. D., FOLAN, M. M., LUSH, R. M., et al., Coadministration of nefazodone and benzodiazepines. I. Pharmacodynamic assessment. *J. Clin. Psychopharmacol.* **1995**, *15*, 306–319.
- 39 GREENE, D. S., SALAZAR, D. E., DOCKENS, R. C., et al., Coadministration of nefazodone and benzodiazepines. IV. A pharmacokinetic interaction study with lorazepam. *J. Clin. Psychopharmacol.* **1995**, *15*, 409–416.
- 40 KUITUNEN, T., Drug and ethanol effects on the clinical test for drunkenness: single doses of ethanol, hypnotic drugs and antidepressant drugs. *Pharmacol. Toxicol.* **1994**, *75*, 91–98.
- 41 SISTEN, J. M. A., ZIKOV, M., Mirtazapine: clinical profile. *CNS Drugs* **1995**, *4* (Suppl. 1), 39–48.

- 42 HERMAN, B. D., FLEISHAKER, J. C., BROWN, M. T., Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin. Pharmacol. Therapeutics* **1999**, 66, 374–379.
- 43 DOSTERT, P., BENEDETTI, M. S., POGGESI, I., Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur. Neuropsychopharmacol.* **1997**, 7 (Suppl. 1), S23–S35.

17

Neuroimaging and Neuropathological Studies of Mood Disorders*Wayne C. Drevets and Joseph L. Price***Abstract**

Neuroimaging studies of major depressive disorder (MDD) and bipolar disorder (BD) have identified abnormalities of brain function, structure, and serotonin receptor pharmacology in areas of the prefrontal cortex, amygdala, striatum, and hippocampus that have been implicated by other types of evidence in the modulation of emotional behavior. The structural imaging abnormalities within these regions persist across episodes, but can be attenuated by some mood-stabilizing therapies. Some of the structural imaging abnormalities appear to exist prior to the onset of depressive episodes in subjects who are at high familial risk for developing mood disorders, while others appear to become more prominent with continuing illness. In many of these regions post mortem histopathological studies have shown abnormal reductions of synaptic markers and glial cells, with no corresponding loss of neurons in MDD and BD. Because these abnormalities appear relatively specific for brain regions that play major roles in modulating or inhibiting the endocrine, autonomic, behavioral, and emotional experiential responses to stressors or threats, they may be associated with impairments of emotion regulation that underlie the clinical manifestations of abnormal mood episodes.

17.1

Introduction

The recent development of neuroimaging technologies that permit *in vivo* characterization of the anatomical, physiological, and receptor pharmacological correlates of mood disorders have enabled a variety of significant advances toward delineating the neurobiological correlates of major depressive disorder (MDD) and bipolar disorder (BD). Because these primary mood disorders were not associated with gross brain pathology or with clear models for spontaneous, recurrent mood episodes in experimental animals, the availability of tools that allowed non-invasive assessment of human brain function proved critical to studies aimed at illuminating

their pathophysiology. The results of studies applying such imaging technologies in mood disorders research and of the post mortem studies that were in turn guided by neuroimaging results have begun to guide clinical neuroscience toward models in which both functional and structural factors play integral roles in the pathogenesis of mood disorders.

Longitudinal PET and MRI studies of MDD and BD identified abnormalities of cerebral blood flow (CBF), glucose metabolism and gray matter volume which in some cases, persisted beyond symptom remission, and in other cases appeared mood state-dependent (reviewed in Drevets, 2003; Figure 17.1). The latter, reversible abnormalities may reflect areas where metabolic activity increases or decreases to mediate or respond to emotional and cognitive manifestations of the major depressive syndrome. In contrast, abnormalities that persist independently of mood state are more likely to reflect neurodevelopmental markers of vulnerability to MDD in cases where they are evident in high risk samples (i.e. healthy individuals who have first degree relatives with mood disorders), or sequelae of recurrent illness, in cases where the magnitude of abnormality correlates with illness duration. Most of the persistent abnormalities of gray matter volume have been confirmed and associated with histopathological correlates in post mortem studies of primary MDD and BD. Because the regions affected by these abnormalities have been shown by electrophysiological, lesion analysis, and/or PET/fMRI studies in experimental animals and healthy humans to play major roles in the modulation of emotional behavior, these findings appear relevant for guiding the development of neural models of emotional dysregulation in mood disorders.

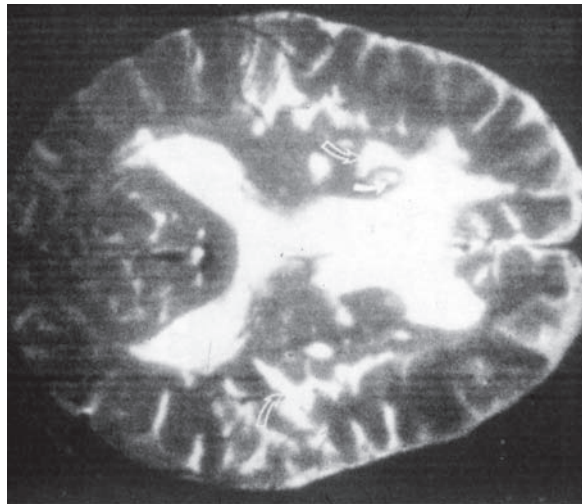


Figure 17.1 Brain MRI, axial view through base of lateral ventricles showing large, confluent, deep white matter hyperintensities (open arrows) and hyperintensity in the right caudate head (closed arrow) in an elderly depressed subject. (Reproduced with permission from Drevets, 1993.)

17.2

Sensitivity for Detecting Neuroimaging Abnormalities in Depression

As has been the case for other psychobiological data obtained in mood disorders research, none of the neuroimaging abnormalities discovered to date has had an effect size sufficient to permit sensitive or specific classification of individual cases. Moreover, the psychiatric imaging literature is in disagreement regarding the specific location and direction of some abnormalities. Many of the limitations in sensitivity and of the inconsistencies in the literature appear related to technical issues of image acquisition and/or to problems associated with selecting subject samples that are homogenous with respect to pathophysiology (reviewed in Drevets, 2003).

For example, the low spatial resolution of imaging technology relative to the size of brain structures of primary interest has substantially limited the effect size of most neuroimaging abnormalities. With respect to neuromorphometric assessments of gray matter volume, the volumetric resolution of state-of-the-art image data has recently been about 1 mm³, which compares with the cortex thickness of only 3 to 4 mm. Consequently MRI studies have been able to show reductions in the mean gray matter across groups of depressives versus controls, but have thus far had insufficient sensitivity to detect the relatively subtle tissue reductions extant in mood disorders in individual subjects. Moreover, this 3- to 4-mm cortex thickness is even smaller than the final, reconstructed, spatial resolution of PET and fMRI images after blurring in preparation for image analysis, which ranges from 7 mm after reconstruction and filtering. Studies relying upon image averaging (which involves a spatial transformation of primary image data into a common stereotaxic array) blur their primary images even further to reduce the effects of anatomical variability across individuals. The latter practice particularly reduces the sensitivity to detect abnormal activity in small structures, such as the amygdala, or in variably shaped structures, such as the orbital cortex, because of the inability to precisely overlay such structures across subjects (Drevets et al., 2002c).

The clinical/biological heterogeneity within mood disorders also contributes to inconsistencies across studies. The diagnostic criteria for major depressive disorder (MDD) presumably encompass a group of disorders that may be heterogeneous with respect to etiology and pathophysiology, and which may, therefore, not share common neuroimaging abnormalities. This problem may account for some disagreements in the results across "neuroimaging studies of depression, and for the observation that neuroimaging studies laboratories selecting depressed subjects according to the MDD criteria alone have rarely been able to replicate their own previous findings in independent subject samples. Instead, neuroimaging abnormalities appear specific to subsets of depressed subjects, based upon studies that have compared subject samples selected on the basis of a clinical course or subtype that had otherwise, previously proven relevant for enriching depressive samples for the likelihood of having abnormalities within other neurobiological domains (e.g. Drevets et al., 2002c).

For example, familial aggregation of illness along with the MDD criteria has typically enhanced sensitivity for identifying subject samples with psychobiological

abnormalities. Both unipolar depressives with familial pure depressive disease (FPDD) and bipolar subjects with primary BD-depressed phase proved more likely than subjects with no first degree relatives with MDD to have abnormal suppression of cortisol secretion in response to dexamethasone, blunted hypoglycemic response to insulin, reduced platelet [^3H]-imipramine binding sites, decreased latency to REM sleep, and greater likelihood of response to ECT (reviewed in Drevets et al., 2002a). In our own studies, subjects with FPDD or familial BD also had highly reproducible abnormalities of CBF, metabolism and serotonin type 1A receptor binding in the PFC, ACC, amygdala, ventral striatum, and posterior cingulate cortex (reviewed in Drevets, 2003).

Clinical differences between depressive samples related to age at onset of illness and capacity for developing mania or psychosis also influence neuroimaging data (reviewed in Drevets, 2003). For example, structural imaging studies of mood disorders demonstrated an elevated prevalence of MRI signal hyperintensities (in T_2 -weighted MRI scans, as putative correlates of cerebrovascular disease) in the deep and periventricular white matter of elderly MDD subjects with a late age at depression onset, but not in elderly depressives whose illness arose prior to age 45 years. Similarly, enlargement of the lateral ventricles has been consistently found in unipolar depressives who are elderly with a late-life onset of MDD (in whom ventricular enlargement is thought to signify *ex vacuo* changes associated with ischemic neuropathology) or are delusional, but not in unipolar depressives who are elderly but have an early age of MDD onset or in midlife depressives who are not delusional. As another example, third ventricle enlargement has been consistently reported in BD relative to healthy control samples, but has generally not been found in unipolar depressives.

17.3

Significance of Cerebral Blood Flow and Metabolism in Depression

Local glucose metabolism and CBF predominantly reflect summations of the local energy utilization associated with terminal field synaptic transmission (DiRocco et al., 1989; Magistretti and Pellerin, 1999; Raichle, 1987). By imaging changes in CBF or metabolism dynamic brain images provide maps of regional neural function associated with ongoing mental activities supporting cognitive, behavioral and emotional states, or with pathological neural transmission. Elevated regional CBF and metabolism thus signifies increased synaptic activity, especially glutamatergic transmission, arising from afferent projections within the same structure or from distal structures (DiRocco et al., 1989; Magistretti and Pellerin, 1999; Raichle, 1987). Conversely, reductions in regional CBF or metabolism may reflect decrements in afferent transmission (e.g. due to inhibitory transmission at “upstream” synapses that inhibits glutamatergic neurotransmission within the area of interest). Differences in resting perfusion or metabolism between depressives and controls may thus reflect physiological correlates of emotional or cognitive symptoms associated with depressive symptoms, compensatory mechanisms invoked to modulate such

processes, and/or pathophysiological changes predisposing to or resulting from affective disease. The physiological correlates of depressive symptoms and behaviors putatively appear as baseline abnormalities of regional CBF or metabolism that normalize following effective treatment, and which may, to some extent, be reproduced in healthy subjects imaged as they engage in tasks that mimic the corresponding depressive manifestation.

Pathological changes in synaptic transmission associated with altered neurotransmitter synthesis, receptor sensitivity/binding, cerebrovascular disease, neuronal arborization or the amount of viable gray matter within a region of interest may also give rise to abnormalities in CBF and metabolism (e.g. Wooten and Collins, 1981).

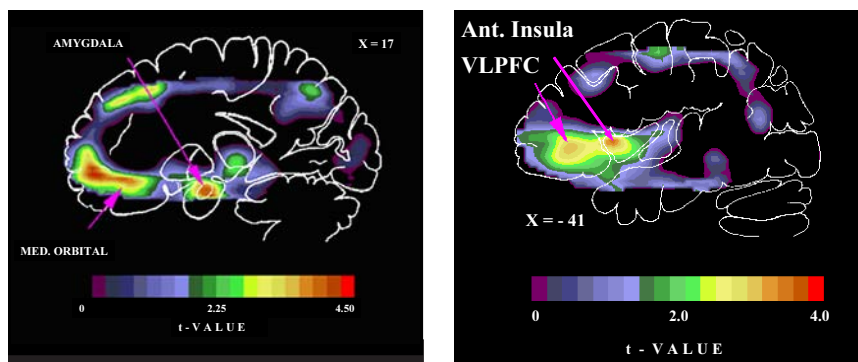


Figure 17.2 Altered metabolism in the prefrontal cortex (PFC) ventral to the genu of the corpus callosum (i.e. subgenual PFC) in mood disorders. The top panel shows negative voxel t -values where glucose metabolism is decreased in depressives relative to controls in the coronal plane (31 mm anterior to the anterior commissure, or $y = 31$) and sagittal (3 mm left of midline, or $x = -3$) planes of a statistical parametric image compares depressives relative to controls (Drevets et al., 1997). This image localized an abnormality in the subgenual portion of the anterior cingulate cortex (subgenual ACC; Drevets et al., 1997), which was subsequently shown to be accounted for by a corresponding reduction in cortex volume on the left side (see text). Anterior or left is to the left of the figure. The bar histogram in the lower panel shows mean, normalized, glucose metabolic values for the left subgenual ACC measured using MRI-based region-of-interest analysis. Metabolism is decreased in depressed subjects with either BD (“Bipolar depressed”) or MDD (“Unipolar depressed”) relative to healthy controls. In contrast, subjects scanned in the manic phase of BD (“Bipolar manic”) have higher metabolism than either depressed or control subjects in this region.

* Difference between controls and bipolar depressives, significant at $p < 0.025$; † difference between depressed and manic, significant at $p < 0.01$; ‡ difference between control and manic, significant at $p < 0.05$.

Although none of these subjects was involved in the study which generated the images shown in Figure 17.3, the mean glucose metabolism in this independent sample of depressives and controls also confirmed the areas of abnormally *increased* activity in the depressives in the amygdala, lateral orbital cortex, ventrolateral PFC and medial thalamus (not shown in the t -image section in Figure 17.2, which only illustrates negative t -values corresponding to hypometabolic areas in the depressives). Reproduced with permission from *Nature* (Drevets et al., 1997, upper panel; Drevets, 2001, lower panel).

Such defects may in some cases appear “trait-like”, insofar as they persist whether subjects are symptomatic or asymptomatic (Drevets et al., 1992). For example, focal tissue reductions were found in some depressive subtypes in areas where CBF and metabolism appeared irreversibly *decreased* in depressives relative to controls in MRI-based morphometric and post mortem histopathological studies (Figure 17.2; Drevets et al., 1997; Öngür et al., 1998). Such abnormalities decrease the magnitude of PET and SPECT imaging measures from the corresponding regions via “partial volume averaging” effects (Drevets et al., 1997; Mazziotta et al., 1981).

Differences in the magnitude of the hemodynamic responses obtained during stimulus presentation or cognitive-behavioral operations in a depressed group relative to a control sample have similarly complex interpretations. In areas where basal neuronal activity is already increased in association with the pathophysiology associated with a psychiatric illness or symptom, mental operations that would further activate the same neuronal fields would be expected to result in attenuated metabolic, CBF and BOLD responses. Nevertheless, blunting of the hemodynamic responses to stimuli or tasks may alternatively reflect impaired activation of that region, as may occur in regions affected by neuropathological changes. Conversely, an area which is “deactivated” at baseline in the ill group relative to the control group may show an exaggerated response during mental operations that would normally activate that region. It is also conceivable that exaggerated hemodynamic responses in an ill group may reflect sensitization or disinhibition involving the target region (Shekhar et al., 2003; Siegle et al., 2002). In all of these cases knowledge about differences in basal CBF or metabolism between psychiatric and control samples becomes critical to interpreting differences in the hemodynamic response obtained during performance of a neuropsychological task.

17.4

Neurophysiological Imaging Abnormalities in Depression

Functional imaging studies have begun to characterize the neuroanatomical correlates of depressive episodes, the neurophysiological effects of antidepressant treatments, and the trait-like abnormalities that persist into remission in MDD and BD. Metabolic and CBF differences between depressives and controls have been identified in multiple regions, consistent with the expectation that the emotional, cognitive, psychomotor, neurovegetative, neuroendocrine and neurochemical disturbances associated with depression involve extended anatomical networks. Moreover, the patterns of abnormal activity evident within these networks appear to differ across some major depressive subtypes.

The benchmark depressed samples studied in the authors’ series to elucidate the neuroimaging correlates of depression have involved the familial, recurrent MDD. During the depressed phase of such cases, CBF and metabolism are abnormally increased in the left amygdala and anatomically related areas of the lateral orbital/ventrolateral PFC, the ACC anterior to the genu of the corpus callosum (i.e. pregenual ACC), the ventral striatum and the medial thalamus (reviewed in Drevets,

2003). Physiological activity is also abnormally elevated in the posterior cingulate cortex, which sends extensive projections to the pregenual ACC, and the medial cerebellum. In addition to these areas of increased metabolic activity, areas of reduced CBF and metabolism in depressives relative to controls were found in the ACC ventral to the genu of the corpus callosum (i.e. “subgenual” ACC; Drevets et al., 1997), the dorsomedial/ dorsal anterolateral PFC (Baxter et al., 1989; Bell et al., 1999; Bench et al., 1992), and the parietal cortex. The subgenual and pregenual ACC, the dorsomedial/dorsal anterolateral PFC, and the lateral orbital/ ventrolateral PFC were subsequently shown to contain a reduction in cortex volume and/or histopathological changes in MDD and BD in both morphometric MRI studies and post mortem neuropathological studies. The reductions in physiological activity seen in PET images from MDD and BD samples may thus be accounted for by structural abnormalities of the corresponding cortex. These reductions in gray matter exist independently of mood state in both MDD and BD (Drevets et al., 1997). The ensuing review highlights major findings from studies of *unmedicated* depressed samples (i.e. data confounded by medication effects are generally not reviewed) together with the relevant neurobiology of the anatomical systems implicated by these data which suggest neural mechanisms that may underlie the dysregulation of emotional behavior manifest in mood disorders.

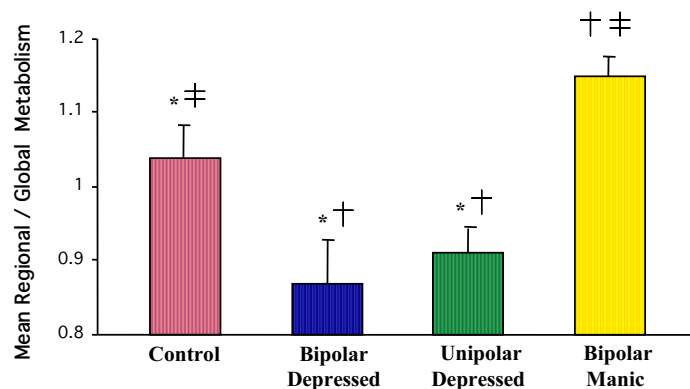
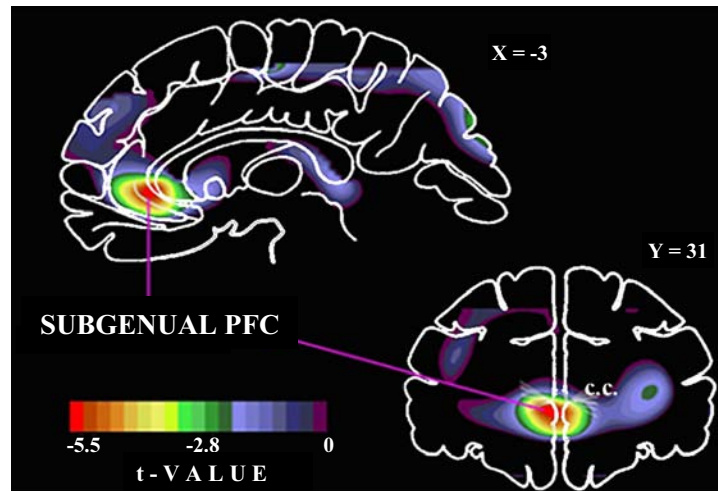
17.4.1

Neurophysiological Imaging Abnormalities in the Prefrontal Cortex (PFC)

17.4.1.1 Ventral Anterior Cingulate Cortex (ACC)

The ACC situated ventral and anterior to the genu of the corpus callosum (termed “subgenual” and “pregenual”, respectively) show complex relationships between CBF, metabolism, and illness state, which appear to be accounted for by a left-lateralized, reduction of the corresponding cortex, initially demonstrated by MRI-based morphometric measures (Figure 17.3; Botteron et al., 2002; Buchsbaum et al., 1997; Drevets et al. 1997; Hirayasu et al., 1999; Kegeles et al., 1999) and later by post mortem neuropathological studies of familial BD and MDD (Öngür et al., 1998). This reduction in volume exists early in the illness in familial BD (Hirayasu et al., 1999) and MDD (Botteron et al., 2002), but may follow illness-onset based upon preliminary evidence in twins discordant for MDD (Botteron et al., 1999). Kimbrell et al. (2002) reported that the subgenual ACC metabolism correlated inversely with the number of lifetime depressive episodes.

Although baseline CBF and metabolism appear abnormally decreased in the subgenual ACC in PET images during MDE, computer simulations that correct PET data for the partial volume effect of reduced gray matter volume conclude the “actual” metabolic activity in the remaining subgenual PFC tissue is *increased* in depressives relative to controls, and decreases to normative levels during effective treatment (Drevets, 1999). This hypothesis appears compatible with the observation that effective antidepressant pharmacotherapy results in a *decrease* in metabolic activity in this region in MDD (Buchsbaum et al., 1997; Drevets et al. 2002b,d; Mayberg et al., 1999), that during depressive episodes metabolism shows a positive



* $p < 0.025$ control v. depressed; † $p < 0.01$ depressed v. manic; ‡ $p < 0.05$ control v. manic

Figure 17.3 (A and B) Areas of abnormally increased blood flow in subjects with major depressive disorder. The image sections shown are from an image of t -values produced by a voxel-by-voxel computation of the unpaired t -statistic to compare regional CBF between a depressed sample selected according to criteria for familial pure depressive disease ($n = 13$) and a healthy control sample ($n = 33$) (Drevets et al., 1992). The positive t -values shown correspond to areas where flow is increased in the depressives relative to the controls. The abnormal activity in these regions was replicated using glucose metabolism imaging in independent subject samples (Drevets et al., 1995b, 2002b,c). (A) Sagittal section at 17 mm

left of midline illustrating areas of increased CBF in depression in the amygdala and orbital cortex. (B) This area of increased flow extended through the lateral orbital cortex (C) to the ventrolateral prefrontal cortex (VLPFC) and anterior (Ant) insula (Drevets et al., 1992, 2002b). The x coordinate locates sagittal sections in mm to the left of the midline. (A–B) The PET images from which the t -image was generated have been stereotactically transformed to the coordinate system of Talairach and Tournoux (1988), from which the corresponding atlas outline is shown. Anterior is to the left of the figure. Illustration A is modified from Price et al. (1996) and B is reproduced from Drevets et al. (1994) with permission.

relationship with depression severity (Drevets et al., 2002b,f; Osuch et al., 2000), and that flow increases in this region in healthy, non-depressed humans during sadness internally induced via contemplation of sad thoughts or memories (Damasio et al., 2000; George et al., 1995; Mayberg et al., 1999).

In the pregenual ACC, Drevets et al. (1992) initially found increased CBF in MDD. While other laboratories also reported abnormalities of CBF and metabolism in this area during depression, the literature has been in disagreement. The variability of these results may have clinical relevance, as several studies report relationships between pregenual ACC activity and subsequent antidepressant treatment outcome. Wu et al. (1992) reported that depressed subjects whose mood improved during sleep-deprivation showed elevated metabolism in the pregenual ACC and amygdala in their pretreatment scans. Mayberg et al. (1997) reported that while metabolism in the pregenual ACC was abnormally increased in depressives who subsequently respond to antidepressant drugs, metabolism was decreased in depressives who later had poor treatment response. Finally, in a tomographic EEG analysis, Pizzagalli et al. (2001) reported that depressives who ultimately showed the best response to nortriptyline showed hyperactivity (higher theta activity) in the pregenual ACC at baseline, as compared to subjects showing the poorer response. The effects of treatment on pregenual ACC flow and metabolism have also differed across studies, with activity decreasing in most PET studies, but increasing in some SPECT studies in post- relative to pre-treatment scans (Table 17.1). The extent to which these discrepant findings are explained by differential effects across sub-regions of this area or between technical aspects of PET versus SPECT technology remains unclear.

In rodents and nonhuman primates the cortex that appears homologous to human subgenual ACC has extensive reciprocal connections with areas implicated in the expression of behavioral, autonomic and endocrine responses to threat, stress, or reward/non-reward, such as the orbital cortex, lateral hypothalamus, amygdala, accumbens, subiculum, ventral tegmentum, raphe, locus coeruleus, periaqueductal gray (PAG), and nucleus tractus solitarius (NTS; Drevets et al., 1998, Öngür and Price, 2000). Humans with lesions that include subgenual PFC show abnormal autonomic responses to emotionally provocative stimuli and inability to experience emotion related to concepts that ordinarily evoke emotion (Damasio, 1994). Similarly, rats with experimental lesions of prelimbic cortex demonstrate altered autonomic, behavioral, and neuroendocrine responses to stress and fear-conditioned stimuli. Diorio et al (1993) demonstrated glucocorticoid receptors in these regions which when stimulated by corticosterone (CORT), reduced stress-related HPA activity, and showed that lesioning the prelimbic and infralimbic cortex resulted in elevated plasma ACTH and CORT responses to restraint stress. In rats, bilateral or *right*-lateralized lesions of the prelimbic and infralimbic cortex *attenuate* sympathetic autonomic responses, stress-induced CORT secretion, and gastric stress pathology during restraint stress or exposure to fear-conditioned stimuli (Fryszak and Neafsey, 1994; Morgan and LeDoux, 1995; Sullivan and Gratton, 1999). In contrast, *left*-sided lesions of this area *increase* sympathetic autonomic arousal and CORT responses to restraint stress (Sullivan and Gratton, 1999). These data suggest that the right subgenual PFC facilitates expression of visceral responses during

Table 17.1 Antidepressant treatment effects on *ventral* prefrontal cortical blood flow and metabolism in major depressive disorder measured using PET or xenon-33 inhalation^{a)}

Authors	Treatment modality	Change in CBF or glucose metabolism post- versus pretreatment scans
Brody et al. (2001)	Paroxetine Interpersonal therapy	9 pregenual ACC and ventrolateral PFC 9 pregenual ACC 8 left anterior insula
Buchsbaum et al. (1997)	Sertraline	9 pregenual ACC, 9 ventromedial PFC ^{b)}
Cohen et al. (1992)	Phototherapy	9 medial orbital C ^{c)}
Drevets and Raichle (1992)	Desipramine	9 left ventrolateral PFC/lateral orbital C
Drevets et al. (2002b)	Sertraline	9 subgenual ACC
Drevets et al. (2002d)	Citalopram	9 ventrolateral PFC/lateral orbital C (BL) 9 subgenual and pregenual ACC 9 anterior insula (BL)
Kennedy et al. (2001)	Paroxetine	9 anterior insula (BL) 8 pregenual ACC
Mayberg et al. (1999, 2000)	Fluoxetine	9 anterior insula 9 subgenual ACC 8 left ventrolateral PFC
Nobler et al. (1994)	ECT	9 left ventrolateral PFC in responders ^{d)}
Nobler et al. (2000)	Nortriptyline or sertraline	9 left ventrolateral PFC in responders ^{d)}
Nobler et al. (2001)	ECT	9 left ventrolateral PFC 9 subgenual PFC
Saxena et al. (2002)	Paroxetine	9 left ventrolateral PFC 9 orbital C (BL)
Smith et al. (1999)	Sleep deprivation	9 right ventrolateral PFC 9 pregenual ACC
Wu et al. (1992)	Sleep deprivation	9 ACC in responders

ACC, anterior cingulate cortex; BL, bilateral; C, cortex; ECT, electroconvulsive therapy; PFC, prefrontal cortex. 8, 9, and n.s. indicate increases, decreases, or no significant changes, respectively, in the treated relative to the untreated state for the regions assessed. Not all studies examined the same regions, and the absence of a listed result for a specific region indicates that no image data were provided for that region.

^{a)} The changes in these ventral PFC regions show similar results to studies of antidepressant drug treatment in obsessive compulsive disordered samples.

In contrast to these ventral prefrontal changes in depression, CBF and metabolism in the dorsal anterior cingulate and the dorsolateral PFC have been shown to increase in some studies of depression (e.g. Baxter et al., 1989; Bonne et al., 1996), but to decrease in others (Nobler et al., 1994; 2001) following effective treatment. Specifically excluded from the studies reviewed above are the results of SPECT imaging studies of perfusion, which are difficult to interpret because the radiotracers most often employed in such studies are not freely diffusible across the blood–brain-barrier (Raichle, 1987).

- b) Abnormally reduced metabolism was found in predefined regions-of-interest in ventral ACC and “rectal gyrus” lying within the same horizontal image plane, implying these ventromedial PFC areas were likely located in subgenual ACC.
- c) The treatment-associated change reported in this study was not shown by paired statistical tests but rather by the observation that in the treatment responders, the abnormal increase that was evident pretreatment was not present post-treatment.
- d) These studies were carried out using the radiotracer, xenon-133, which only provides CBF measurements near the scalp. Thus results were not available for the orbital or the cingulate cortices (see text).

emotional processing, while the left subgenual PFC modulates such responses (Sullivan and Gratton, 1999). The left-lateralized gray matter reduction of the ventral ACC in MDD and BD may thus contribute to dysregulation of neuroendocrine and autonomic function in depression (Carney et al., 1993; Dioro et al., 1993; Veith et al., 1994).

The pregenual ACC has a similar anatomical connectivity as the subgenual ACC. The pregenual ACC shows elevated CBF during a greater variety of emotional conditions elicited in healthy or anxiety disordered humans (Charney and Drevets, 2002; Drevets and Raichle, 1998). Electrical stimulation of this region elicits fear, panic or a sense of foreboding in humans, and vocalization in experimental animals (reviewed in Price et al., 1996).

The pre- and subgenual ACC also appear to participate in evaluating the reward-related significance of stimuli. These areas send efferent projections to the VTA and substantia nigra, and receive dense dopaminergic innervation from VTA (Öngür and Price, 2000). In rats, electrical or glutamatergic stimulation of medial PFC areas that include prelimbic cortex elicits burst firing patterns from DA cells in the VTA and increases DA release in the accumbens (reviewed in Drevets, 1999). These phasic, burst firing patterns of DA neurons appear to encode information regarding stimuli that predict reward and deviations between such predictions and occurrence of reward (Schultz, 1997). Ventral ACC dysfunction may thus conceivably contribute to disturbances of hedonic perception and motivated behavior in mood disorders. The extent of abnormal activity in the subgenual PFC may relate to switches between depression and mania, as subgenual PFC activity appears abnormally increased in manic subjects (e.g. Drevets et al., 1997).

17.4.1.2 Dorsomedial/Dorsal Anterolateral PFC

Several studies reported abnormally decreased CBF and metabolism in areas of the dorsolateral and dorsomedial PFC in unipolar depressives (reviewed in Drevets, 2003). The dorsomedial region where flow and metabolism are decreased in MDD appears to include the dorsal ACC (Bench et al., 1992) and an area rostral to the dorsal ACC involving the cortex on the medial and lateral surface of the superior frontal gyrus (approximately corresponding to Brodmann area 9, and possibly 32; Baxter et al., 1989; Bell et al., 1999; Drevets et al., 2002b). Post mortem studies of MDD and BD have found abnormal reductions in the size of neurons and/or the density of glia in this portion of BA 9 (Cotter et al., 2001a, 2002; Rajkowska et al.,

1999, 2001; Uranova et al., 2004). These histopathological changes may thus account for the reduction in metabolism in this region in the unmedicated-depressed condition, and for the failure of antidepressant drug treatment to correct metabolism in these areas (Bell et al., 1999; Drevets et al., 2002b). It is noteworthy that currently remitted subjects with MDD who experience depressive relapse during tryptophan depletion, increase metabolic activity within these areas (Neumeister et al., in press). This region would thus appear similar to other structures where histopathological and gray matter volume changes exist in depression in showing increased glucose utilization (which predominantly reflects glutamatergic transmission; see below) in the depressed relative to the remitted conditions.

Flow normally increases in the vicinity of this dorsomedial/dorsal anterolateral PFC in healthy humans as they perform tasks that elicit emotional responses or require emotional evaluations (reviewed in Drevets, 2003). In healthy humans scanned during anxious anticipation of an electrical shock, CBF increases in this region to an extent that correlates inversely with changes in anxiety ratings and heart rate, suggesting that this region functions to attenuate emotional expression. In rats lesions of the dorsomedial PFC result in exaggerated heart rate responses to fear-conditioned stimuli, and stimulation of these sites attenuate defensive behavior and cardiovascular responses evoked by amygdala stimulation (reviewed in Frysztak and Neafsey, 1994), although the homolog to these areas in primates has not been established. In primates the BA 9 cortex sends efferent projections to the lateral PAG and the dorsal hypothalamus through which it may modulate cardiovascular responses associated with emotional behavior (Öngür and Price, 2000). It is thus conceivable that dysfunction of the dorsomedial/dorsal anterolateral PFC may impair the ability to modulate emotional responses in mood disorders.

In contrast, the reduction in CBF in the dorsal ACC appears reversible with treatment, and has been associated with impaired mnemonic and attentional processing derived from neuropsychological test scores obtained near the time of scanning (Dolan et al., 1994). This area has been implicated in selective attention during cognitive tasks, and Drevets and Raichle (1998) demonstrated that hemodynamic activity decreases in this area in healthy subjects during anxious anticipation of a painful electrical shock. The reciprocal pattern of activation/deactivation in this region during cognitive versus emotional processing may conceivably relate to attentional impairments during depression (Drevets and Raichle, 1998).

17.4.1.3 Lateral Orbital/Ventrolateral PFC

In the lateral orbital cortex, ventrolateral PFC, and anterior insula, CBF and metabolism have been abnormally increased in *unmedicated* subjects with primary MDD scanned while resting with eyes closed (reviewed in Drevets, 2003). The elevated activity in these areas in MDD appears to be mood-state dependent (Drevets et al., 1992), and during treatment with somatic antidepressant therapies flow and metabolism decreases in these regions (Table 17.1). The relationship between depression severity and physiological activity in the lateral orbital cortex/ventrolateral PFC is complex. While CBF and metabolism increase in these areas in the depressed relative to the remitted phase of MDD, the magnitude of these measures is inversely

correlated with ratings of depressive ideation and severity (Drevets et al., 1992, 1995b, 2002f). Moreover, while metabolic activity is abnormally increased in these areas in treatment-responsive, unipolar and bipolar depressives, more severely ill or treatment-refractory samples show CBF and metabolic values lower than or not different from those of controls (Mayberg et al., 1994, 1997). This inverse relationship between orbital cortex/ventrolateral PFC activity and ratings of depression severity also appear to extend to some other emotional states. For example, posterior orbital cortex flow also increases in subjects with obsessive-compulsive disorder or simple animal phobias during exposure to phobic stimuli and in healthy subjects during induced sadness (Drevets et al., 1995a; Rauch et al., 1994; Schneider et al., 1995), with the change in posterior orbital CBF correlating inversely with changes in obsessive thinking, anxiety, and sadness, respectively.

These data appear consistent with electrophysiological and lesion analysis data showing that parts of the orbital cortex participate in modulating behavioral and visceral responses associated with defensive, emotional, and reward-directed behavior as reinforcement contingencies change (Rolls, 1995). These cells are thought to play roles in extinguishing unreinforced responses to aversive or appetitive stimuli, via their anatomical projections to neurons in the amygdala, striatum, hippocampal subiculum, hypothalamus, periaqueductal gray, and other limbic and brainstem structures (Öngür and Price, 2000; Rolls, 1995). The orbital cortex and amygdala send overlapping projections to each of these structures as well as to each other through which they appear to modulate each other's neural transmission (Garcia et al., 1999; Öngür and Price, 2000; Timms, 1977).

Activation of the orbital cortex during depression may thus reflect endogenous attempts to attenuate emotional expression or interrupt unreinforced aversive thought and emotion. Consistent with this hypothesis, cerebrovascular lesions and tumors involving the frontal lobe increase the risk for developing major depression (e.g. Starkstein and Robinson, 1989), with the orbital cortex being specifically implicated as the area where such lesions result in increased risk for depression (MacFall et al., 2001). These observations also suggest that the reduction of CBF and metabolism in the orbital cortex and ventrolateral PFC during antidepressant drug treatment (Table 17.1) may not be a primary mechanism through which such agents ameliorate depressive symptoms. Instead, direct inhibition of pathological limbic activity in areas such as the amygdala and ventral ACC may modulate the pathophysiology associated with the production of depressive symptoms (Drevets et al., 2002b). The orbital cortex neurons may consequently "relax", as reflected by the return of metabolism to normal levels, as antidepressant drug therapy attenuates the pathological limbic activity to which these neurons putatively respond.

The lateral orbital cortex also participates in integrating experiential stimuli with affective salience and in associating reward-directed behavioral responses with the outcome of such responses, allowing redirection of behavior as reinforcement contingencies change (Rolls, 1995; Schultz, 1997). The lateral orbital cortex area implicated in MDD includes BA47, which receives projections from sensory association cortices and shares extensive, reciprocal, anatomical connections with the amygdala, ACC, ventral striatum, hypothalamus, and other structures involved

in the processing of rewarding stimuli and behavioral incentive (Öngür and Price, 2000). The abnormal reduction in gray matter in this area in MDD (Rajkowska et al., 1999) may thus conceivably contribute to the deficits in generating motivated behavior and reward salience that are experienced during depression.

17.4.2

The Amygdala

In the amygdala, neurophysiological activity is altered in some depressive subgroups both at rest and during exposure to emotionally-valenced stimuli. The basal CBF and metabolism are elevated in mood disordered subgroups who meet criteria for either FPDD (Figure 17.3A; Drevets et al., 1992, 1995b, 2002b, 2002c), MDD-melancholic subtype (Nofzinger et al. 1999), Type II BD or nonpsychotic, Type I BD (Drevets et al., 2002c; Ketter et al., 2001), or who prove responsive to sleep deprivation (Wu et al., 1992). In contrast, metabolism has not been abnormal in

Elevated Left Amygdala Activity in Depression

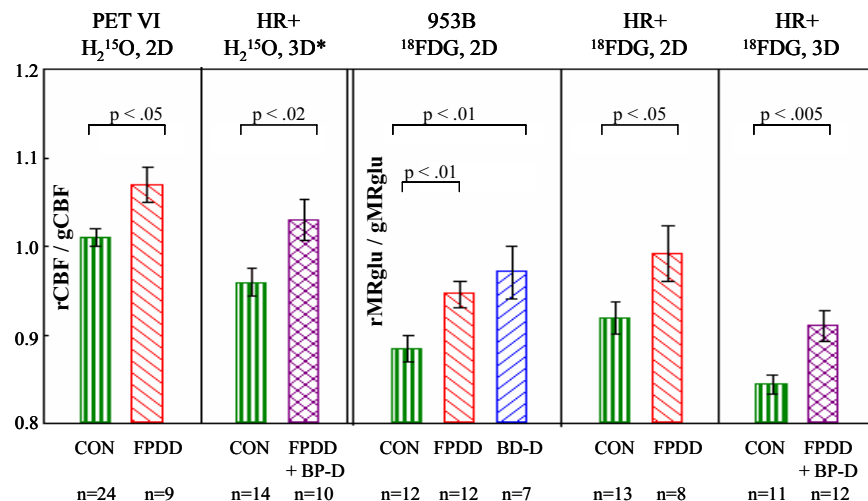


Figure 17.4 Elevation of mean normalized physiological activity (\pm SEM) in the left amygdala, measured in terms of CBF or glucose metabolism in mid-life depressed subjects relative to healthy controls. The five consecutive studies which used different PET cameras (PET VI, HR+ and 953B are PET scanner model numbers, the latter two manufactured by Siemens/CTI; 2D and 3D refer to distinct image acquisition modes) in different laboratories in independent subject samples are summarized in Drevets et al.

(1992, 1995b, 1999, 2002b,c). Because the first glucose metabolism study (center) showed that FPDD and BD-D samples both significantly differed from controls, but not from each other, subjects from these categories were combined for two subsequent studies (panels 2 and 4). rCBF/gCBF, regional-to-global CBF ratio; rMRglu/gMRglu, ratio of regional-to-global metabolic rates for glucose; CON, healthy controls; FPDD, familial pure depressive disease; BD-D, depressed phase of bipolar disorder.

unipolar depressives meeting criteria for depression spectrum disease (Drevets et al., 1995b, 2002c), or in MDD samples meeting DSM criteria for MDD as the sole inclusion criterion (Abercrombie et al., 1998; Brody et al., 2001), although the interpretation of the latter results was confounded by technical problems that reduced sensitivity for measuring amygdala activity (discussed in Drevets et al., 2002c).

In FPDD the magnitude of the abnormal elevation of flow and metabolism averages about 6% measured with state-of-the-art PET cameras (Figure 17.4). When corrected for spatial resolution effects, this difference would reflect an increase in the actual CBF and metabolism of about 50 to 70% (Drevets et al., 1992; Links et al., 1996). These magnitudes are in the physiological range, as CBF increases ~ 50% in the rat amygdala during exposure to fear-conditioned stimuli as measured by tissue autoradiography (LeDoux et al., 1983). During antidepressant treatment that both attenuate depressive symptoms and prophylaxes against relapse, amygdala metabolism decreases toward normative levels (Drevets et al., 2002b).

The amygdala CBF normally increases *during exposure* to emotionally-salient sensory stimuli, but not during anxiety or sadness states elicited by internally-generated thoughts (Drevets and Raichle, 1992). In contrast, amygdala flow and metabolism are abnormally elevated in MDD in the absence of such stimuli. Consistent with this observation, Nofzinger et al. (1999) reported that while amygdala metabolism was increased in depressives versus controls during wakefulness, the increase in metabolism occurring in the amygdaloid complex during rapid eye movement (REM) sleep was also greater in depressives than among controls. If confirmed in a larger sample, these data would imply that amygdala hypermetabolism exists in MDD even when conscious processing of stressors is dormant. Although it is conceivable that the elevated physiological activity in the amygdala in depression reflects an exaggerated response to the stress of scanning (Drevets et al., 2002c), normally the hemodynamic response of the amygdala to stressors or threats rapidly habituates (reviewed in Charney and Drevets, 2002), and would not be expected to persist as long as the period required for ^{18}F FDG uptake during glucose metabolism imaging.

Functional imaging data acquired as subjects view emotionally-valenced stimuli that normally activate the amygdala also demonstrate altered physiological responses in MDD. In the left amygdala, the hemodynamic response to viewing fearful faces is blunted in depressed children (Thomas et al., 2001) and depressed adults (Drevets, 2001). This finding was consistent with the elevation of basal CBF and metabolism in the *left* amygdala in such cases, since tissue that is physiologically activated is expected to show an attenuation of further rises in the hemodynamic/metabolic signal in response to tasks that normally engage the same tissue (MacFall et al., 1998). The duration of the amygdala response to emotionally valenced stimuli is also abnormal in depression. Drevets (2001) observed that although the initial amygdala CBF response to sad faces was similar in depressives and controls, this response habituated during repeated exposures to the same stimuli in the controls, but not in the depressives over the imaging period. Similarly, Siegle et al. (2002) reported that hemodynamic activity increased in the amygdala during exposure to

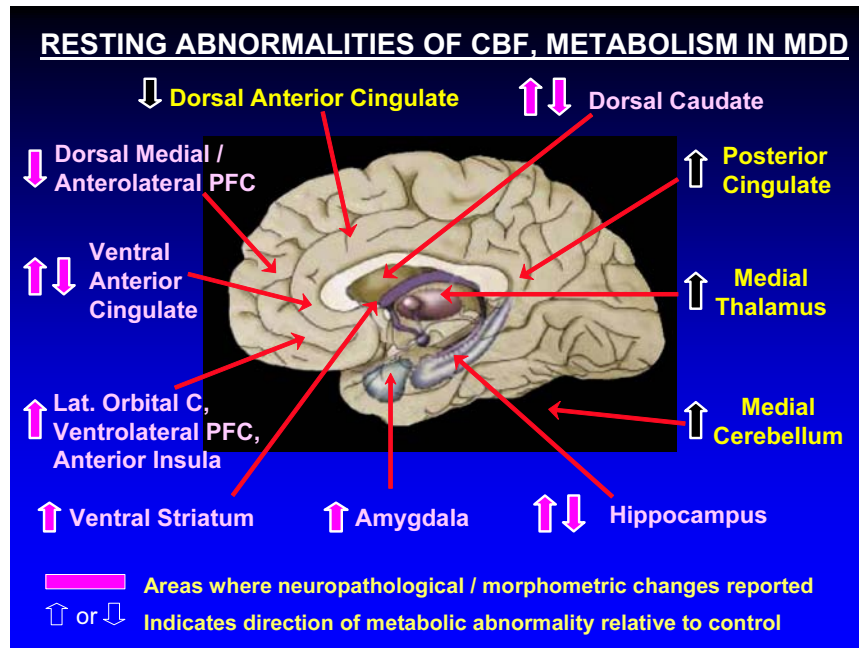


Figure 17.5 Summary of neuroimaging abnormalities in early-onset, primary, major depressive disorder (MDD). The regions where neurophysiological imaging abnormalities have been consistently reported in unmedicated MDD samples are listed and shown approximately on this midsagittal diagram of the brain in which subcortical structures are highlighted onto the medial surface. Because only the medial wall of the cortex is shown, the location of the lateral orbital/ventrolateral PFC/anterior insular region is better illustrated in Figure 17.3B. The “ventral anterior cingulate” region refers to both pregenual and

subgenual portions (see text and Figure 17.2). The arrows in front of each region name indicate the direction of resting state abnormalities in glucose metabolism in unmedicated, depressed MDD samples relative to healthy control samples. In some cases abnormalities in both directions have been reported which may depend either on the specific region involved or on the clinical state (e.g. treatment responsive versus non-responsive; see text). The regions shaded in pink have been shown to have histopathological and/or gray matter volumetric abnormalities in post mortem studies of primary mood disorders.

negatively-valenced words to a similar extent in depressives and controls, but while the hemodynamic response rapidly fell to baseline in the controls, it remained elevated for > 30 s in the depressives.

The amygdala plays major roles in organizing other behavioral, neuroendocrine, and autonomic aspects of emotional/stress responses to experiential stimuli, potentially compatible with reports that amygdala CBF and metabolism correlate positively with ratings of depression severity that assess both emotional and neurovegetative aspects of the major depressive syndrome (Abercrombie et al., 1998; Drevets et al., 1992, 1995b, 2002c). For example, the amygdala facilitates stress-related corticotropin releasing hormone (CRH) release (Herman and Cullinan, 1997)

and electrical stimulation of the amygdala in humans increases cortisol secretion (Rubin et al., 1966), suggesting a mechanism via which excessive amygdala activity may participate in inducing the CRH and cortisol hypersecretion that is evident in MDD (Nemeroff et al., 1992). In PET studies of MDD and BD, CBF and metabolism in the left amygdala correlates positively with stressed plasma cortisol secretion, which may reflect either the effect of amygdala activity on CRH secretion or the effect of cortisol or CRH on amygdala function (Drevets et al., 2002c).

17.4.3

Abnormalities in Anatomically-related Limbic and Subcortical Structures

The ventrolateral, ventral anterior cingulate and orbital PFC areas where CBF and metabolism are abnormal in major depression share extensive interconnections with the amygdala, mediodorsal nucleus of the thalamus, ventral striatum and medial caudate (Öngür and Price, 2000; Price et al., 1996). In the medial thalamus and ventral striatum CBF and metabolism are abnormally elevated in the depressed phase of MDD and BD, and decrease during antidepressant pharmacotherapy (Drevets et al., 1992, 1995b, 2002d; Saxena et al., 2002; Videbech et al., 2001; Wilson et al., 2002).

In the caudate, some PET studies reported that CBF and metabolism were abnormally reduced in MDD (Baxter et al., 1985; Drevets et al., 1992; Schwartz et al., 1987). These abnormalities may be specific to subtype, as melancholic subjects show decreased activity in the dorsal caudate, yet Brody et al. (2001) reported that metabolism was abnormally increased in MDD, and decreased during both paroxetine treatment and interpersonal psychotherapy.

Several groups reported abnormally increased CBF in the posterior cingulate cortex in the unmedicated, depressed phase of MDD (e.g. Bench et al., 1993; Buchsbaum et al., 1997; Drevets et al., 2002b), and some have shown that posterior cingulate flow and metabolism decreased during antidepressant treatment (Buchsbaum et al., 1997; Nobler et al., 2001). Bench et al. (1993) specifically reported that the elevation of posterior cingulate flow in depressives relative to controls correlated positively with anxiety ratings. Exposure to aversive stimuli of various types results in increased physiological activity in the posterior cingulate cortex (reviewed in Charney and Drevets, 2002). Nevertheless, Mayberg et al. (1999) reported that script-driven sadness resulted in decreased activity in healthy subjects in the dorsal posterior cingulate cortex, and that flow was decreased in the depressed relative to the remitted phase of MDD, raising the possibility that this large region is functionally heterogeneous with respect to emotional behavior. The posterior cingulate cortex appears to serve as a sensory association cortex, and may participate in processing the affective salience of sensory stimuli. The posterior cingulate cortex sends a major anatomical projection to the pregenual ACC, through which it may relay such information into the limbic circuitry (Vogt, 1993).

17.4.4

Abnormalities in Other Brain Areas

Abnormally increased CBF has also been consistently reported in the medial cerebellum in MDD (e.g. Bench et al., 1992; Videbech et al., 2001). Flow increases in this region in experimentally-induced states of anxiety or sadness in healthy subjects and in anxiety states elicited in subjects with anxiety disorders (reviewed in Charney and Drevets, 2002, George et al., 1995). Activation of this structure during depression and anxiety may conceivably reflect either the activation of established anatomical loops between the cortex and cerebellum, or the role of the paleocerebellum in modulating autonomic function.

Regional CBF and metabolic abnormalities in other structures have been less consistently replicated. In the lateral temporal and inferior parietal cortex, some studies found reduced regional CBF and metabolism (e.g. Biver et al., 1994; Cohen et al., 1992; Drevets et al., 1992; Philpot et al., 1993). Some of these areas have been implicated in processing sensory information. The significance of reduced activity in such areas in depression remains unclear (Drevets and Raichle, 1998).

17.4.5

Implications for Anatomical Circuits Related to Depression

Because alterations in regional CBF and metabolism predominantly reflect a summation of energy utilization associated with terminal field synaptic transmission, interpreting the regional abnormalities in depression involves consideration of anatomical connectivity (Drevets et al., 1992; Raichle, 1987). The glucose metabolic signal (to which the CBF signal is tightly coupled) is particularly dominated by glutamatergic transmission (Magistretti and Pellerin, 1999; Rothman et al., 1999; Shen et al., 1999; Shulman and Rothman, 1998; Sibson et al., 1998). The functional and structural imaging data in primary depression converge with evidence from lesion analysis studies to implicate circuits involving parts of the PFC and mesiotemporal cortex along with anatomically-related areas of the striatum, pallidum and thalamus in the pathophysiology of depression. The abnormally increased CBF and metabolism in the ventrolateral and orbital PFC, ventral ACC, amygdala, ventral striatum, and medial thalamus evident in unipolar depressives (Figure 17.3A–C) more specifically implicate a limbic–thalamo–cortical circuit involving the amygdala, the mediodorsal nucleus of the thalamus and the orbital and medial PFC, and a limbic–striatal–pallidal–thalamic circuit involving related parts of the striatum and the ventral pallidum along with the components of the other circuit (Drevets et al., 1992).

The first of these circuits can be conceptualized as an excitatory triangular circuit whereby the basolateral nucleus of the amygdala and the orbital and medial prefrontal regions are interconnected by excitatory (especially glutamatergic) projections with each other and with the mediodorsal nucleus (reviewed in Drevets et al., 1992), so increased metabolic activity in these structures would presumably reflect increased synaptic transmission through the limbic–thalamo–cortical circuit.

The limbic–striatal–pallidal–thalamic circuit constitutes a disinhibitory side loop between the amygdala or PFC and the mediodorsal nucleus. The amygdala and the PFC send excitatory projections to overlapping parts of the ventromedial striatum (Russchen and Price, 1984). This part of the striatum sends an inhibitory projection to the ventral pallidum (Graybiel, 1990) which in turn sends GABA-ergic, inhibitory fibers to the mediodorsal nucleus (Kuroda and Price, 1991).

It is, nevertheless, unclear how increased synaptic transmission through this circuit would ultimately affect cellular activity in a particular structure. For example, the morphological, histochemical, and electrophysiological evidence collectively indicate that while the reciprocal prefrontal-amygdalar projections are excitatory in nature, these connections appear to ultimately activate inhibitory interneurons that in turn lead to functional inhibition in the projected field of the amygdala (for PFC to amygdalar projections) or the medial PFC and ventrolateral PFC (for review see Drevets, 2003; Rosenkranz and Grace, 2001, 2002). The function of the PFC in modulating the amygdala appears to be impaired in mood disorders, based upon evidence from *in vivo* fMRI data showing that abnormally sustained amygdala activity in response to aversive words or sad faces in MDD is associated with blunted activation of PFC areas (Drevets, 2003; Siegle et al., 2002), and from post mortem studies of MDD and BD showing volumetric and/or histopathological changes in the subgenual and pregenual ACC, lateral orbital cortex, dorsomedial/dorsal anterolateral PFC, hippocampal subiculum, amygdala, and ventral striatum, as described below.

Synaptic transmission through these circuits may differ across depressive subtypes, since the lesions involving the PFC (i.e. tumors or infarctions) and the diseases of the basal ganglia (e.g. Parkinson's or Huntington's disease) that are associated with higher rates of depression than other similarly debilitating conditions, result in dysfunction at distinct points within these circuits and affect synaptic transmission in diverse ways (reviewed in Drevets and Todd, 1997; Starkstein and Robinson, 1989). Consistent with this hypothesis, imaging studies of depressive syndromes arising secondary to neurological disorders have generally shown results that differ from those reported for primary mood disorders. For example, in contrast to the findings of increased CBF or metabolism in parts of the orbital cortex in primary depressives, orbital cortex flow is reportedly decreased or not significantly different in subjects with depressive syndromes arising secondary to Parkinson's disease, Huntington's disease, or basal ganglia infarction relative to non-depressed subjects with the same illnesses (Mayberg et al., 1990, 1991, 1992; Ring et al., 1994). Primary and secondary depressive syndromes may thus involve the same neural network, although the direction of the physiological abnormalities within individual structures may differ across conditions. A common substrate in these cases may be the dysfunction of the frontal-striatal modulation of limbic and visceral functions, as both the idiopathic and neuropathological changes evident in the orbital and medial PFC and ventral striatum in primary mood disorders (see above) and those found in neurodegenerative conditions that can induce depressive syndromes (e.g. Parkinson's disease, Huntington's disease, cerebrovascular disease), would be expected to alter function within these regions.

This model also has relevance for considering the pathophysiology of neuropsychiatric syndromes that occurs comorbidly with major depression. For example, neuroimaging studies implicate the same neural circuits in the pathophysiology of OCD, providing insights into the common coincidence of depressive and obsessional syndromes (Drevets and Todd, 1997). Notably the differences found in the ventral PFC between primary and secondary depression parallel the findings in primary and secondary obsessive-compulsive syndromes, in which ventral PFC metabolism is increased in the former but decreased or unchanged in the latter (reviewed in Drevets et al., 2004).

17.5

Volumetric MRI Imaging Abnormalities in Mood Disorders

17.5.1

Morphometric Abnormalities in Frontal Lobe Structures

The volumes of the whole brain and the entire frontal lobe have not differed between depressed and healthy control samples in most studies. In contrast, volumetric abnormalities have been identified in several specific prefrontal cortical, mesio-temporal, and basal ganglia structures in mood disorders. The most prominent reductions of cortex have been identified within the anterior cingulate gyrus ventral to the genu of the corpus callosum, where the gray matter volume has been decreased by 20 to 40% in depressed subjects with familial pure depressive disease and familial bipolar disorder (Botteron et al., 2002; Drevets et al., 1997; Hirayasu et al., 1999) relative either to healthy controls or to mood disordered subjects with no family history of mood disorders. These findings have been confirmed by post mortem studies of clinically similar samples, as reviewed below. Effective treatment with selective serotonin reuptake inhibitors did not alter the subgenual PFC volume in MDD (Drevets et al., 1997), although this cortex appeared significantly larger in BD subjects chronically medicated with lithium or divalproex than among BD subjects who were either unmedicated or medicated with other agents, compatible with evidence that chronic administration of these mood stabilizers increases expression of the neuroprotective protein, Bcl-2, in the frontal cortex of experimental animals (Manji et al., 2001).

In the posterior orbital cortex and the ventrolateral PFC, the volume has also been reported to be reduced in both *in vivo* volumetric MRI studies (Bremner et al., 2000) and post mortem neuropathological studies of MDD (Bowen et al., 1989; Rajkowska et al., 1999). Reductions in gray matter volume were also found in the dorsomedial/dorsal anterolateral PFC in MDD subjects versus controls (Bell et al., 1999). Post mortem studies of MDD and BD have found abnormal reductions in the size of neurons and/or the density of glia in this portion of BA9 (Cotter et al., 2001a, 2002; Rajkowska et al., 1999, 2001; Uranova et al., 2004).

17.5.2

Temporal Lobe Structures

Multiple morphometric MRI studies of specific temporal lobe structures reported significant reductions in hippocampal volume in MDD, with the magnitudes of difference ranging from 8 to 19% with respect to healthy controls (Bremner et al., 2000; Mervaala et al., 2000; Sheline et al., 1996, 1999; Steffens et al., 2000; Wymore et al., 2003). Sheline et al. (1996) reported that the hippocampal volume was negatively correlated with the total time spent depressed or with the number of depressive episodes in MDD. However, many groups found no significant differences between MDD and control samples (Ashtari et al., 1999; Axelson et al., 1993; Hauser et al., 1989; Pantel et al., 1997; Shah et al., 1998; Vakili et al., 2000; von Gunten et al., 2000). The inconsistency in the results of MDD studies may reflect pathophysiological heterogeneity within the MDD samples studied. For example, Vythilingam et al. (2002) reported that the hippocampal volume was abnormally decreased in depressed women who had a history of early-life trauma, but not in women who had depression without early-life trauma.

In BD, reductions in hippocampal volume were identified by Noga et al. (2001) and Swayze et al. (1990) relative to healthy controls, although Pearlson et al. (1997) and Nugent et al. (2004) found no differences between BD and control samples. In post mortem studies of BD, abnormal reductions in the mRNA concentrations of synaptic proteins (Eastwood and Harrison, 2000) and in apical dendritic spines of pyramidal cells (Rosoklija et al., 2000) were specifically observed in the subicular and ventral CA1 sub-regions, but not in most other hippocampal regions examined. A recent study using high resolution 3T MRI scans found that the volume of the subiculum, but not of the remainder of the hippocampus, was decreased in BD relative to control samples.

Two studies reported abnormalities of the hippocampal T1 MR signal in MDD. Krishnan et al. (1991a) observed that the T1 relaxation time was reduced in the hippocampus, but not in the entire temporal lobe in unipolar depressives relative to healthy controls, and Sheline et al. (1996) observed that elderly subjects with MDD have a higher number of areas showing low MR signal than age-matched controls in T1-weighted images. The significance of such abnormalities remains unclear.

A study employing high resolution MRI images acquired at 3 T magnetic field strength, recently established that mean amygdala volumes were decreased bilaterally ($p < 0.001$) in MDD relative both to BD and control samples (Drevets et al., 2002d). The amygdala volumes were decreased both in currently depressed and currently remitted MDD sub-samples. Although mean amygdala volumes did not differ between BD and control samples, they were smaller in BD subjects who had not recently been medicated with mood stabilizers than in BD subjects who had been taking such agents.

These data clarified disagreements across studies that had measured the amygdala volume using scanners of lower magnetic field strength. The small size of the amygdala and its proximity to other gray matter structures limited the validity and

reliability of volumetric measures in images acquired at ≤ 1.5 T field strength. Thus, such studies had previously reported that the amygdala volume was decreased (Sheline et al., 1998; Siegle et al., 2003), increased (Frodl et al., 2002) or not different (Mervaala et al., 2000) in MDD samples relative to healthy control samples. Similarly in BD the amygdala volume was reported to be increased (Altshuler et al., 1998; Brambilla et al., 2003; Strakowski et al., 1999), decreased (Blumberg et al., 2003; DelBello et al., 2004; Pearlson, et al., 1997), or not different (Swayze et al., 1990) relative to healthy controls. Although the extent to which the disagreements across these studies may be explained by confounding factors such as medication effects, remains unclear; however, it appears more likely that MRI images acquired at < 1.5 T simply lack the spatial and tissue contrast resolution needed to measure amygdala volumes with sufficient validity and reliability.

17.5.3

Basal Ganglia

Some MRI studies reported that the volumes of basal ganglia structures are abnormally decreased in MDD. Husain et al. (1991) reported that the putamen was smaller in depressives (mean age = 55 years) than controls, and Krishnan et al. (1992) found a smaller caudate nucleus volume in depressives (mean age = 48 years) than controls. In a sample limited to elderly depressives, Krishnan et al. (1993) also reported smaller putamen and caudate volumes relative to controls. However, Dupont et al. (1995) and Lenze and Sheline (1999) failed to find significant differences in caudate or lentiform nucleus (putamen plus globus pallidus) volumes between younger samples of unipolar depressives and controls. In addition, MRI-based studies of BD have not found significant differences in the volumes of basal ganglia structures with respect to controls (reviewed in Drevets and Botteron, 1997). The factors accounting for the discrepant results across studies remain unclear.

17.5.4

Other Cerebral Structures

Morphometric studies of other brain structures in depression have produced less consistent results. Of the MRI studies that assessed the thalamus, Dupont et al. (1995) reported that the thalamic volume was decreased in unipolar depressives relative to controls, but Krishnan et al. (1991a, 1993) found no differences between depressives and controls. Two studies of thalamic volume in bipolar disorder have also reported conflicting results. Of the MRI studies of the cerebellum, two reported that the vermal volume is reduced in depressives relative to controls (Escalona et al., 1993; Shah et al., 1992) while a third did not.

17.5.5

Endocrine Glands

Consistent with evidence that the hypothalamic–pituitary–adrenal axis function is elevated in some mood disordered subgroups, enlargement of the adrenal and pituitary glands has been reported in MDD. Using abdominal CT or MRI to evaluate adrenal size, four studies found enlargement of the adrenal gland in MDD relative to control samples (Amsterdam et al., 1987; Nemeroff et al., 1992; Rubin et al., 1995). Rubin et al. (1995) additionally showed that the median adrenal volume of the depressives decreased to approximately the volume seen in the controls in a second scan acquired following remission. The results of these studies are potentially consistent with the finding that the mean adrenal gland weight is abnormally increased in suicide victims (Zis and Zis, 1987). The cause of adrenal hypertrophy in MDD is putatively related to chronically elevated stimulation of the adrenal cortex by ACTH.

Pituitary size has been less consistently reported to be enlarged in MRI studies of depression. Krishnan et al. (1991b) showed that MRI-based measures of cross-sectional area and volume of the pituitary were increased (by 34 and 41%, respectively) in depressives ($n = 19$) versus controls ($n = 19$).

17.5.6

Abnormalities of Corpus Callosal Volume in Mood Disorders

The genual subsection of the corpus callosum was reduced in volume in both depressed women with MDD and their high-risk, female offspring (Martinez et al., 2002). These white matter regions contain the transcallosal fibers that connecting the orbital cortex, ACC, and medial PFC regions with their homologous cortices in the contralateral hemisphere. Insufficient numbers of males were studied to determine whether the abnormality extended to males. The volumes of other corpus callosal regions did not differ between mood disordered and control samples except in the splenial region, which contains transcallosal fibers from the posterior cingulate cortex.

17.6

Post Mortem Neuropathological Assessments of Mood Disorders

Post mortem studies of MDD and BD have shown histopathological or gray matter volume changes in several of the regions where MRI studies demonstrated volumetric abnormalities in mood disorders (Table 17.2). Reductions of gray matter volume, thickness or wet weight have been reported in the subgenual ACC, posterolateral orbital cortex, and ventral striatum in MDD and/or BD subjects relative to controls (Baumann et al., 1999; Bowen et al., 1989; Drevets et al., 1998; Öngür et al., 1998; Rajkowska et al., 1999). The histopathological correlates of these abnormalities included reductions in glial cells with no equivalent loss of neurons,

Table 17.2 Post mortem studies of mood disorders

Region	Reductions found in			
	Glial Markers	Synaptic Markers	Inter-Neurons	Pyramidal cells
Dorsolateral PFC (BA9)	↓			↓ MDD
Subgenual ACC	↓	↓		
Pregenual ACC	↓	↓	↓ BD	
Orbital C	↓ caudal			↓ rostral
Ventrolateral PFC	↓			
Frontal polar C (BA 10)	↓ BD			
Amygdala	↓ MDD			
Caudate	↓ BD			
Hippocampus		↓ BD	↓ BD	

reductions in synapses or synaptic proteins, elevations in neuronal density, and reductions in neuronal size (Bowen et al., 1989; Cotter et al., 2000, 2001a; Eastwood and Harrison, 2000, 2001; Öngür et al., 1998; Rajkowska et al., 1999). Abnormal reductions in glial cell counts and density, and/or glia-to-neuron ratios have also been found in MDD in Brodmann area 24 cortex of the *pregenual* ACC (Cotter et al., 2001a), the dorsal anterolateral PFC (BA9; Cotter et al., 2002; Uranova et al., 2004), and the left amygdala (Bowley et al., 2002; Hamidi et al., 2004). *Neuron counts* have been reported to be abnormally decreased in the orbital cortex of depressed suicide victims and in the anterior cingulate cortex of bipolar disorder subjects (Arango et al., 2001; Benes et al.,). Finally, the mean *size of neurons* was reduced in the dorsal anterolateral PFC (BA9) in MDD subjects relative to controls (Rajkowska et al., 1999). In several of these studies, the decreases were largely accounted for by differences in the left hemisphere (Bowen et al., 1989; Bowley et al., 2002; Drevets et al., 1998; Öngür et al., 1998; Hamidi et al., 2004).

In the amygdala the glial type that specifically differed between mood-disordered and control samples was the oligodendroglia. Oligodendrocyte counts were decreased in MDD, while the astrocyte and microglial counts did not significantly differ between MDD and BD samples versus control samples (Hamidi et al., 2004). Oligodendroglia are best characterized for their role in myelination, and the reduction in oligodendrocytes may conceivably arise secondary to an effect on myelin, either through demyelination, abnormal development, or atrophy in the number of myelinated axons. Notably, the myelin basic protein concentration was found to be decreased in the frontal polar C (BA10) in brain tissue from subjects with both major depression and schizophrenia (Honer et al., 1999). Compatible with these data, the concentration of white matter within the vicinity of the amygdala (Nugent et al., 2004) and the white matter volume of the genu and splenial portions of the corpus callosum are abnormally reduced in MDD and BD (Brambilla et al.,

2003; Martinez et al., 2002). These regions of the corpus callosum were also smaller in child and adolescent offspring of women with MDD who had not yet experienced a major depressive episode, in comparison to age-matched controls. This finding suggested that the reduction in white matter in MDD reflects a developmental defect that exists prior to the onset of depressive episodes. All of these observations would support the suggestion that the glial cell loss in mood disorders is accounted for by a reduction in myelinating oligodendrocytes.

Another observation that supports this hypothesis is that several reports of deficits in glia in the cerebral cortex depended upon laminar analysis, with the greatest effects in layers III, V, and VI (Cotter et al., 2001a, 2002; Rajkowska et al., 1999, 2001). The intracortical plexuses of myelinated fibers known as “Bands of Baillarger” are generally concentrated in layers III and V. The size of these plexuses varies across cortical areas, so if the oligodendrocytes related to these plexuses were affected, different areas would be expected to show greater or lesser deficits. Layer VI in particular has a relatively large component of myelinated fibers running between the gray and white matter.

Given this possible connection between myelination and depression, it is striking that a very high prevalence of MDD exists in patients with multiple sclerosis (MS). For example, the prevalence of major depression in subjects from the Canadian Community Health Survey who suffer from multiple sclerosis is approximately double that among subjects who do not have MS (Patten et al., 2003). In contrast, subjects with other chronic disorders showed only about a 20% increase in the prevalence of depression. A recent structural MRI study that compared MS cases with and without MDD found that the depressed subjects specifically had greater lesion volume and less gray matter volume in the medial prefrontal cortex on the left (Feinstein et al., 2004).

In addition to myelinating oligodendrocytes, a population of satellite (or perineuronal) oligodendrocytes exists next to neuronal cell bodies that have largely unknown functions. Satellite oligodendrocytes do not appear to have a role in myelination under normal conditions (Ludwin, 1984). An electron microscopic study of the PFC in BD revealed decreased nuclear size, clumping of chromatin and other types of damage to satellite oligodendrocytes, including indications of both apoptotic and necrotic degeneration (Uranova, et al., 2001, 2004). Fewer signs of degeneration were seen in myelin-related oligodendrocytes in white matter.

Satellite oligodendrocytes may play a role in maintaining the extracellular environment for the surrounding neurons that resembles the functions mediated by astrocytes. These oligodendrocytes are immunohistochemically reactive for glutamine synthetase, suggesting that they function like astrocytes to take up synaptically-released glutamate for conversion to glutamine and cycling back into neurons (D’Amelio et al., 1990). Many studies of glial function have not distinguished astrocytes from oligodendrocytes, and the two glial types may share several functions.

In other brain regions, reductions in astroglia have been reported by post mortem studies of mood disorders. A reduction in astrocyte density was reported in MDD, based upon Nissl and S-100 β and HLA staining of the PFC. Johnston-Wilson et al.

(2000) used proteomic methods to characterize protein differences in the frontal cortex between mood disorder, schizophrenic and control brains. Four forms of the astrocytic product, glial fibrillary acidic protein (GFAP), were decreased in mood disorder cases and schizophrenic cases, although it remained unclear whether this decrement reflected a reduction in the astrocyte density or in the GFAP expression. Webster et al. (2001) analyzed immunohistochemical staining for GFAP, and did not find significant differences in cortical astrocytes between controls, and MDD, BD, or schizophrenic cases. Other studies also did not find differences in GFAP between mood disorder cases and controls (reviewed in Cotter et al., 2001b).

Factors that may conceivably contribute to a loss of oligodendroglia in mood disorders include the elevated glucocorticoid secretion and glutamatergic transmission evident during depression and mania. Glucocorticoids affect glia as well as neurons (Cheng and de Vellis, 2000), and elevated glucocorticoid levels decrease the proliferation of oligodendrocyte precursors (Alonso, 2000). The chronically elevated glucocorticoid concentrations observed in depression may thus result in a reduction in oligodendrocyte density.

Oligodendrocytes express both AMPA and kainite-type glutamate receptors, and are sensitive to excitotoxic damage from excess glutamate and to oxidative stress (reviewed in Hamidi et al., 2004). These vulnerabilities are thought to contribute to oligodendrocyte degeneration in ischemic brain injury and demyelinating diseases (Dewar et al., 2003; Matute et al., 1997), although no data exist to suggest a similar role in mood disorders. The targeted nature of the reductions in gray matter volume and glial cells to specific areas of the limbic-cortical circuits that show increased glucose metabolism during depressive episodes is noteworthy given the evidence reviewed above that the glucose metabolic signal is dominated by glutamatergic transmission (Magistretti and Pellerin, 1999). The hypothesis that glutamate transmission is elevated in these areas in depression was also supported by the post mortem study of Nowak et al. (1995) in depressed suicide victims.

Finally, elevations of cortisol secretion and glutamatergic transmission may conceivably contribute to reductions in gray matter volume and synaptic markers by inducing dendritic atrophy in some brain regions. In the medial PFC and parts of the hippocampus and amygdala of adult rodents, the dendritic arbors undergo atrophy or debranching in response to specific types of repeated or chronic stress (references). This process depends upon interactions between the elevations of glucocorticoid secretion and excitatory amino acid neurotransmission associated with stress (McEwen, 1999).

17.7

Neuroreceptor Imaging Studies of Depression

The development of neuroreceptor radioligands is providing expanding capabilities for non-invasive quantitation of *in vivo* receptor binding and dynamic neurotransmitter function. While this area is expected to become an increasingly common application for PET and SPECT technology, radioligands are available for relatively

few receptor species. Partly because of this limitation, the studies conducted to date in mood-disordered samples have largely been limited to assessments of monoamine receptor systems.

17.7.1

Dopamine Receptor Imaging

In BD, Suhara et al. (1992) reported that binding of the dopamine (DA) D₁ receptor radioligand, [¹¹C]SCH-23990, was below the age-adjusted normal range in the frontal cortex in nine of 10 subjects scanned in a variety of mood states. This finding awaits replication using D₁ receptor ligands that are more amenable to quantitation. In addition, Pearlson et al. (1995) showed that psychotic bipolar subjects have an increased striatal uptake of [¹¹C]-N-methylspiperone binding, a ligand for D₂-like dopamine receptor sites, relative to controls or to non-psychotic bipolar subjects. The striatal D₂ binding in the psychotic bipolar subjects correlated positively with psychosis ratings in this study.

In MDD, two SPECT studies performed using [¹²³I]-iodobenzamide (IBZM), a DA D₂ receptor ligand that is sensitive to endogenous DA concentrations, found increased striatal DA D₂/D₃ receptor availability during the depressed phase, which could potentially be accounted for by a reduction of endogenous DA release (D'haenen and Bossuyt, 1994; Shah et al., 1997). Ebert et al. (1996) found a nonsignificant trend toward increased [¹²³I]-IBZM binding in depressives versus controls, which was significant in a subgroup who displayed overt psychomotor retardation. Interpretation of these data was confounded however, by the presence of drug effects. Moreover, a PET study of the DA D₂/D₃ receptor radioligand, [¹¹C]raclopride did not replicate these results, and found no difference either in the baseline DA D₂/D₃ receptor binding or in the magnitude of dextroamphetamine-induced DA release in unmedicated MDD subjects (Parsey et al., 2001).

Other preliminary PET data appear compatible with the hypothesis that DA release is reduced in MDD. Meyer et al. (2001) found decreased DA transporter binding in depressives versus controls, which could potentially reflect a compensatory effect to reduced DA release. In addition, Ågren et al. (1993) found abnormally reduced uptake of the catecholamine precursor, [¹¹C]L-DOPA, and the serotonin precursor, [¹¹C]5-hydroxytryptophan, across the blood–brain barrier in MDD (although, the *regional* [¹¹C]5-hydroxytryptophan utilization was *increased* in the depressives relative to controls in a ventromedial PFC area that included pregenual ACC). If confirmed by replication, these data would suggest that the rate of DA synthesis is reduced in MDD.

17.7.2

Serotonin Receptor Imaging

Within the serotonin system, the most robust findings have been that both pre- and post-synaptic serotonin type 1A (5-HT_{1A}) receptor BP is abnormally decreased in MDD. These studies have demonstrated this reduction in 5-HT_{1A} receptor BP

in unmedicated depressives relative to healthy controls using PET and [*carbonyl*-¹¹C]WAY-100635 in the raphe, hippocampus, amygdala, temporopolar cortex, insula, anterior and posterior cingulate cortex, and left orbital cortex/VLPFC (Drevets et al., 1999, 2002e; Parsey et al., 2002, Sargent et al., 2000). The magnitudes of these differences have been similar to those found by post mortem studies of *primary* mood-disordered samples (Bowen et al., 1989; Lopez et al., 1998) or depressed, non-alcoholic suicides (Arango et al., 2001). These data were also compatible with the results of studies showing that unmedicated MDD subjects have blunted hypothalamic and adrenocorticotropin (ACTH) and cortisol release in response to 5-HT_{1A} receptor agonist challenge (reviewed in Drevets et al., 1999). Image data acquired both pre- and post-paroxetine treatment did not find significant treatment-associated changes in 5-HT_{1A} receptor BP in any area (Sargent et al., 2000). The serotonin type 1A (5-HT_{1A}) receptor BP is abnormally decreased in the raphe in panic disorder (irrespective of comorbid depression or past drug treatment) and in the anterior cingulate and insular cortex in both panic disorder and bipolar disorder (Bain et al., 2003; Neumeister et al., 2004).

Neuroimaging studies of other 5HT binding sites found less prominent differences in depression. Serotonin type 2A (5HT_{2A}) receptor imaging studies of depression have generally not identified significant differences in BP between depressives and controls when age effects were controlled (Meltzer et al., 1999; Meyer et al., 1999). The abnormal reductions in serotonin transporter (5HTT) binding reported in depressed suicides post mortem in the raphe and ventral PFC (Arango et al., 2001; Mann et al., 2000) have also been identified in a SPECT-beta-CIT (Malison et al., 1998) study, but not in a PET study using [¹¹C]McN5652 (Ichimiya et al., 2002). In the striatum 5HTT binding was reported to be increased in MDD by Ichimiya et al. (2002), but to not differ between depressives and controls by Meyer et al. (2001).

17.8

Concluding Remarks

The convergent results from studies of mood disorders conducted using neuroimaging, lesion analysis and post mortem techniques support models in which the signs and symptoms of major depression can emanate from dysfunction within PFC, striatal, and brainstem systems that modulate emotional behavior. Anti-depressant therapies may compensate for this dysfunction by attenuating the pathological limbic activity that mediates such symptoms (Drevets et al., 2002b,d), and by increasing genetic transmission of neurotrophic factors that exert neuroplastic effects within the pathways modulating emotional expression (Manji et al., 2001).

References

- ABERCROMBIE, H. C., SCHAEFER, S. M., LARSON, C. L., OAKES, T. R., LINDGREN, K. A., HOLDEN, J. E., PERLMAN, S. B., TURSKI, P. A., KRAHN, D. D., BENCA, R. M., DAVIDSON, R. J., Metabolic rate in the right amygdala predicts negative affect in depressed patients. *Neuroreport* **1998**, 3301–3307.
- ÅGREN, H., REIBRING, L., HARTVIG, P., TEDROFF, J., BJURLING, P., LUNDQVIST, H., LÄNGSTRÖM, B., Monoamine metabolism in human prefrontal cortex and basal ganglia. PET studies using [¹¹C]L-hydroxytryptophan and [¹¹C]L-DOPA in healthy volunteers and patients with unipolar depression. *Depression* **1993**, 1, 71–81.
- ALONSO, G., Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia* **2000**, 31, 219–231.
- ALTSHULER, L. L., BARTZOKIS, G., THOMAS, G., CURRAN, J., MINTZ, J., Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study demonstrating neuro-anatomic specificity. *Arch. Gen. Psychiatry* **1998**, 55, 663–664.
- AMSTERDAM, J. D., MARINELLI, D. L., ARGER, P., et al., Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers: a pilot study. *Psychiatry Res.* **1987**, 21, 384–387.
- ARANGO, V., UNDERWOOD, M. D., BOLDRINI, M., TAMIR, H., KASSIR, S. A., HSIUNG, S., CHEN, J. J., MANN, J. J., Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. *Neuropsychopharmacology* **2001**, 25, 892–903.
- ASHTARI, M., GREENWALD, B. S., KRAMER-GINSBERG, E., HU, J., WU, H., PATEL, M., AUPPERLE, P., POLLACK, S., Hippocampal/amygdala volumes in geriatric depression. *Psychol. Med.* **1999**, 29, 629–638.
- AXELSON, D., DORAISWAMY, P. M., McDONALD, W. M., et al., Hypercortisolemia and amygdala hippocampal changes in depression. *Psychiatry Res.* **1993**, 47, 167–173.
- BAUMANN, B., DANOS, P., KRELL, D., DIEKMANN, S., LESCHINGER, A., STAUCH, R., WÜRTHMAN, C., BERNSTEIN, H.-G., BOGERTS, B., Reduced volume of limbic system-affiliated basal ganglia in mood disorders: preliminary data from a post mortem study. *J. Neuropsych. Clin. Neurosci.* **1999**, 11, 71–78.
- BAXTER, L. R., PHELPS, M. E., MAZZIOTTA, J. C., SCHWARTZ, J. M., GERNER, R. H., SELIN, C. E., SUMIDA, R. M., Cerebral metabolic rates for glucose in mood disorders. *Arch. Gen. Psychiatry* **1985**, 42, 441–447.
- BAXTER, L. R., SCHWARTZ, J. M., PHELPS, M. E., MAZZIOTA, J. C., GUZE, B. H., SELIN, C. E., GERNER, R. H., SUMIDA, R. M., Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch. Gen. Psychiatry* **1989**, 46, 243–250.
- BELL, K. A., KUPFER, D. J., DREVETS, W. C., Decreased glucose metabolism in the dorsomedial prefrontal cortex in depression. *Biol. Psychiatry* **1999**, 45, 118S.
- BENCH, C. J., FRISTON, K. J., BROWN, R. G., FRACKOWIAK, R. S., DOLAN, R. J., Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. *Psychol. Med.* **1993**, 23, 579–590.
- BENCH, C. J., FRISTON, K. J., BROWN, R. G., SCOTT, L. C., FRACKOWIAK, R. S., DOLAN, R. J., The anatomy of melancholia – focal abnormalities of cerebral blood flow in major depression. *Psychol. Med.* **1992**, 22, 607–615.
- BIVER, F., GOLDMAN, S., DELVENNE, V., LUXEN, A., DeMAERTELAER, V., HUBAIN, P., MENDLEWICZ, J., LOTSTRA, F., Frontal and parietal metabolic disturbances in unipolar depression. *Biol. Psychiatry* **1994**, 36, 381–388.
- BLUMBERG, H. P., KAUFMAN, J., MARTIN, A., WHITEMAN, R., ZHANG, J. H., GORE, J. C., CHARNEY, D. S., KRISTAL, J. H., PETERSON, B. S., Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. *Arch. Gen. Psychiatry* **2003**, 60, 1201–1208.

- BONNE, O., KRAUSZ, Y., SHAPIRA, B., BOCHER, M., KARGER, H., GORFINE, M., CHISIN, R., LERER, B., Increased cerebral blood flow in depressed patients responding to electroconvulsive therapy. *J. Nucl. Med.* **1996**, 37, 1075–1080.
- BOTTERON, K. N., RAICHEL, M. E., DREVETS, W. C., HEATH, A. C., TODD, R. D., Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol. Psychiatry* **2002**, 51, 342–344.
- BOTTERON, K. N., RAICHEL, M. E., HEATH, A. C., et al., An epidemiological twin study of prefrontal neuromorphometry in early onset depression. *Biol. Psychiatry* **1999**, 45, 59S.
- BOWEN, D. M., NAJLERAHIM, A., PROCTER, A. W., FRANCIS, P. T., MURPHY, E., Circumscribed changes of the cerebral cortex in neuropsychiatric disorders of later life. *Proc. Natl. Acad. Sci. USA* **1989**, 86, 9504–9508F.
- BOWLEY, M. P., DREVETS, W. C., ÖNGÜR, D., PRICE, J. L., Low glial numbers in the amygdala in mood disorders. *Biol. Psychiatry* **2002**, 52, 404–412.
- BRAMBILLA, P., HARENSKI, K., NICOLETTI, M., SASSI, R. B., MALLINGER, A. G., FRANK, E., KUPFER, D. J., KESHAVAN, M. S., SOARES, J. C., MRI investigation of temporal lobe structures in bipolar patients. *J. Psychiatr. Res.* **2003**, 37, 287–295.
- BREMNER, J. D., NARAYAN, M., ANDERSON, E. R., STAIB, L. H., MILLER, H. L., CHARNEY, D. S., Hippocampal volume reduction in major depression. *Am. J. Psychiatry* **2000**, 157, 115–118.
- BRODY, A. L., SAXENA, S., STOESEL, P., GILLIES, L. A., FAIRBANKS, L. A., ALBORZIAN, S., PHELPS, M. E., HUANG, S. C., WU, H. M., HO, M. L., HO, M. K., AU, S. C., MAIDMENT, K., BAXTER, L. R., Regional brain metabolic changes in patients with major depressive disorder from pre- to post-treatment with paroxetine. *Arch. Gen. Psychiatry* **2001**, 58, 631–640.
- BUCHSBAUM, M. S., WU, J., SIEGEL, B. V., HACKETT, E., TRENARY, M., ABEL, L., REYNOLDS, C., Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biol. Psychiatry* **1997**, 41, 15–22.
- CARNEY, R. M., FREEDLAND, K. E., RICH, M. W., SMITH, L. J., JAFFE, A. S., Ventricular tachycardia and psychiatric depression in patients with coronary artery disease. *Am. J. Med.* **1993**, 95, 23–28.
- CHARNEY, D. S., DREVETS, W. C., The neurobiological basis of anxiety disorders. In DAVIS, K., CHARNEY, D. S., COYLE, J., NEMEROFF, C. B. (Eds.), *Psychopharmacology the Fifth Generation of Progress*. New York: Lippincott, Williams and Wilkins, Chapter 63, **2002**, 901–930.
- CHENG, J. D., DE VELLIS, J., Oligodendrocytes as glucocorticoids target cells: functional analysis of the glycerol phosphate dehydrogenase gene. *J. Neurosci. Res.* **2000**, 59, 436–445.
- COHEN, R. M., GROSS, M., NORDAHL, T. E., SEMPLE, W. E., OREN, D. A., ROSENTHAL, N., Preliminary data on the metabolic brain pattern of patients with winter seasonal affective disorder. *Arch. Gen. Psychiatry* **1992**, 49, 545–552.
- COTTER, D., MACKAY, D., BEASLEY, C., KERWIN, R., EVERALL, I., Reduced glial density and neuronal volume in major depressive disorder and schizophrenia in the anterior cingulate cortex. *Schizophrenia Res.* **2000**, 41, 106.
- COTTER, D., MACKAY, D., CHANA, G., BEASLEY, C., LANDAU, S., EVERALL, I., Reduced neuronal size and glial cell density in Area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb. Cortex* **2002**, 12, 386–394.
- COTTER, D. R., MACKAY, D., LANDAU, S., KERWIN, R., EVERALL, I., Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch. Gen. Psychiatry* **2001a**, 58, 545–553.
- COTTER, D. R., PARIANTE, C. M., EVERALL, I. P., Glial cell abnormalities in major psychiatric disorders: the evidence and implications. *Brain Res. Bull.* **2001b**, 55, 585–595.
- DAMASIO, A. R., *Descartes' Error: Emotion, Reason, and the Human Brain*. New York: Grosset/Putnam, **1994**. London: Picador MacMillan, **1995**.
- DAMASIO, A., GRABOWSKI, T. J., BECHARA, A., DAMASIO, H., PONTO, L. L. B., PARVIZI, J., HICHA, R. D., Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neurosci.* **2000**, 3, 1049–1056.

- D'AMELIO, F., ENG, L. F., GIBBS, M. A., Glutamine synthetase immunoreactivity present in oligodendroglia of various regions of the central nervous system. *Glia* **1990**, 3, 335–341.
- DEWAR, D., UNDERHILL, S. M., GOLDBERG, M. P., Oligodendrocytes and ischemic brain injury. *J. Cereb. Blood Flow Metab.* **2003**, 23, 263–274.
- D'HAENEN, H. A., BOSSUYT, A., Dopamine D₂ receptors in depression measured with single photon emission computed tomography. *Biol. Psychiatry* **1994**, 35, 128–132.
- DIORO, D., VIAU, V., MEANEY, M. J., The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *J. Neurosci.* **1993**, 13, 3839–3847.
- DIRROCCO, R. J., et al., The relationship between CNS metabolism and cytoarchitecture: a review of ¹⁴C-deoxyglucose studies with correlation to cytochrome oxidase histochemistry. *Comput. Med. Imaging Graphics* **1989**, 13, 81–92.
- DOLAN, R. J., BENCH, C. J., BROWN, R. G., SCOTT, L. C., FRACKOWIAK, R. S. J., Neuropsychological dysfunction in depression: the relationship to regional cerebral BF. *Psychol. Med.* **1994**, 24, 849–857.
- DOLAN, R. J., BENCH, C. J., LIDDLE, P. F., et al., Dorsolateral prefrontal cortex dysfunction in the major psychoses: symptom or disease specificity? *J. Neurol. Neurosurg. Psychiatry* **1993**, 56, 1290–1294.
- DREVETS, W. C., Brain imaging in psychiatry. In SIERLES, F. S. (Ed.), *Behavioral Science for Medical Students*. Williams and Wilkins, **1993**.
- DREVETS, W. C., Prefrontal cortical-amygdalar metabolism in major depression. In *Advancing from the Ventral Striatum to the Extended Amygdala: Implications for Neuropsychiatry and Drug Abuse*. *Annals of the New York Academy of Sciences*. New York: New York Academy of Sciences, **1999**, 614–637.
- DREVETS, W. C., Neuroimaging and neuro-pathological studies of depression: implications for the cognitive emotional manifestations of mood disorders. *Curr. Opin. Neurobiol.* **2001**, 11, 240–249.
- DREVETS, W. C., Neuroimaging abnormalities in the amygdala in mood disorders. In *The Amygdala in Brain Function: Basic and Clinical Approaches*. *Annals of the New York Academy of Sciences*. New York: New York Academy of Sciences, **2003**.
- DREVETS, W. C., BOTTERON, K., Neuroimaging in psychiatry. In GUZE, S. B. (Ed.), *Adult Psychiatry*. St. Louis, MO: Mosby Press, **1997**, 53–81.
- DREVETS, W. C., RAICHEL, M. E., Neuro-anatomical circuits in depression: implications for treatment mechanisms. *Psychopharm. Bull.* **1992**, 28, 261–274.
- DREVETS, W. C., RAICHEL, M. E., Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. *Cognition Emotion* **1998**, 12, 353–385.
- DREVETS, W. C., TODD, R. D., Depression, mania and related disorders. In GUZE, S. B. (Ed.), *Adult Psychiatry*. St. Louis, MO: Mosby Press, **1997**, 99–141.
- DREVETS, W. C., BOGERS, W., RAICHEL, M. E., Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur. Neuropsychopharmacol.* **2002a**, 12, 527–544.
- DREVETS, W. C., BOGERS, W., RAICHEL, M. E., Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur. J. Neuropharmacol.* **2002b**.
- DREVETS, W. C., FRANK, E., PRICE, J. C., KUPFER, D. J., HOLT, D., GREER, P. J., HUANG, H., GAUTIER, C., MATHIS, C., PET imaging of serotonin 1A receptor binding in depression. *Biol. Psychiatry* **1999**, 46, 1375–1387.
- DREVETS, W. C., ÖNGÜR, D., PRICE, J. L., Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for pathophysiology of familial mood disorders. *Mol. Psychiatry* **1998**, 3, 220–226.
- DREVETS, W. C., PRICE, J. L., BARDGETT, M. E., REICH, T., TODD, R., RAICHEL, M. E., Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and stressed plasma cortisol levels. *Pharmacol. Biochem. Behav.* **2002c**, 71, 431–447.

- DREVETS, W. C., PRICE, J. L., SIMPSON, J. R., TODD, R. D., REICH, T., VANNIER, M., RAICHLER, M. E., Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **1997**, 386, 824–827.
- DREVETS, W. C., SIMPSON, J. R., RAICHLER, M. E., Regional blood flow changes in response to phobic anxiety and habituation. *J. Cerebral Blood Flow Metab.* **1995a**, 15, S856.
- DREVETS, W. C., SPITZNAGEL, E., RAICHLER, M. E., Functional anatomical differences between major depressive subtypes. *J. Cerebral Blood Flow Metab.* **1995b**, 15, S93.
- DREVETS, W. C., THASE, M., PRICE, J. C., BOGERS, W., GREER, P. J., KUPFER, D. K., Antidepressant drug effects on regional glucose metabolism in major depression. *Soc. Neurosci. Abstr.* **2002d**, 32 (in press).
- DREVETS, W. C., THASE, M., PRICE, J., MATHIS, C., KUPFER, D. J., Serotonin type-1A receptor imaging in unipolar and bipolar depression. *Biol. Psychiatry* **2002e**, 51, 102S.
- DREVETS, W. C., THASE, M., BOGERS, W., GREER, P., KUPFER, D. J., Glucose metabolic correlates of depression severity and antidepressant treatment response. *Biol. Psychiatry* **2002f**, 51, 176S.
- DREVETS, W. C., VIDEEN, T. O., PRICE, J. L., PRESKORN, S. H., CARMICHAEL, S. T., RAICHLER, M. E., A functional anatomical study of unipolar depression. *J. Neurosci.* **1992**, 12, 3628–3641.
- DREVETS, W. C., VIDEEN, T. O., SNYDER, A. Z., MACLEOD, A. K., RAICHLER, M. E., Regional cerebral blood flow changes during anticipatory anxiety. *Soc. Neurosci. Abstr.* **1994**, 20, 368.
- DUPONT, R. M., JERNIGAN, T. L., HEINDEL, W., et al., Magnetic resonance imaging and mood disorders – localization of white matter and other subcortical abnormalities. *Arch. Gen. Psychiatry* **1995**, 52, 747–755.
- EASTWOOD, S. L., HARRISON, P. J., Hippocampal synaptic pathology in schizophrenia, bipolar disorder, and major depression: a study of complexin mRNAs. *Mol. Psychiatry* **2000**, 5, 425–432.
- EASTWOOD, S. L., HARRISON, P. J., Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin, GAP 43, and the complexins. *Brain Res. Bull.* **2001**, 55, 569–578.
- EBERT, D., FEISTEL, H., LOEW, T., PIRNER, A., Dopamine and depression-striatal dopamine D2 receptor: SPECT before and after antidepressant therapy. *Psychopharmacology* **1996**, 126, 91–94.
- ESCALONA, P. R., McDONALD, W. M., DORAISWAMY, P. M., et al., Reduction of cerebellar volume in major depression: A controlled MRI study. *Depression* **1993**, 1, 156–158.
- FEINSTEIN, A., ROY, P., LOBAUGH, N., et al., Structural brain abnormalities in multiple sclerosis patients with major depression. *Neurology* **2004**, 62, 586–590.
- FRODL, T., MEISENZAHN, E., ZETZSCHE, T., BOTTLENDER, R., BORN, C., GROLL, C., JAGER, M., LEINSINGER, G., HAHN, K., MOLLER, H. J., Enlargement of the amygdala in patients with a first episode of major depression. *Biol. Psychiatry* **2002**, 51, 708–714.
- FRYSZTAK, R. J., NEAFSEY, E. J., The effect of medial frontal cortex lesions on cardiovascular conditioned emotional responses in the rat. *Brain Res.* **1994**, 643, 181–193.
- GARCIA, R., VOUMBA, R.-M., BAUDRY, M., THOMPSON, R. F., The amygdala modulates prefrontal cortex activity relative to conditioned fear. *Nature* **1999**, 402, 294–296.
- GEORGE, M. S., KETTER, T. A., PAREKH, P. I., HORWITZ, B., HERSCOVITCH, P., POST, R. M., Brain activity during transient sadness and happiness in healthy women. *Am. J. Psychiatry* **1995**, 152, 341–351.
- HAMIDI, M., DREVETS, W. C., PRICE, J. L., Glial reduction in the amygdala in major depressive disorder is due to oligodendrocytes. *Biol. Psychiatry* **2004**, 55, 563–569.
- HAUSER, P., ALTSCHULER, L. L., BERRETTINI, W., et al., Temporal lobe measurement in primary affective disorder by magnetic resonance imaging. *J. Neuropsychiatry Clin. Neurosci.* **1989**, 1, 128–134.
- HERMAN, J. P., CULLINAN, W. E., Neurocircuitry of stress: central control of the hypothalamo–pituitary–adrenocortical axis. *Trends Neurosci.* **1997**, 20, 78–84.
- HIRAYASU, Y., SHENTON, M. E., SALISBURY, D. F., KWON, J. S., WIBLE, C. G., FISCHER,

- I. A., YURGELON-TODD, D., ZARATE, C., KIKINIS, R., JOLLESZ, F. A., MCCARLEY, R. W., Subgenual cingulate cortex volume in first-episode psychosis. *Am. J. Psychiatry* **1999**, *156*, 1091–1093.
- HONER, W. G., FALKAI, P., CHEN, C., ARANGO, V., MANN, J. J., DWORKS, A. J., Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience* **1999**, *91*, 1247–1255.
- HUSAIN, M. M., McDONALD, W. M., DORAISWAMY, P. M., et al., A magnetic resonance imaging study of putamen nuclei in major depression. *Psychiatry Res.* **1991**, *40*, 95–99.
- ICHIMIYA, T., SUHARA, T., SUDO, Y., OKUBO, Y., NAKAYAMA, K., NANKAI, M., INOUE, M., YASUNO, F., TAKANO, A., MAEDA, J., SHIBUYA, H., Serotonin transporter binding in patients with mood disorders: a PET study with [¹¹C](+)McN5652. *Biol. Psychiatry* **2002**, *51*, 715–722.
- JOHNSTON-WILSON, N. L., SIMS, C. D., HOFMANN, J. P., ANDERSON, L., SHORE, A. D., TORREY, E. F., YOLKEN, R. H., Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder. The Stanley Neuropathology Consortium. *Mol. Psychiatry* **2000**, *5*, 142–149.
- KENNEDY, S. H., EVANS, K. R., KRUGER, S., MAYBERG, H. S., MEYER, J. H., MCCANN, S., ARIFUZZMAN, A. I., HOULE, S., VACCARINO, F. J., Changes in regional brain glucose metabolism measured with PET after paroxetine treatment of major depression. *Am. J. Psychiatry* **2001**, *158*, 899–905.
- KETTER, T. A., KIMBRELL, T. A., GEORGE, M. S., DUNN, R. T., SPEER, A. M., BENSON, B. E., WILLIS, M. W., DANIELSON, A., FRYE, M. A., HERSCOVITCH, P., POST, R. M., Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol. Psychiatry* **2001**, *49*, 97–109.
- KIMBRELL, T. A., KETTER, T. A., GEORGE, M. S., LITTLE, J. T., BENSON, B. E., WILLIS, M. W., HERSCOVITCH, P., POST, R. M., Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. *Biol. Psychiatry* **2002**, *51*, 237–252.
- KRISHNAN, K. R. R., Neuroanatomical substrates of depression in the elderly. *J. Geriatr. Psychiatry Neurol.* **1993**, *1*, 39–58.
- KRISHNAN, K. R. R., DORAISWAMY, P. M., FIGIEL, G. S., et al., Hippocampal abnormalities in depression. *J. Neuropsychiatry Clin. Neurosci.* **1991a**, *3*, 387–391.
- KRISHNAN, K. R. R., DORAISWAMY, P. M., LURIE, S. N., et al., Pituitary size in depression. *J. Clin. Endocrinol. Metab.* **1991b**, *72*, 256–259.
- KRISHNAN, K. R. R., McDONALD, W. M., ESCALONA, P. R., et al., Magnetic resonance imaging of the caudate nuclei in depression: preliminary observations. *Arch. Gen. Psychiatry* **1992**, *49*, 553–557.
- KRISHNAN, K. R. R., McDONALD, W. M., DORAISWAMY, P. M., et al., Neuroanatomical substrates of depression in the elderly. *Eur. Arch. Psychiatry Neurosci.* **1993**, *243*, 41–46.
- LEDoux, J. E., THOMPSON, M. E., IADECOLA, C., TUCKER, L. W., REIS, D. J., Local cerebral blood flow increases during auditory and emotional processing in the conscious rat. *Science* **1983**, *221*, 576–578.
- LENZE, E. J., SHELINE, Y. I., Absence of striatal volume differences between depressed subjects with no comorbid medical illness and matched comparison subjects. *Am. J. Psychiatry* **1999**, *156*, 1989–1991.
- LINKS, J. M., ZUBIETA, J. K., MELTZER, C. C., STUMPF, M. J., FROST, J. J., Influence of spatially heterogeneous background activity on “hot object” quantitation in brain emission computed tomography. *J. Comput. Assist. Tomogr.* **1996**, *20*, 680–687.
- LOPEZ, J. F., CHALMERS, D. T., LITTLE, K. Y., WATSON, S. J., A. E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. *Biol. Psychiatry* **1998**, *43*, 547–573.
- LUDWIN, S. K., The function of perineuronal satellite oligodendrocytes: an immunohistochemical study. *Neuropathol. Appl. Neurobiol.* **1984**, *10*, 143–149.
- MAGISTRETTI, P. J., PELLERIN, L., Cellular mechanisms of brain imaging metabolism and their relevance to functional

- brain imaging. *Phil. Trans. Royal Soc. London – Series B: Biol. Sci.* **1999**, 354, 1155–1163.
- MALISON, R. T., PRICE, L. H., BERMAN, R., VAN DYCK, C. H., PELTON, G. H., CARPENTER, L., SANACORA, G., OWENS, M. J., NEMEROFF, C. B., RAJEEVAN, N., BALDWIN, R. M., SEIBYL, J. P., INNIS, R. B., CHARNEY, D. S., Reduced brain serotonin transporter availability in major depression as measured by [123 I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)-tropane and single photon emission computed tomography. *Biol. Psychiatry* **1998**, 44, 1090–1098.
- MANJI, H., DREVETS, W. C., CHARNEY, D., The cellular neurobiology of depression. *Nature Med.* **2001**, 7, 541–547.
- MANN, J. J., HUANG, Y. Y., UNDERWOOD, M. D., KASSIR, S. A., OPPENHEIM, S., KELLY, T. M., DWORK, A. J., ARANGO, Z. V., A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch. Gen. Psychiatry* **2000**, 57, 729–738.
- MARTINEZ, P., RONSAVILLE, D., GOLD, P. W., HAUSER, P., DREVETS, W. C., Morphometric abnormalities in adolescent offspring of depressed mothers. *Soc. Neurosci. Abstr.* **2002**, 32.
- MATUTE, C., SANCHEZ-GOMEZ, M. V., MARTINEZ-MILLAN, L., MILEDI, R., Glutamate receptor-mediated toxicity in optic nerve oligodendrocytes. *Proc. Natl. Acad. Sci. USA* **1997**, 94, 8830–8835.
- MAYBERG, H. S., BRANNAN, S. K., MAHURIN, R. K., JERABEK, P. A., BRICKMAN, J. S., TEKELL, J. L., SILVA, J. A., MCGINNIS, S., GLASS, T. G., MARTIN, C. C., FOX, P. T., Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* **1997**, 8, 1057–1061.
- MAYBERG, H. S., BRANNAN, S. K., TEKELL, J. L., SILVA, J. A., MAHURIN, R. K., MCGINNIS, S., JERABEK, P. A., Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol. Psychiatry* **2000**, 48, 830–843.
- MAYBERG, H. S., LEWIS, P. J., REGINALD, W., WANGER JR., H. N., Paralimbic hypoperfusion in unipolar depression. *J. Nucl. Med.* **1994**, 35, 929–934.
- MAYBERG, H. S., LIOTTI, M., BRANNAN, S. K., MCGINNIS, B. S., MAHURIN, R. K., JERABEK, P. A., et al., Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry* **1999**, 156, 675–682.
- MAYBERG, H. S., STARKSTEIN, S. E., MORRIS, P. L., et al., Remote cortical hypometabolism following focal basal ganglia injury: relationship to secondary changes in mood. *Neurology* **1991**, 41 (Suppl.), 266.
- MAYBERG, H. S., STARKSTEIN, S. E., PEYSER, C. E., BRANDT, J., DANNALS, R. F., FOLSTEIN, S. E., Paralimbic frontal lobe hypometabolism in depression associated with Huntington's disease. *Neurology* **1992**, 42, 1791–1797.
- MAYBERG, H. S., STARKSTEIN, S. E., SADZOT, B., PREZIOSI, T., ANDREZEJEWSKI, P. L., DANNALS, R. F., WANGER JR., H. N., ROBINSON, R. G., Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Ann. Neurol.* **1990**, 28, 57–64.
- MACFALL, J. R., PAYNE, M. E., PROVENZALE, J. E., KRISHNAN, K. R. R., Medial orbital frontal lesions in late onset depression. *Biol. Psychiatry* **2001**, 49, 803–806.
- MAZZIOTTA, J. C., PHELPS, M. E., PLUMMER, D., KUHLE, D. E., Quantitation in positron emission computed tomography. 5. Physical-anatomical effects. *J. Comput. Assist. Tomogr.* **1981**, 5, 734–743.
- MCDONALD, W. M., KRISHNAN, K. R. R., DORAISWAMY, P. M., et al., Occurrence of subcortical hyperintensities in elderly subjects with mania. *Psychiatry Res.* **1991**, 40, 211–220.
- MC EWEN, B. S., Stress and hippocampal plasticity. *Ann. Rev. Neurosci.* **1999**, 22, 105–122.
- MELTZER, C. C., PRICE, J. C., MATHIS, C. A., GREER, P. J., CANTWELL, M. N., HOUCK, P. R., MULSANT, B. H., BEN-ELIEZER, D., LOPRESTI, B., DEKOSKY, S. T., REYNOLDS III, C. F., PET imaging of serotonin type 2A receptors in late-life neuropsychiatric disorders. *Am. J. Psychiatry* **1999**, 156, 1871–1878.
- MERVAALA, E., FOHR, J., KONONEN, M., VALKONEN-KORHONEN, M., VAINIO, P., PARTANEN, K., et al., Quantitative MRI of

- the hippocampus and amygdala in severe depression. *Psychol. Med.* **2000**, *30*, 117–125.
- MEYER, J. H., KAPUR, S., HOULE, S., DASILVA, J., OWCZAREK, B., BROWN, G. M., WILSON, A. A., KENEDY, S. H., Prefrontal cortex 5-HT₂ receptors in depression: An [¹⁸F] Setoperone PET imaging study. *Am. J. Psychiatry* **1999**, *156*, 1029–1034.
- MEYER, J. H., KRUGER, S., WILSON, A. A., CHRISTENSEN, B. K., GOULDING, V. S., SCHAFER, A., MINIFIE, C., HOULE, S., KENNEDY, S. H., Lower dopamine transporter binding potential in striatum during depression. *NeuroReport* **2001**, *12*, 4121–4125.
- MORGAN, M. A., LEDOUX, J. E., Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav. Neurosci.* **1995**, *109*, 681–688.
- NEMEROFF, C. B., KRISHNAN, K. R. R., REED, D., et al., Adrenal gland enlargement in major depression: a computed tomographic study. *Arch. Gen. Psychiatry* **1992**, *49*, 384–387.
- NEUMEISTER, A., BAIN, E., NUGENT, A., CARSON, R. E., BONNE, O., LUCKENBAUGH, D., ECKELMAN, W., HERSCOVITCH, P., CHARNEY, D. S., DREVETS, W. C., Reduced serotonin type 1A receptor binding in panic disorder. *J. Neurosci.* **2004**, *24*, 589–591.
- NEUMEISTER, A., NUGENT, A. C., WALDECK, T., GERACI, M., SCHWARZ, M., BONNE, O., LUCKENBAUGH, D., HERSCOVITCH, P., CHARNEY, D. S., DREVETS, W. C., Behavioral and neural responses to tryptophan depletion in unmedicated remitted patients with major depressive disorder and controls. *Arch. Gen. Psychiatry* (in press).
- NOBLER, M. S., OQUENDO, M. A., KEGELES, L. S., MALONE, K. M., CAMPBELL, C., SACKEIM, H. A., MANN, J. J., Decreased regional brain metabolism after ECT. *Am. J. Psychiatry* **2001**, *158*, 305–308.
- NOBLER, M. S., ROOSE, S., PROHOVNIK, I., MOELLER, J. R., LOUIE, J., VAN HEERTUM, R. L., SACKEIM, H. A., Regional cerebral blood flow in mood disorders. V. Effects of antidepressant medication in late-life depression. *Am. J. Geriatr. Psychiatry* **2000**, *8*, 289–296.
- NOBLER, M. S., SACKEIM, H. A., PROHOVNIK, I., MOELLER, J. R., MUKHERJEE, S., SCHNUR, D. B., PRUDIC, J., DEVANAND, D. P., Regional cerebral BF in mood disorders. III. Treatment and clinical response. *Arch. Gen. Psychiatry* **1994**, *51*, 884–897.
- NOFZINGER, E. A., NICHOLS, T. E., MELTZER, C. C., PRICE, J., STEPPE, D. A., MIEWALD, J. M., KUPFER, D. J., MOORE, R. Y., Changes in forebrain function from waking to REM-sleep in depression: preliminary analyses of [¹⁸F]FDG PET studies. *Psychiatry Res.* **1999**, *91*, 59–78.
- NOGA, J. T., VLADAR, K., TORREY, E. F., A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. *Psychiatry Res.* **2001**, *106*, 25–34.
- NOWAK, G., ORDWAY, G. A., PAUL, I. A., Alterations in the N-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. *Brain Res.* **1995**, *675*, 157–164.
- NUGENT, A. C., WOOD, S., BAIN, E. E., MAH, L., CANNON, D., NEUMIESTER, A., ZARATE, C., MARRETT, S., KORETSKY, A., TALAGALA, L., PRICE, J., CHARNEY, D., DREVETS, W. C., High resolution MRI neuro-morphometric assessment of the hippocampal subiculum in mood disorders. ISMRM Twelfth Scientific Meeting, **2004**.
- ÖNGÜR, D., PRICE, J. L., The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys, and humans. *Cereb. Cortex* **2000**, *10*, 206–219.
- ÖNGÜR, D., DREVETS, W. C., PRICE, J. L., Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 13290–13295.
- OSUCH, E. A., KETTER, T. A., KIMBRELL, T. A., GEORGE, M. S., BENSON, B. E., WILLIS, M. W., HERSCOVITCH, P., POST, R. M., Regional cerebral metabolism associated with anxiety symptoms in affective disorder patients. *Biol. Psychiatry* **2000**, *48*, 1020–1023.
- PANTEL, J., SCHRODER, J., ESSIG, M., et al., Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J. Affect. Disord.* **1997**, *42*, 69–83.
- PARSEY, R. V., OQUENDO, M. A., SIMPSON, N. R., HUANG, Y., VAN HEERTUM, R.,

- ARANGO, V., MANN, J. J., Altered serotonin 1A binding in major depression: a [^{11}C]WAY100635 PET study. 57th Annual Convention and Scientific Program of the Society of Biological Psychiatry. Philadelphia, May 16–18, 2002, Abstract 300. *Biol. Psychiatry* **2002**, 51 (8S), 106S.
- PARSEY, R. V., OQUENDO, M. A., YOLANDA, Z. P., RODENHISER, J., KEGELES, L. S., PRATAP, M., COOPER, T. B., HEERTUM, R. V., MANN, J. J., LARUELLE, M., Dopamine D2 receptor availability and amphetamine-induced dopamine release in unipolar depression. *Biol. Psychiatry* **2001**, 50, 313–322.
- PATTEN, S. B., BECK, C. A., WILLIAMS, J. V., et al., Major depression in multiple sclerosis: a population-based perspective. *Neurology* **2003**, 61, 1524–1527.
- PEARLSON, G. D., BARTA, P. E., POWERS, R. E., MENON, R. R., RICHARDS, S. S., AYLWARD, E. H., FEDERMAN, E. B., CHASE, G. A., PETTY, R. G., TIEN, A. Y., Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. *Biol. Psychiatry* **1997**, 41, 1–14.
- PEARLSON, G. D., WONG, D. F., TUNE, L. E., et al., *In vivo* D₂ dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. *Arch. Gen. Psychiatry* **1995**, 52, 471–477.
- PHILPOT, M. P., BANERJEE, S., NEEDHAM-BENNETT, H., COSTA, D. C., ELL, P. J., $^{99\text{mTc}}$ -HMPAO single photon emission tomography in late life depression: a pilot study of regional cerebral blood flow at rest and during a verbal fluency task. *J. Affect Dis.* **1993**, 28, 233–240.
- PIZZAGALLI, D., PASCUAL MARQUI, R. D., NITSCHKE, J. B., OAKES, T. R., LARSON, C. L., ABERCROMBIE, H. C., et al., Anterior cingulate activity predicts degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am. J. Psychiatry* **2001**, 158, 405–415.
- POSTOLACHE, T. T., MATTHEWS, J. R., TURNER, E. H., BENSON, B. E., GUZMAN, A., ROSENTHAL, N. E., DREVETS, W. C., Cerebral blood flow in depressed individuals with seasonal affective disorder as compared to matched controls. *Chronobiol. Int.* **2002**, 19, 986–987.
- PRICE, J. L., CARMICHAEL, S. T., DREVETS, W. C., Networks related to the orbital and medial prefrontal cortex: a substrate for emotional behavior? *Prog. Brain Res.* **1996**, 107, 523–536.
- RAICHLE, M. E., Circulatory and metabolic correlates of brain function in normal humans. In BROOKHART, J. M., MOUNTCASTLE, V. B. (Eds.), *Handbook of Physiology – The Nervous System V*, Vol. V. Baltimore, MD: American Physiological Society, Chapter 16, **1987**, 643–674.
- RAJKOWSKA, G., HALARIS, A., SELEMON, L. D., Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol. Psychiatry* **2001**, 49, 741–752.
- RAJKOWSKA, G., MIGUEL-HIDALGO, J. J., WEI JINRONG, DILLEY, G., PITTMAN, S. D., MELTZER, H. Y., OVEERHOLSEER, J. C., ROTH, B. L., STOCKMEIER, C. A., Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol. Psychiatry* **1999**, 45, 1085–1098.
- RAUCH, S. L., JENIKE, M. A., ALPERT, N. M., BAER, L., BREITER, H., SAVAGE, C. R., FISCHMAN, A. J., Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch. Gen. Psychiatry* **1994**, 51, 62–70.
- RING, H. A., BENCH, C. J., TRIMBLE, M. R., BROOKS, D. J., FRACKOWIAK, R. S. J., DOLAN, R. J., Depression in Parkinson's Disease: a positron emission study. *Br. J. Psychiatry* **1994**, 165, 333–339.
- ROLLS, E. T., A theory of emotion and consciousness and its application to understanding the neural basis of emotion. In GAZZANIGA, M. (Ed.), *The Cognitive Neurosciences*. Cambridge, MA: MIT Press, **1995**, 1091–1106.
- ROSOKLIJA, G., TOOMAYAN, G., ELLIS, S. P., KELLP, J., MANN, J., LATOV, N., HAYS, A. P., DWORK, A. J., Structural abnormalities in subicular dendrites in subjects with schizophrenia and mood disorders. *Arch. Gen. Psychiatry* **2000**, 57, 349–356.
- ROTHMAN, D. L., et al., *In vivo* nuclear magnetic resonance spectroscopy studies

- of the relationship between the glutamate–glutamine neurotransmitter cycle and functional neuroenergetics. *Phil. Trans. Roy. Soc. Lond – Series B: Biol. Sci.* **1999**, 354, 1165–1177.
- RUBIN, R. T., MANDELL, A. J., CRANDALL, P. H., Corticosteroid responses to limbic stimulation in man: localization of stimulus sites. *Science* **1966**, 153, 767–768.
- RUBIN, R. T., PHILLIPS, J. J., SADOW, T. F., et al., Adrenal gland volume in major depression: increase during the depressive episode and decrease with successful treatment. *Arch. Gen. Psychiatry* **1995**, 52, 213–218.
- SARGENT, P. A., KJAER, K. H., BENCH, C. J., RABINER, E. A., MESSA, C., MEYER, J., GUNN, R. N., GRASBY, P. M., COWEN, P. J., Brain serotonin_{1A} receptor binding measured by positron emission tomography with [¹¹C]WAY-100635: effects of depression and antidepressant treatment. *Arch. Gen. Psychiatry* **2000**, 57, 174–180.
- SAXENA, S., BRODY, A. L., HO, M. L., ALBORZIAN, S., MAIDMENT, K., ZOHRABI, N., HO, M. K., HUANG, S. C., WU, H. M., BAXTER, L. R., Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs. major depression. *Arch. Gen. Psychiatry* **2002**, 59, 250–261.
- SCHNEIDER, F., GUR, R. E., ALAVI, A., MOZLEY, L. H., SMITH, R. J., MOZLEY, P. D., CENSITS, D. M., GUR, R. C., Mood effects on limbic blood flow correlate with emotion self-rating: a PET study with oxygen-15 labeled water. *Psychiatry Res. Neuroimaging* **1995**, 61, 265–283.
- SCHULTZ, W., Dopamine neurons and their role in reward mechanisms. *Curr. Opin. Neurobiol.* **1997**, 7, 191–197.
- SCHWARTZ, J. M., BAXTER, L. R., MAZZIOTA, J. C., GERNER, R. H., PHELPS, M. E., The differential diagnosis of depression: relevance of Positron Emission Tomography studies of cerebral glucose metabolism to the bipolar–unipolar dichotomy. *JAMA* **1987**, 258, 1368–1373.
- SHAH, S. A., DORAISWAMY, P. M., HUSAIN, M. M., et al., Posterior fossa abnormalities in major depression: a controlled magnetic resonance imaging study. *Acta Psychiatr. Scand.* **1992**, 85, 474–479.
- SHAH, P. J., EBMEIER, K. P., GLABUS, M. F., GOODWIN, G. M., Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br. J. Psychiatry* **1998**, 172, 527–532.
- SHAH, P. J., OGILVIE, A. D., GOODWIN, G. M., EBMEIER, K. P., Clinical and psychometric correlates of dopamine D₂ binding in depression. *Psychol. Med.* **1997**, 27, 1247–1256.
- SHELINE, Y. I., GADO, M. H., PRICE, J. L., Amygdala core nuclei volumes are decreased in recurrent major depression. *Neuroreport* **1998**, 9, 2023–2028.
- SHELINE, Y. I., SANGHAVI, M., MINTUN, M. A., GADO, M., Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J. Neurosci.* **1999**, 19, 5034–5043.
- SHELINE, Y. I., WANG, P. W., GADO, M. H., CSERNANSKY, J. G., VANNIER, M. W., Hippocampal atrophy in recurrent major depression. *Proc. Natl. Acad. Sci. USA* **1996**, 93, 3908–3913.
- SHEN, J., et al., Determination of the rate of the glutamate/glutamine cycle in the human brain by *in vivo* ¹³C NMR. *Proc. Natl. Acad. Sci. USA* **1999**, 96, 8235–8240.
- SHULMAN, R. G., ROTHMAN, D. L., Interpreting functional imaging studies in terms of neurotransmitter cycling. *Proc. Natl. Acad. Sci. USA* **1998**, 95, 11993–11998.
- SIBSON, N. R., et al., Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. *Proc. Natl. Acad. Sci. USA* **1998**, 95, 316–321.
- SIEGLE, G. J., KONECKY, R. O., THASE, M. E., CARTER, C. S., Relationships between amygdala volume and activity during emotional information processing tasks in depressed and never-depressed individuals: an fMRI investigation. *Ann. NY Acad. Sci.* **2003**, 985, 481–484.
- SIEGLE, G. J., STEINHAEUER, S. R., THASE, M. E., STENGER, V. A., CARTER, C. C., Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol. Psychiatry* **2002**, 51, 693–707.
- SMITH, G. S., REYNOLDS, C. F., POLLOCK, B., DERBYSHIRE, S., NOFZINGER, E., DEW, M. A., HOUCK, P. A., MILKO, D., MELTZER, C. C., KUPFER, D. J., Cerebral

- glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. *Am. J. Psychiatry* **1999**, *156*, 683–689.
- STARKSTEIN, S. E., ROBINSON, R. G., Affective disorders and cerebral vascular disease. *Br. J. Psychiatry* **1989**, *154*, 170–182.
- STEFFENS, D. C., BYRUM, C. E., MCQUOID, D. R., GREENBERG, D. L., PAYNE, M. E., BLITCHINGTON, T. F., MACFALL, J. R., KRISHNAN, K. R., Hippocampal volume in geriatric depression. *Biol. Psychiatry* **2000**, *48*, 301–309.
- STRAKOWSKI, S. M., DELBELLO, M. P., SAX, K. W., ZIMMERMAN, M. E., SHEAR, P. K., HAWKINS, J. M., LARSON, E. R., Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Arch. Gen. Psychiatry* **1999**, *56*, 254–260.
- SUHARA, T., NAKAYAMA, K., INOUE, O., FUKUDA, H., SHIMIZU, M., MORI, A., TATENO, Y., D1 Dopamine receptor binding in mood disorders measured by PET. *Psychopharmacology* **1992**, *106*, 14–18.
- SULLIVAN, R. M., GRATTON, A., Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. *J. Neurosci.* **1999**, *19*, 2834–2840.
- SWAYZE, V. W., ANDREASEN, N. C., ALLIGER, R. J., et al., Structural brain abnormalities in bipolar affective disorder. Ventricular enlargement and focal signal hyperintensities. *Arch. Gen. Psychiatry* **1990**, *47*, 1054–1059.
- TALAIRACH, T., *Co-Planar Stereotaxic Atlas of the Human Brain*. Stuttgart: Thieme, **1988**.
- THOMAS, K. M., DREVETS, W. C., DAHL, R. E., RYAN, N. D., BIRMAHER, B., ECCARD, C. H., AXELSON, D., WHALEN, P. J., CASEY, B. J., Abnormal amygdala response to faces in anxious and depressed children. *Arch. Gen. Psychiatry* **2001**, *58*, 1057–1063.
- TIMMS, R. J., Cortical inhibition and facilitation of the defence reaction. *J. Physiol. Lond.* **1977**, *266*, 98P–99P.
- URANOVA, N., ORLOVSKAYA, D., VIKHREVA, O., ZIMINA, I., KOLOMEETS, N., VOSTRIKOV, V., RACHMANOVA, V., Electron microscopy of oligodendroglia in severe mental illness. *Brain Res. Bull.* **2001**, *55*, 597–610.
- URANOVA, N. A., VOSTRIKOV, V. M., ORLOVSKAYA, D. D., RACHMANOVA, V. I., Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr. Res.* **2004**, *67* (2–3), 269–275.
- VAKILI, K., PILLAY, S. S., LAFER, B., FAVA, M., RENSHAW, P. F., BONELLO-CINTRON, C. M., Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. *Biol. Psychiatry* **2000**, *47*, 1087–1090.
- VEITH, R. C., LEWIS, N., LINARES, O. A., BARNES, R. F., RASKIND, M. A., VILLACRES, E. C., MURBURG, M. M., ASHLEIGH, E. A., CASTILLO, S., PESKIND, E. R., PASCUALY, M., HALTER, J. B., Sympathetic nervous system activity in major depression. *Arch. Gen. Psychiatry* **1994**, *51*, 411–422.
- VIDEBECH, P., RAVNKILDE, B., PEDERSEN, A. R., EGANDER, A., LANDBO, B., RASMUSSEN, N. A., ANDERSEN, F., STODKILDE-JORGENSEN, H., GJEDDE, A., ROSENBERG, R., The Danish PET/ depression project: PET findings in patients with major depression. *Psychol. Med.* **2001**, *31*, 1147–1158.
- VOGT, B., Structural organization of cingulate cortex. In VOGT, B. A., GABRIEL, M. (Eds.), *Neurobiology of Cingulate Cortex and Limbic Thalamus*. Boston: Birkhauser, **1993**.
- VON GUNTEN, A., FOX, N. C., CIPOLOTTI, L., RON, M. A., A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. *J. Neuropsychiatry Clin. Neurosci.* **2000**, *12*, 493–498.
- VYTHILINGAM, M., HEIM, C., NEWPORT, J., MILLER, A. H., ANDERSON, E., BRONEN, R., BRUMMER, M., STAIB, L., VERMETTEN, E., CHARNEY, D. S., NEMEROFF, C. B., BREMNER, J. D., Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am. J. Psychiatry* **2002**, *159*, 2072.
- WEBSTER, M. J., KNABLE, M. B., JOHNSTON-WILSON, N., NAGATA, K., INAGAKI, M., YOLKEN, R. H., Immunohistochemical localization of phosphorylated glial fibrillary acidic protein in the prefrontal cortex and hippocampus from patients with schizophrenia, bipolar disorder, and depression. *Brain Behav. Immun.* **2001**, *15*, 388–400.

- WILSON, J., KUPFER, D. J., THASE, M., BOGERS, W., GREER, P., DREVETS, W. C., Ventral striatal metabolism is increased in depression, and decreases with treatment. *Biol. Psychiatry* **2002**, *51*, 122S.
- WOOTEN, G. F., COLLINS, R. C., Metabolic effects of unilateral lesion of the substantia nigra. *J. Neurosci.* **1981**, *1*, 285–291.
- WU, J. C., GILLIN, J. C., BUCHSBAUM, M. S., HERSHEY, T., JOHNSON, J. C., BUNNEY, W. E., Effect of sleep deprivation on brain metabolism of depressed patients. *Am. J. Psychiatry* **1992**, *149*, 538–543.
- ZIS, K. D., ZIS, A. P., Increased adrenal weight in victims of violent suicide. *Am. J. Psychiatry* **1987**, *144*, 1214–1215.

18

Dysregulation of Circadian Rhythms in Mood Disorders: Molecular Mechanisms

Blynn G. Bunney, Steven G. Potkin and William E. Bunney

Abstract

There is a growing body of evidence to suggest that abnormal circadian function may be involved in behaviors associated with major depressive disorder (MDD), bipolar disorder (BPD) and seasonal affective disorder (SAD). Data include observations of disturbances in diurnal rhythms of circadian-regulated processes including sleep, hormones and temperature. Circadian manipulations such as sleep deprivation, phase advance and bright light therapy can often produce robust and rapid antidepressant responses in a subgroup of patients. One purported role of circadian clock genes is to help in the entrainment or adaptation of organisms to changes in the length of the photoperiod. It is hypothesized that a subgroup of mood disorder patients may have abnormalities in entrainment-related mechanisms. SAD patients are of particular interest in that they are characterized by mood changes that fluctuate in tandem with the change in seasons, frequently with a worsening of depressive symptoms in low light conditions (fall, winter and more frequently during “dark” months at extreme latitudes) and a remission in spring and summer during longer daylight periods. Converging evidence indicates that the primary site of the mammalian circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. This relatively small but diverse nucleus provides the master control of central as well as peripheral clock gene function. The SCN contains core clock genes that appear essential to the maintenance of circadian rhythms throughout the organism. It is theorized that abnormalities in these core clock genes or their promoters may play either a direct or indirect role in the etiology of mood disorders. Recently identified mutant core clock genes have been demonstrated to have the capacity to slow, speed or even stop circadian oscillations. This chapter focuses on evidence from animal and clinical data supporting the hypothesis of abnormal clock gene function in mood disorders (MDD, BPD and SAD), the efficacy of circadian manipulations in these disorders and suggests a strategy for the future study of core clock genes in the SCN of patients and controls.

18.1

Introduction

The recent behavioral and molecular characterization of clock genes is providing new clues to the possible role of altered circadian genes in major mood disorders including bipolar disorder (BPD), major depressive disorder (MDD) and seasonal affective disorder (SAD). Diurnal abnormalities are characteristic of these illnesses and include: disturbances in the sleep/wake cycle; abnormalities in clock-regulated hormone secretion; abnormal patterns of nocturnal core body temperature; and symptoms of depression and mania that show a pattern of variation over the course of the day. Some patients exhibit predictable and regularly occurring switches between depression and mania. Switches can occur seasonally as in SAD patients or sometimes as rapidly as every few hours for periods of weeks. Circadian manipulations involving bright light therapy and phase advance of sleep can produce rapid antidepressant effects. Taken together, these data support a role for abnormal clock gene function in a subgroup of mood disorder patients. The identification of novel clock genes and their potential roles in humans provides new directions for future research and treatments in the major mood disorders.

18.2

Evolutionary-conserved Clock Genes

Clock genes have evolutionary-conserved structures that are found in virtually every eukaryotic cell ranging from single cell organisms to humans. These genes drive circadian rhythms by means of a complex set of transcription factors that are associated with autoregulatory feedback loops. In the presence of light/dark cycles and other environmental changes, organisms adapt via entrainment mechanisms that affect transcriptional cycles. Entrainment to the 24-h light/dark cycle involves a cascade of molecular events that facilitate the daily synchronization of thousands of genes throughout the organism. The “generic” circadian clock serves three functions: (1) can spontaneously maintain sustained oscillations (endogenous rhythms) in the absence of environmental cues; (2) functionally links endogenous rhythms to changes in environmental stimuli (e.g. light) via an input pathway; and (3) regulates downstream physiological and behavioral rhythms via an output pathway. These actions are mediated through an evolutionary-conserved bHLH (basic helix-loop-helix)-PAS period clock protein (PER), aryl hydrocarbon receptor nuclear translocator (ARNT) and single-minded protein (SIM). The PAS domain and its proteins comprise a prominent class of transcriptional factors that mediate protein–protein interactions and regulate circadian rhythms. These domains are found in clock genes which span over 700,000 years of evolution and have been observed in plants (e.g. photoactive yellow protein), in *Neurospora* (e.g. mesophytochromes and algae cytochromes), in *Drosophila* and in mammals. Each of these clock-associated genes is almost identical in respect to their PAS domain, suggesting a common evolutionary origin and conservation of structure [1]. Physiological

abnormalities associated with major mood disorders are mediated by PAS domains, either directly or indirectly, to influence the regulation of sleep, hormones (melatonin, cortisol, growth hormone) and core body temperature. Studies of the neural PAS (NPAS) gene family are providing intriguing data [2, 3] in psychiatric disorders. New data suggests the involvement of NPAS3 in schizophrenia [3] and of NPAS2 in seasonal affective disorder (SAD) [2]. These genes may play significant roles in brain development (npas3) and in the regulation of the core circadian clock (npas2) [4, 5].

18.3

Selected Research Strategies

Research strategies for investigating clock genes in mammals include the characterization of clock genes by genotyping, expression profiling and the cellular localization of genes to specific tissues. Microarrays provide a method for screening tens of thousands of genes at a time, quantitative real-time reverse-transcriptase polymerase chain reaction (qRT-PCR) validates the initial microarray findings, and *in situ* hybridization histochemistry (ISH) can localize the expressed genes to specific tissue and cell type. Studies in postmortem human brain tissue have recently established the importance of high quality RNA in evaluating gene function [6, 7]. Additional strategies for the study of circadian gene function includes the study of specialized “immortalized cells” which are individual cultured mammalian fibroblasts that are rhythmically induced with serum shock which serve as simple models of circadian gene expression [8]. The cultured fibroblasts and tissue explants can then be analyzed with microarrays and related analyses. A novel cell line has been developed which is derived from rat suprachiasmatic nucleus (SCN) and exhibits circadian oscillations of glucose utilization, expression of neuropeptides (arginine vasopressin (AVP), vasointestinal peptide (VIP)) and melatonin [9, 10]. Cultures from this SCN cell line, in contrast to fibroblasts, can restore locomotor activity in arrhythmic SCN-lesioned rats. Finally, clock gene promoters which drive a luciferase reporter gene allow the continuous monitoring of clock gene activity (luciferase constructs can be fused to the promoter regions of clock genes). Circadian reporter gene expression is found in mammalian liver, lung, skeletal muscle and many brain regions [11, 12].

Since the discovery of the first clock genes in the fruit fly, *Drosophila* [13, 14] many hundreds of cycling genes have been identified. However, only a few of these genes are considered essential to SCN function. These genes, which are evolutionarily conserved, are referred to as core clock genes as they confer essential functions to the SCN circadian clock. Information from positional cloning, nucleotide sequences of known clock genes and genome databases has been very helpful in the identification of novel cycling genes. Additionally, it is now possible to screen the entire coding regions of genes with the polymerase chain reaction (PCR) to search for polymorphisms, a technique that has been used successfully in the identification of three polymorphisms in the human clock gene (CLOCK) [15].

The identification of novel genes, proteins and functional polymorphisms are redefining our understanding of many diseases (mutations in clock genes may be associated with diseases such as cancer [16, 17], viral diseases [18] and mood disorders).

18.4 Mammalian Clock Genes

Non-human primate brain has approximately 650 cycling transcripts of clock genes with the majority localized to, but not exclusively in, the suprachiasmatic nucleus (SCN) of the hypothalamus [19]. Clock genes are also found in the mammalian forebrain [4] particularly in regions rich in neuroendocrine cells [19]. It is estimated that 2% of the peripheral nervous system has rhythmic genes [12, 20] although higher concentrations are found in organs such as the heart (8–10%) [12] and liver (9%) [21]. Clock genes, the majority of which belong to a class of transcriptional regulators, have been classified into functional gene clusters and suggest a role for clock genes in the regulation of transcriptional activation, signaling and protein turnover involving ubiquitin-associated factors, proteasome components and Ras/MAPK signaling pathway components [20]. Phase analyses show that the majority of clock genes peak during the subjective day (68%) as compared to subjective night (32%) with a tendency for the genes to peak at a phase corresponding to the “anticipation” of dawn or dusk [20]. Comparisons of central and peripheral clock genes from microarray analyses reveal relatively little overlap in the genes that cycle in the periphery and brain. For example, of the 101 rhythmic clock genes identified in mouse SCN and the 393 rhythmic clock genes found in mouse liver, only 21 of the identified clock genes exhibited rhythmicity in both tissues [21]. Other differences between brain and periphery involve entrainment periods which can vary dramatically depending on the tissue. With the exception of the liver, which has a relatively rapid entrainment to food, phase resetting in other organs (e.g. kidney, heart, pancreas, and lung) takes place over a period of 5–10 days and appears to be under the entrainment of locomotor activity rather than food (as seen in liver) or light (as occurs in SCN) [22].

18.5 Suprachiasmatic Nucleus (SCN)

One of the most consistent findings from circadian research is the necessity of intact SCN functioning for the maintenance of rhythmicity in gene expression throughout the organism. Ablation studies demonstrate that intact SCN functioning is necessary for the maintenance of circadian rhythms (e.g. hormone levels and behavior) [23]. The SCN, located in the anterior hypothalamus above the optic chiasm, exerts control over multiple effector systems throughout the body by imposing a temporal rhythm on local and peripheral organs. Cytoarchitectural

studies of the SCN reveal a dense, highly complex structure that is anatomically and functionally organized into two compartments, a core and an outer shell, each having the capability of independently generating rhythms. Output from the core is probably modulated by photic entrainment as it is located adjacent to the optic chiasm. It receives dense visual input via the glutamatergic retinohypothalamic tract and serotonergic projections arising from the midbrain raphe. Many SCN neurons are GABAergic and are interconnected via synapses with GABA_A receptors that mediate pre- and postsynaptic control of the circadian clock [23]. The shell, which surrounds the core, is modulated by entraining input from the core and non-visual input from cortical and subcortical regions (e.g. limbic cortex, brainstem, and thalamus). The shell contains mainly arginine vasopressin (AVP)-producing neurons and a smaller population of calretinin (CAR)-producing neurons. The AVP neurons appear to be important in the transduction of SCN rhythms to other areas [24].

The SCN is only one component of a large circadian network comprised of semiautonomous clocks. Clock genes within the SCN provide signals to drive multiple transcriptional/translational feedback loops which help organisms adapt to fluctuating environmental conditions. The next section reviews selected aspects of SCN regulatory feedback loops in mammals. The integration of the various loops to maintain homeostasis appears to require regulation through additional circadian transcription factors to promote synchronization.

18.6 Mammalian Clock Gene System

Figure 18.1 illustrates two of the primary interacting feedback loops involved in the generation of circadian rhythms. Basically, circadian clock genes operate at local and peripheral levels and react through a cascade of molecular events involving gene transcription, translation and post-translational phosphorylation processes. Each cell generates local rhythms through an autoregulatory system composed of transcriptional and post-translational feedback loops. The feedback loops operate by exerting positive and negative controls over the synthesis and repression of clock genes. The positive regulators include the transcription factors CLOCK (circadian locomotor output cycle kaput) and Bmal1 (brain and muscle ARNT-like protein 1). These proteins contain both bHLH and PAS domains (protein–protein binding regions) and serve critical roles in circadian function. The PAS domains enable heterodimerization (PER1/PER2) while the bHLH domain enables binding to E-box (target site for circadian genes [25]) components to promote transcription. In mammals, the heterodimers (Clock/Bmal1 or nPAS2/Bmal1) serve as transcriptional regulators of clock genes (nPAS2 and Clock), although having high sequence homology and many similar actions are differentially expressed in the brain and do not appear to overlap in the same regions. Thus far, it appears that Clock genes are expressed only in the SCN [4, 26]. These heterodimers drive the expression of genes that encode clock components including period (per1, per2, per3) and

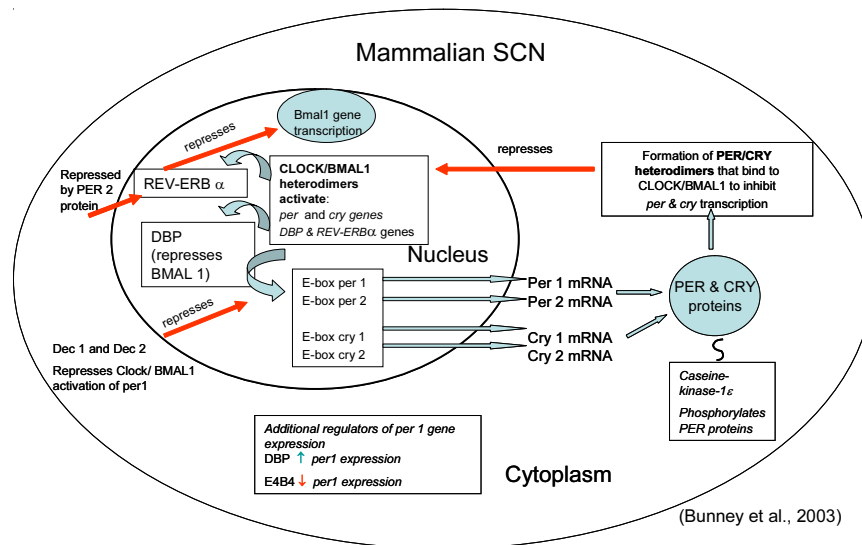


Figure 18.1 Mammalian clock genes and their interaction in the SCN. Clock signals from the SCN affect output pathways including hormones, neuropeptides, and mood and behavioral rhythms.

cryptochrome (*cry1*, *cry2*) genes which contain E-boxes in their promoter regions. The transcription of *per* and *cry* genes into their respective mRNAs takes place in the cell nucleus, after which the mRNAs move to the cytoplasm where their encoded proteins are translated. In the cytoplasm, the *per* proteins form heterodimers (Per1/Per2) that can interact with Cry1 and Cry2 proteins. The proteins then translocate into the nucleus to form stable complexes with their respective genes. In mammals, *per* and *cry* proteins repress Clock/Bmal1 heterodimer activity resulting in the suppression of *per1* and *per2* genes [27]. The approximate 24-h cycle results, in part, from a delay in transcriptional and post-translation processes allowing the protein products of *per* and *cry* to accumulate in the cytoplasm. This cycle is modulated by additional factors, some of which have recently been characterized. Below is a description of some of these factors. Newer studies involving animals with triple mutants are trying to identify the contributions of the individual genes to the clock gene cycle. Data suggests that a single *per* or *cry* gene is not sufficient to drive circadian rhythms [28].

18.7

Entrainment

Circadian rhythms can be entrained to both photic (light) and non-photoc (e.g. serotonin, exercise, fasting) stimuli. Entrainment involves input to the SCN from (1) specialized retinal ganglion cells (which also project to the lateral geniculate

nucleus), (2) serotonin neurons in the raphe nuclei [29, 30] and (3) neurons from the intergeniculate leaflet containing neuropeptide Y (NPY) [31]. A major output from the SCN is to the pineal gland which regulates many physiological activities including sleep, nocturnal temperature, and the secretion of cortisol and melatonin.

Both light and melatonin can phase-shift circadian rhythms. Melatonin plays a role in the entrainment of circadian rhythms to seasonal changes in day-length. It is synthesized during the dark period of the 24-h cycles; its onset and/or offset may also serve as a signal of transitions between diurnal and nocturnal circadian phases affecting core body temperature and sleepiness [32]. The duration of melatonin secretion is greater during long winter nights than in the shorter nights of summer. The administration of melatonin during the optimal times of the day can phase advance rhythms and extend the duration of nocturnal melatonin secretion. The administration of melatonin is shown to increase the duration of melatonin secretion (if given at specific times during the day) and has been used as a treatment for SAD patients [33, 34], shift workers [35] and for time-zone travel [35] although its use can be associated with sleepiness as a side-effect [36]. Pinealectomy abolishes the rhythm of circulating melatonin in mammals including humans and is thought to disrupt entrainment to changes in day-length in photoperiodic species [37]. In clinical studies [38] markers of melatonin can help identify “larks and owls” in terms of preference for early or late sleep. The synthesis of melatonin involves serotonin and the enzyme AANAT (arylalkylamine N-acetyltransferase). AANAT is referred to as a “melatonin rhythm enzyme” and is thought to function as a molecular interface [39] to signal seasonal changes and to synchronize day–night cycles [40]. A proposed mechanism for the rhythmic regulation of melatonin synthesis involves the interactions of ICER (inducible cAMP early transcription repressor) and CREM (cyclic-AMP-responsive element modulator) such that increasing amounts of the ICER protein turns off the cAMP inducible genes (including the AANAT gene) that control melatonin synthesis [33, 41].

18.8

Mutant Clock Genes

Mutant clock genes (containing mutations or deletions) can exert a potentially significant effect on the circadian regulation of locomotor activity, sleep, responses to light and hormonal secretions including cortisol and melatonin (see [42, 43] for reviews). Various mutant forms can delay, accelerate, shorten or lengthen circadian rhythms and/or produce arrhythmicity. Moreover, mutant genes can be dominant such that they “override” or interfere with normal function [44]. Mutant clock genes identified in *Drosophila* include: doubletime (*dbt*) which significantly speeds up period length [45], cycle (*cyc*) which alters circadian rhythms by interfering with the transcription of *per* and *tim* genes [46], *per*SLIH which produces a delayed evening peak of locomotion [47], *cryb* mutations which are associated with a poor synchronization to light–dark cycles [48] and *tim*SL mutants which alter period length [49]. In the hamster, the mutant gene, *tau*, produces robust reductions in

the period of circadian activity, melatonin and cortisol rhythms. In mouse, mutant CLOCK-Δ19, after forming a heterodimer with Bmal1, fails to perform its normal action of activating transcription of the period genes [49]. Mutant mice lacking the cryptochrome2 blue light photoreceptor gene (*mcry2*) have a lower sensitivity to acute light induction of *mper1* in the SCN and have an intrinsic circadian period 1 h longer than normal [50]. A novel unique family of putative ion channels associated with voltage-gated sodium and calcium channels has been identified in genomic and cDNA studies of metazoans. Flies with a mutant of this gene (CG1517, *Dmalpha1U*) have an inversion of locomotor activity in light versus dark (and also show changes in the sensitivity to anesthetics). The authors of this study suggest that the altered behaviors of these flies resemble the diurnal variations seen in BPD [51]. Evidence for circadian abnormalities and possible contributions of mutant clock genes to the core pathophysiology of the major mood disorders are reviewed below.

18.9

Clinical Evidence of the Potential Relevance for a Clock Gene Defect in BPD and MDD

Abnormal circadian rhythms may be characterized by mood changes that occur within a 24-h period (diurnal) and/or that are associated with specific seasonal periods. Major mood disorder patients can switch regularly in and out of depression and mania. Rare, but dramatic, are the patients that change from a retarded non-verbal depression to a hyperactive psychotic manic condition within the course of an hour. Longitudinal studies of these patients, sometimes over years, were suggested to reflect an underlying abnormal rhythmic process [52–63]. Switches into mania can be precipitated by virtually all efficacious treatments for depression including those that affect clock genes such as bright light, sleep deprivation, antidepressants (although not all are documented to affect circadian rhythm) and travel across time-zones [64]. The underlying contributions of mutant clock genes to the induction of the switch process have been hypothesized [65]. Subgroups of depressed patients may have clock gene abnormalities related to deficits in photoentrainment [54, 66, 68]. Others, such as the rapidly cycling patients, may have mutant clock genes affecting period length.

18.10

Seasonal Affective Disorder

Seasonal affective disorder (SAD) is characterized by several subtypes of seasonal mood disorders. In typical cases, SAD patients become depressed in winter (shortening of the photoperiod) and go into remission in early spring or summer (lengthening of the photoperiod). SAD affects approximately 1–3% of the population in the United States at temperate latitudes or about 11 million people per year, mostly females. SAD tends to run in families [68] and is heritable as evidenced

by studies in twins [69]. SAD-associated depressive phases include “hibernation-like” activities such as hypersomnia, overeating, and carbohydrate craving. Some patients can become very suicidal. Higher incidences of SAD are reported in latitudes where there are significant decreases in the hours of daylight in fall/winter periods. For example, the incidence of SAD in Maine and Washington (latitudes 45–50°) is over 10% compared to Florida where the incidence is as low as 1.4% [70, 71]. SAD is an issue in susceptible individuals relocating to Northern latitudes and is of concern to US soldiers, for example, who are stationed in Alaska [72]. Additionally, a subgroup of patients is observed to have weather-associated changes in mood [73].

Seasonal patterns of mania (BPD) have also been described [74, 75]. One study estimates that seasonal BPD patients comprise about 20% of the SAD population [75]. Variations in seasonal symptoms include subtypes such as (1) fall/winter depression with or without spring/summer mania or hypomania and (2) spring/summer depression with or without fall/winter mania or hypomania [68]. Seasonal mania is reported to peak in spring and summer in some studies [76–79] but not in others [80, 81]. Additionally, a study of first-episode switches into mania in more than 100 BPD female patients in Korea documents a peak in spring (e.g. March) that correlated with the amount of sunshine [79].

Other temporal variations in mood are associated with diurnal variations in SAD symptoms with a typical pattern of morning worsening [82]. Phase delays in circadian rhythms including cortisol, melatonin and temperature are also characteristic of the illness [83–87]. Finally, recent data implicates seasonal variations in suicide rates associated with hours of sunlight. The incidence of suicide worldwide shows peaks during longer photoperiods (spring and summer) and is at a low during winter months [88, 89] although suicidal thoughts and behaviors of many SAD patients are more frequent during periods of decreased daylight.

18.11 Circadian Manipulations in SAD

Circadian manipulations in SAD include light therapy, sleep deprivation and the administration of melatonin, all of which are associated with improvement in SAD symptoms [86]. The treatment of choice for SAD is light therapy, particularly dawn stimulation [90]. According to the phase-shift hypothesis proposed by Lewy et al. [91] for winter depression, morning light (which causes a circadian phase advance) has a greater antidepressant effect than evening light (which causes a delay). Sleep deprivation is effective for treatment of seasonal depression; however, the response rates are comparable to those among non-seasonal depressed patients [92]. Of interest is a report showing that a subgroup of sleep deprivation responders is more likely to be responders to bright light therapy [93]. Also, the addition of bright light to sleep deprivation may prolong the antidepressant response [94].

These findings raise the question as to whether changes in photic-sensitive clock genes could contribute to downstream antidepressant effects. Evidence for this

comes from a study showing that responders (versus non-responders) to sleep deprivation have attenuated photic responses [95] and that patients treated with lithium compared to non-treated controls have increased thresholds to dark adaptation suggesting a subsensitivity to light [96, 97]. Data in animal studies demonstrate that clorgyline also dampens responsivity to light [96–99]. Physiological studies in mood disorder patients show no changes in retinal sensitivity in lithium-treated BPD patients [100] nor are there physiological differences in light sensitivity between SAD patients and controls [100, 101]. These findings may implicate additional mechanisms, possibly related to photic clock genes. For example, clorgyline, an antidepressant modulates the firing rates of photic input cells (intergeniculate leaflet cells) to the SCN [98].

18.12

Circadian Rhythms in BPD and MDD

A review of studies conducted over more than 25 years suggests that a subgroup of mood disorder patients have altered circadian rhythms. A meta-analysis of 177 studies suggests that circadian rhythm abnormalities recorded during sleep are most likely to distinguish subgroups of mood disorder patients from controls [102]. A subgroup of patients has disturbances in circadian rhythms that are manifested by daily mood swings. Some patients have marked diurnal mood swings in which they are severely psychotically depressed in the early morning and become almost euthymic every evening. This pattern of striking 24-h alterations in mood can persist for many months in untreated individuals. Another rare form of BPD implicating a role for altered clock genes involves a 48-h cycle where patients have been documented to cycle almost without exception from depression to mania every 24 h over a number of years [55, 60, 103, 104]. Elevated nocturnal body temperature is one of the more consistently observed circadian abnormalities in mood disorders [84, 105–108]. This effect may be due to the blunted amplitude of the central circadian pacemaker. However, this is not the case in all patients. Masking effects of nighttime arousal and sleep could complicate the interpretation of some studies [84]. A phase-advance in the overall 24-h pattern of body temperature is reported in many mood disorder patients [52, 83, 109–111]. A non-significant trend has been reported in other studies [105, 106, 112–114]. Von Zerossen et al. [115] reported a lack of phase-advance in patients compared to themselves after clinical recovery. They reported a reduction in the amplitude of body temperature but suggested that it might be due to a negative masking of the temperature rhythm by the patients' sleep disturbances. Also, Buysse et al. [116] studied circadian patterns of sleep episodes in remitted mood disorder patients. They reported no phase or amplitude changes in sleep propensity. However, they note that these patients had only minor sleep changes and normal temperature profiles even while depressed which they suggest could have biased against finding significant differences. In addition, a subgroup of mood disorder patients has increases in diurnal and nocturnal cortisol secretion [105, 117–121]. Phase advances in nocturnal cortisol secretion relative to

sleep onset provide clinical evidence compatible with a disturbance in circadian rhythms [117, 119, 122–124]. Abnormal sleep patterns including shortened REM latency and early morning awakening are associated with mood disorders [125]. It is also suggested that the depressive phase may involve abnormal sensitivity to environmental cues such as light [105]. This could be a result of mutant clock genes or allelic variations, leading to abnormal clock cycles or altered photosensitivity. Circadian abnormalities associated with BPD include disturbances in sleep [126], mood [127], core body temperature [128] and secretion of circadian-regulated hormones including cortisol [129] and melatonin [130]. Longitudinal studies of the switch process in BPD suggest that patients are phase-advanced with lengthened circadian rest–activity cycles [111].

18.13

Manipulations of the Circadian Cycle as Therapeutic Treatment for Mood Disorders

Three treatment approaches, each involving circadian manipulations, have been used to treat mood disorders and may provide important clues concerning the possible role of clock genes. Specifically, sleep deprivation, light therapy, and phase-advance treatments have been used either separately or in combination to treat BPD and other mood disorders. Results from these studies, as reviewed below, document a striking and sometimes rapid 24-h treatment response in a subgroup of BPD patients. Data from these studies support a role for dysregulated clock genes in BPD.

18.13.1

Sleep Deprivation

Sleep deprivation in major depressive disorder and in the depressive phase of BPD is one of the most robust rapidly-acting (response within 24 h) treatments for depression as investigated by Bunney and others [131–137]. BPD patients appear to have higher response rates to sleep deprivation than MDD patients [138, 139]. A review by Wu and Bunney [140] documents that in more than 61 studies with 2000 patients during the last three decades, one night of total sleep deprivation completely reversed the depressive symptoms in 50% of mood disorder patients. Relapse often occurs with recovery sleep and even sleep for very short periods (e.g. 90 s) can induce switches back into depression [140] (see Figure 18.2 as an example of a typical patient's response to total sleep deprivation followed by relapse with recovery sleep). Sleep deprivation responses can be extended with the use of add-on therapies including phase advances, light therapy and antidepressants [141].

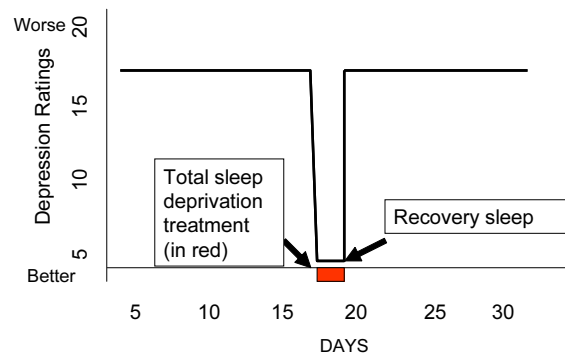


Figure 18.2 A 35-year-old BPD female, severely and continuously depressed for 30 days responded within 24 h to a night of total sleep deprivation and relapsed following the next night of sleep. Her symptoms changed from psychotic suicidal depression to mild euphoria and talkativeness following sleep deprivation.

18.13.2

Bright Light Therapy

Animal data demonstrates that light has the capacity of phase-shifting circadian rhythms [142]. The use of bright light therapy in the treatment of depression may work by altering abnormal circadian rhythms, at least temporarily, in a subgroup of patients. Bright light therapy is effective in the treatment of seasonal affective disorder (SAD) including the treatment of the depressive phase of seasonal BPD patients. Patients are usually exposed to 3000 lux of bright light for 1 week or longer [71]. Bright light therapy is also associated with improvement in mood, concentration and psychomotor symptoms in non-seasonal patients. These changes are accompanied by normalization of sleep, cortisol and melatonin rhythms [143–146]. In contrast, manic patients can be successfully treated with dark and prolonged rest [147–149]. Evidence that BPD patients may have abnormal photic clock genes is based on studies showing that lithium, one of the most efficacious treatments for BPD, decreases sensitivity to light [96, 97].

18.13.3

Phase Advance of the Sleep/Wake Cycle as an Antidepressant

Wehr et al. [150] in a pioneer study, treated depression in a BPD patient by advancing the time of sleep and awakening in an attempt to synchronize the circadian rhythms. Advancing the sleep and awake times on two occasions by 6 h earlier than normal, produced a rapid and striking, although temporary, improvement in symptoms. An explanatory theory suggests that advancing the sleep/wake activity cycle to coincide with hypothesized already-advanced circadian rhythms in cortisol and temperature will synchronize the cycles and produce an improvement in mood disorder patients. Sack et al. [151] conducted a phase-advance study on four patients

in a depressive phase who were unresponsive to antidepressants and reported successful antidepressant effects. One patient, for example, presented with constant and severe depression that persisted for 30 days. Within 2 days after a 5-h phase advance in the sleep/wake cycle, there was a striking and long-lasting decrease in depressive symptoms.

18.14

Combination Treatment Strategies which Manipulate Circadian Rhythms

Recent studies have focused on the following question: given the established and documented rapid, but brief, clinically significant improvement produced by sleep deprivation, “How can the therapeutic response be extended or the relapse blocked by the addition of other strategies that manipulate circadian rhythms (phase advance, phototherapy) or the addition of antidepressant or mood-stabilizing medications some of which have reported effects on circadian rhythms?”

18.14.1

Sleep Deprivation plus Phase Advance

A strategy to block relapse in successful sleep deprivation responders includes therapeutic interventions combining the two modalities of sleep deprivation and phase advance [126, 152–155]. Following a night of total sleep deprivation, Berger et al. [156] advanced sleep-deprivation responders by 5 h by putting them on a sleep schedule from 17.00 to 00.00 hours. A significant decrease in relapses following recovery sleep occurred. In contrast, sleep deprivation combined with a 5-h phase delay in sleep each night (bedtime after total sleep deprivation at 02.00 hours) was not as effective in blocking post-sleep deprivation relapses [156]. In a larger sample of 40 depressed patients, Riemann [157] reported that 75% were stabilized by the phase-advance condition compared to 40% of the patients in the phase-delayed condition. Phase advances of 3 and even 6 days appear to be particularly effective in prolonging sleep deprivation responses in about 60% of patient responders [158].

18.14.2

Sleep Deprivation plus Phase Advance with Bright Light Therapy

An alternative treatment involves the combination of sleep deprivation with bright light therapy. Data suggests that exposure to bright light on the night of [94] or on the night following sleep deprivation [159] decreases the incidence of relapses associated with recovery sleep in sleep-deprivation responders. Dim light, in contrast, was not as efficacious [159]. Other combined treatment approaches to blocking the relapse following sleep deprivation include the use of both phase advance and bright light; the use of sleep deprivation plus phase advance; the use of bright light and lithium [160–163]; and finally, co-treatment with an antidepressant [140, 141].

18.14.3

Effects of Bright Light and Sleep Deprivation and Travel across Time Zones as Circadian Manipulations Associated with Rapid Mood Changes

All efficacious treatments for the depressive phase of BPD including antidepressants, ECT, sleep deprivation [126, 164], bright light therapy [165] have been documented to switch a small subset of patients into mania within 24 h of initiating treatment. Travel across time zones is also associated with switches into hypomania/mania on eastbound flights and into depressive episodes on west-bound flights [64, 166]. It is unlikely that these switches are part of the naturally-occurring alterations in mood in these patients since the rapid onset of the mania occurs within 24 h of the travel across time zones. Differential adaptation of mPer and mCry genes to phase advances or delays in light/dark cycle transitions is described in a mouse SCN study. The data suggest that eastbound travel (phase advance) may be associated with longer periods of adjustment in clock gene adaptation than westbound travel (phase delay). Thus, in phase advances, mPer adjusts rapidly while there is a delay in mCry expression to advances in the light/dark cycle. Alternatively, where local time is delayed (e.g. westbound travel) both mPer and mCry cycles are more rapidly synchronized [167].

18.15

Clock Gene Studies in Mood Disorders

To our knowledge there are no investigations of the core clock gene in the SCN of mood disorder patients. There is one postmortem investigation of the AVP neurons in the SCN comparing BPD and MDD patients with controls [168]. To date, a number of studies have used genotyping methodologies to investigate possible polymorphisms in MDD, BPD and SAD. A summary of these findings is detailed below.

18.15.1

3111CLOCK Variants

Healthy subjects with a polymorphism (T to C nucleotide substitution in position 3111 of the DNA sequence) in the 3' flanking regions of the human CLOCK gene had a preference for delayed sleep [169]. A follow-up study suggests that MDD (with a trend in BPD) patients are more likely to have a decreased need for sleep (insomnia) if they have an increase in the C variant for 3111 CLOCK [170]. Additional data shows that CLOCK gene variants are not associated with diurnal variation in mood, although a post-hoc analysis suggests that BPD patients with the variant have higher rates of recurrent episodes [171]. An earlier study, however, reported no differences in the CLOCK variants in MDD [172].

18.15.2

NPAS2

NPAS2 is not expressed in mammalian SCN but may be an important component of the forebrain clock as it is a functional analog of CLOCK. Johansson et al. [2] reported a significant difference between SAD patients and controls in the NPAS2 471 Leu/Ser mutant suggesting a recessive effect of the leucine allele in susceptibility to SAD [2].

18.15.3

PERIOD 2 (PER2)

Allelic variations in casein kinase I epsilon (CKIε) which degrades PER2 by phosphorylating hPER2 was studied in a group of 88 BPD and 127 control subjects. Deficient phosphorylation of hPER2 may decrease its degradation and accelerate its entry into the cell nucleus to repress its own transcription. Results failed to show any significant polymorphisms on the binding region of the hper2 gene (23 exons) in BPD versus controls [173]. In a separate investigation [2], comparing SAD patients and controls, no differences were found in the PER2 1244 mutant.

18.15.4

PERIOD 3 (PER3)

Disruption of the per3 gene has relatively little effect on the circadian cycle in mammals and is not a necessary component of the clock gene cycle [174]. Investigations of mutant PER3 647 showed no differences between SAD patients and controls although the subjects with the mutant PER3 647 Val/Glu subtype showed diurnal preferences [2].

18.15.5

Arginine Vasopressin (AVP)

AVP is a clock-controlled gene located in the SCN. AVP gene transcription and rapid turnover of mRNA are thought to contribute to the diurnal variation in AVP mRNA levels in the SCN [175]. A postmortem investigation of SCN neurons in three BPD and eight MDD subjects compared to controls ($N = 11$) showed an increase in the number of arginine vasopressin (AVP) immunoreactive neurons and a decrease in AVP-mRNA in the SCN [168]. The results were not related to duration of the illness nor to medication. Daily rhythms in clock-driven AVP gene expression are reported in the SCN and appear to be sensitive to changes in photoperiod [176]. Thus, reductions in both the synthesis and release of AVP in the SCN in BPD patients may reflect impaired circadian function. This study provides some of the first preliminary data suggesting alterations in the human SCN associated with depression.

18.15.6

5HTT-linked Polymorphic Receptor (5-HTTLPR)

The expression of the serotonin transporter (5-HTT) is regulated in part by an insertion/deletion polymorphism in the serotonin transporter gene promoter region (5-HTTLPR) and may increase susceptibility to mood disorders in subgroups of patients [177]. 5HTTLPR variants have a unique DNA secondary structure that appears to regulate the transcriptional activity of the 5HTT promoter [178]. Studies in human postmortem brain showed that subjects that are homozygote for the l-allele have higher 5-HTT mRNA levels than those who were heterozygote or homozygote for the short variant (s-allele) [179]. Low 5HTTLPR transcriptional activity may be a genetic susceptibility factor for depression [180]. Rosenthal et al. [181] reported that SAD patients were more likely to have the s-allele than the l-allele as compared to non-seasonal controls. Furthermore, Benedetti et al. [182] found that BPD patients homozygote for the l-allele had a better response to sleep deprivation than if they were heterozygote or homozygote for the s-allele. This same group reported extended sleep-deprivation antidepressant responses in the l-allele BPD patients with 30 min of bright light therapy as compared to patients with the short form allele [149]. However, a separate group conducted a study with MDD patients using partial sleep deprivation and found no relationship between response and 5-HTTLPR polymorphisms [183]. Other investigations of serotonergic polymorphisms include those of the 5HT2A gene (1438G/A and 102-T/C). Of three studies, two showed a relationship between the 5HT2A polymorphism and SAD [184, 185] while one study failed to replicate the findings [186].

18.16

Concluding Remarks

MDD, BPD and SAD are characterized by disturbances in the 24-h sleep/wake cycle, abnormalities in clock-related hormone secretion (e.g. cortisol, melatonin), and abnormalities in nocturnal core body temperature [84]. Moreover, patients can have mood changes that regularly fluctuate throughout the course of the day and/or with the seasons. For many years, researchers have hypothesized that mood changes could reflect an underlying rhythmic disorder [52, 54], but it is only until recently that new tools have been developed to identify and study the function of clock genes.

For the most part, recent studies of the circadian genes in mood disorder patients have failed to find a definitive mutant clock gene defect. There is evidence that some alleles may be associated with related symptoms: sleep disturbances (3111 CLOCK, C variant) [170, 171], increased vulnerability to SAD (PER 2 associated CK1ε [173] s-allele of the 5-HTTLPR [181]), depression (s-allele, 5-HTTLPR) [187] and increased response rates to sleep deprivation (l-allele, 5-HTTLPR) with [183] and without [149] light therapy. To our knowledge, only one study has investigated clock-associated neuropeptides in the SCN of mood disorder patients [168].

The observation that AVP-IR neurons are increased while AVP mRNA is decreased in BPD and MDD patients versus controls [168] provides some of the first evidence that the SCN function may be compromised in depression.

Additional clues to potential mutant clock gene function may be derived from observations related to the mood switch process. In some individuals, rapid phase-shifting as associated with travel across time-zones or work-shifts, can affect mood and sleep and suggests an underlying abnormality of clock gene function associated with decreased adaptive responses to perturbations in the clock gene system. In vulnerable individuals, these same phase shifts can precipitate switches into or out of mania or depression [64]. A small percentage of depressed patients will switch into mania or hypomania following sleep deprivation [164] or bright light therapy [165] and in response to antidepressant medications including the SSRIs [188] that may affect the circadian clock. Whether these switches are specific to defects in photic entrainment processes is not yet known. However, it is reasonable to speculate that a subgroup of SAD patients has defects in the genes associated with the synchronization of the circadian clock with changes in the light/dark cycle.

Since a limited set of genes found in the SCN including Clock, Bmal1, mPer1, mPer2, mCry1 and mCry2 is essential for the generation of circadian rhythms in mammals, it is hypothesized that these core clock genes and their related pathways could contribute to some of the symptoms of major mood disorders. Future studies of the major mood disorders should include the analysis of clock genes in the human SCN. The relatively small and highly heterogeneous composition of the human SCN makes this a difficult region to study. Data from peripheral cells including that from blood probably does not accurately reflect SCN function as the expression of mammalian clock genes varies from tissue to tissue and shows relatively little overlap between oscillating genes in the periphery with those in the brain [189]. The role of the SCN, as the master regulator of circadian rhythms, is not yet understood, but important clues to its function are emerging to explain mechanisms involved in cell synchrony and the maintenance of neuronal oscillation [190]. Future circadian research might emphasize studies in the SCN of patients with mood disorders to help better understand how this relatively small but powerful structure can influence mood and orchestrate the vast ensembles of gene expression throughout the human body to affect mood.

References

- 1 NAMBU, J. R., LEWIS, J. O., WHARTON JR., K. A., CREWS, S. T., The *Drosophila* single-minded gene encodes a helix-loop-helix protein that acts as a master regulator of CNS midline development. *Cell* **1991**, 67, 1157–1167.
- 2 JOHANSSON, C., WILLEIT, M., SMEDH, C., et al., Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* **2003**, 28, 734–739.
- 3 KAMNASARAN, D., MUIR, W. J., FERGUSON-SMITH, M. A., COX, D. W., Disruption of the neuronal PAS3 gene in a family affected with schizophrenia. *J. Med. Genet.* **2003**, 40, 325–332.

- 4 REICK, M., GARCIA, J. A., DUDLEY, C., MCKNIGHT, S. L., NPAS2: an analog of clock operative in the mammalian forebrain. *Science* **2001**, 293, 506–509.
- 5 BRUNSKILL, E. W., WITTE, D. P., SHREINER, A. B., POTTER, S. S., Characterization of npas3, a novel basic helix-loop-helix PAS gene expressed in the developing mouse nervous system. *Mech. Dev.* **1999**, 88, 237–241.
- 6 TOMITA, H. V. M., WALSH, D. M., EVANS, S., et al., Effect of agonal and post-mortem factors on microarray expression profile: Quality control methods in microarray analyses of postmortem human brain. *Biol. Psychiatry* (in press).
- 7 LI, J., VAWTER, M. P., WALSH, D. M., TOMITA, H., EVANS, S. J., CHOUDARY, P. V., JONES, E. G., WATSON, S. J., AKIL, H., BUNNEY JR., W. E., MYERS, R. M., Systematic changes in gene expression in postmortem human brains associated with tissue pH and terminal medical conditions. Submitted for publication.
- 8 BALSALOBRE, A., DAMIOLA, F., SCHIBLER, U., A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell* **1998**, 93, 929–937.
- 9 RIVERA-BERMEDEZ, M. A., GERDIN, M. J., EARNEST, D. J., DUBOCOVICH, M. L., Regulation of basal rhythmicity in protein kinase C activity by melatonin in immortalized rat suprachiasmatic nucleus cells. *Neurosci. Lett.* **2003**, 346, 37–40.
- 10 ALLEN, G., RAPPE, J., EARNEST, D. J., CASSONE, V. M., Oscillating on borrowed time: diffusible signals from immortalized suprachiasmatic nucleus cells regulate circadian rhythmicity in cultured fibroblasts. *J. Neurosci.* **2001**, 21, 7937–7943.
- 11 ALBRECHT, U., EICHELE, G., The mammalian circadian clock. *Curr. Opin. Genet. Dev.* **2003**, 13, 271–277.
- 12 UEDA, H. R., CHEN, W., ADACHI, A., et al., A transcription factor response element for gene expression during circadian night. *Nature* **2002**, 418, 534–539.
- 13 YOUNG, M. W., JACKSON, F. R., SHIN, H. S., BARGIELLO, T. A., A biological clock in *Drosophila*. *Cold Spring Harb. Symp. Quant. Biol.* **1985**, 50, 865–875.
- 14 BARGIELLO, T. A., JACKSON, F. R., YOUNG, M. W., Restoration of circadian behavioural rhythms by gene transfer in *Drosophila*. *Nature* **1984**, 312, 752–754.
- 15 IWASE, T., KAJIMURA, N., UCHIYAMA, M., et al., Mutation screening of the human Clock gene in circadian rhythm sleep disorders. *Psychiatry Res.* **2002**, 109, 121–128.
- 16 FU, L., PELICANO, H., LIU, J., HUANG, P., LEE, C., The circadian gene Period2 plays an important role in tumor suppression and DNA damage response in vivo. *Cell* **2002**, 111, 41–50.
- 17 ROSBASH, M., TAKAHASHI, J. S., Circadian rhythms: the cancer connection. *Nature* **2002**, 420, 373–374.
- 18 SIGWORTH, L. A., LIAO, L., CHANDLER, T. R., GEUSZ, M. E., Luciferase expression controlled by a viral gene promoter in a mammalian circadian pacemaker. *Neuroreport* **2003**, 14, 443–447.
- 19 KRIEGSFELD, L. J., KORETS, R., SILVER, R., Expression of the circadian clock gene Period 1 in neuroendocrine cells: an investigation using mice with a Per1: GFP transgene. *Eur. J. Neurosci.* **2003**, 17, 212–220.
- 20 DUFFIELD, G. E., BEST, J. D., MEURERS, B. H., BITTNER, A., LOROS, J. J., DUNLAP, J. C., Circadian programs of transcriptional activation, signaling, and protein turnover revealed by microarray analysis of mammalian cells. *Curr. Biol.* **2002**, 12, 551–557.
- 21 AKHTAR, R. A., REDDY, A. B., MAYWOOD, E. S., et al., Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. *Curr. Biol.* **2002**, 12, 540–550.
- 22 RUTTER, J., REICK, M., MCKNIGHT, S. L., Metabolism and the control of circadian rhythms. *Annu. Rev. Biochem.* **2002**, 71, 307–331.
- 23 BELENKY, M. A., SAGIV, N., FRITSCHY, J. M., YAROM, Y., Presynaptic and postsynaptic GABA(A) receptors in rat suprachiasmatic nucleus. *Neuroscience* **2003**, 118, 909–923.
- 24 SCHAAAP, J., PENNARTZ, C. M., MEIJER, J. H., Electrophysiology of the circadian pacemaker in mammals. *Chronobiol. Int.* **2003**, 20, 171–188.
- 25 MUNOZ, E., BALER, R., The circadian E-box: when perfect is not good enough. *Chronobiol. Int.* **2003**, 20, 371–388.

- 26 DUDLEY, C. A., ERBEL-SIELER, C., ESTILL, S. J., et al., Altered patterns of sleep and behavioral adaptability in NPAS2-deficient mice. *Science* **2003**, 301, 379–383.
- 27 RUTTER, J., REICK, M., WU, L. C., MCKNIGHT, S. L., Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. *Science* **2001**, 293, 510–514.
- 28 OSTER, H., VAN DER HORST, G. T., ALBRECHT, U., Daily variation of clock output gene activation in behaviorally arrhythmic mPer/mCry triple mutant mice. *Chronobiol. Int.* **2003**, 20, 683–695.
- 29 HAY-SCHMIDT, A., VRANG, N., LARSEN, P. J., MIKKELSEN, J. D., Projections from the raphe nuclei to the suprachiasmatic nucleus of the rat. *J. Chem. Neuroanat.* **2003**, 25, 29–310.
- 30 TISCHLER, R. C., MORIN, L. P., Reciprocal serotonergic connections between the hamster median and dorsal raphe nuclei. *Brain Res.* **2003**, 981, 126–132.
- 31 IBATA, Y., OKAMURA, H., TANAKA, M., et al., Functional morphology of the suprachiasmatic nucleus. *Front Neuroendocrinol.* **1999**, 20, 241–268.
- 32 WEHR, T. A., AESCHBACH, D., DUNCAN JR., W. C., Evidence for a biological dawn and dusk in the human circadian timing system. *J. Physiol.* **2001**, 535 (Pt 3), 937–951.
- 33 SASSONE-CORSI, P., Coupling gene expression to cAMP signalling: role of CREB and CREM. *Int. J. Biochem. Cell Biol.* **1998**, 30, 27–38.
- 34 LEWY, A. J., Melatonin as a marker and phase-resetter of circadian rhythms in humans. *Adv. Exp. Med. Biol.* **1999**, 460, 425–434.
- 35 ZISAPEL, N., Circadian rhythm sleep disorders: pathophysiology and potential approaches to management. *CNS Drugs* **2001**, 15, 311–328.
- 36 SKENE, D. J., Optimization of light and melatonin to phase-shift human circadian rhythms. *J. Neuroendocrinol.* **2003**, 15, 438–441.
- 37 ARENDT, J., Importance and relevance of melatonin to human biological rhythms. *J. Neuroendocrinol.* **2003**, 15, 427–431.
- 38 TOH, K. L., JONES, C. R., HE, Y., et al., An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* **2001**, 291, 1040–1043.
- 39 GANGULY, S., COON, S. L., KLEIN, D. C., Control of melatonin synthesis in the mammalian pineal gland: the critical role of serotonin acetylation. *Cell Tissue Res.* **2002**, 309, 127–137.
- 40 PERREAU-LENZ, S., KALSBECK, A., GARIDOU, M. L., et al., Suprachiasmatic control of melatonin synthesis in rats: inhibitory and stimulatory mechanisms. *Eur. J. Neurosci.* **2003**, 17, 221–228.
- 41 STEHLE, J. H., VON GALL, C., KORF, H. W., Analysis of cell signalling in the rodent pineal gland deciphers regulators of dynamic transcription in neural/endocrine cells. *Eur. J. Neurosci.* **2001**, 14, 1–9.
- 42 CERMAKIAN, N., BOIVIN, D. B., A molecular perspective of human circadian rhythm disorders. *Brain Res. Brain Res. Rev.* **2003**, 42, 204–220.
- 43 DUNLAP, J. C., LOROS, J. J., LIU, Y., CROSTHWAITE, S. K., Eukaryotic circadian systems: cycles in common. *Genes Cells* **1999**, 4, 1–10.
- 44 KING, D. P., TAKAHASHI, J. S., Molecular genetics of circadian rhythms in mammals. *Annu. Rev. Neurosci.* **2000**, 23, 713–742.
- 45 PRICE, J. L., DEMBINSKA, M. E., YOUNG, M. W., ROSBASH, M., Suppression of PERIOD protein abundance and circadian cycling by the *Drosophila* clock mutation timeless. *EMBO J.* **1995**, 14, 4044–4049.
- 46 RUTILA, J. E., SURI, V., LE, M., SO, W. V., ROSBASH, M., HALL, J. C., CYCLE is a second bHLH-PAS clock protein essential for circadian rhythmicity and transcription of *Drosophila* period and timeless. *Cell* **1998**, 93, 805–814.
- 47 HAMBLIN-COYLE, M., KONOPKA, R. J., ZWIEBEL, L. J., et al., A new mutation at the period locus of *Drosophila melanogaster* with some novel effects on circadian rhythms. *J. Neurogenet.* **1989**, 5, 229–256.
- 48 STANEWSKY, R., KANEKO, M., EMERY, P., et al., The cryb mutation identifies cryptochrome as a circadian photoreceptor in *Drosophila*. *Cell* **1998**, 95, 681–692.
- 49 RUTILA, J. E., ZENG, H., LE, M., CURTIN, K. D., HALL, J. C., ROSBASH, M., The timSL mutant of the *Drosophila* rhythm gene timeless manifests allele-specific interactions with period gene mutants. *Neuron* **1996**, 17, 921–929.

- 50 VITATERNA, M. H., SELBY, C. P., TODO, T., et al., Differential regulation of mammalian period genes and circadian rhythmicity by cryptochromes 1 and 2. *Proc. Natl. Acad. Sci. USA* **1999**, 96, 12114–12119.
- 51 NASH, H. A., SCOTT, R. L., LEAR, B. C., ALLADA, R., An unusual cation channel mediates photic control of locomotion in *Drosophila*. *Curr. Biol.* **2002**, 12, 2152–2158.
- 52 KRIPKE, D. F., MULLANEY, D. J., ATKINSON, M., WOLF, S., Circadian rhythm disorders in manic-depressives. *Biol. Psychiatry* **1978**, 13, 335–351.
- 53 STODDARD, F. J., POST, R. M., BUNNEY JR., W. E., Slow and rapid psychobiological alterations in a manic-depressive patient: clinical phenomenology. *Br. J. Psychiatry* **1977**, 130, 72–78.
- 54 SITARAM, N., GILLIN, J. G., BUNNEY JR., W. E., Circadian variation in the time of “switch” of a patient with 48-hour manic-depressive cycles. *Biol. Psychiatry* **1978**, 13, 567–574.
- 55 SITARAM, N., GILLIN, J. C., BUNNEY JR., W. E., The switch process in manic-depressive illness. Circadian variation in time of switch and sleep and manic ratings before and after switch. *Acta Psychiatr. Scand.* **1978**, 58, 267–278.
- 56 GILLIN, J. C., MAZURE, C., POST, R. M., JIMMERSON, D., BUNNEY JR., W. E., An EEG sleep study of a bipolar (manic-depressive) patient with a nocturnal switch process. *Biol. Psychiatry* **1977**, 12, 711–718.
- 57 POST, R. M., STODDARD, F. J., GILLIN, J. C., et al., Alterations in motor activity, sleep, and biochemistry in a cycling manic-depressive patient. *Arch. Gen. Psychiatry* **1977**, 34, 470–477.
- 58 BUCHSBAUM, M. S., POST, R. M., BUNNEY JR., W. E., Average evoked responses in a rapidly cycling manic-depressive patient. *Biol. Psychiatry* **1977**, 12, 83–99.
- 59 BUNNEY JR., W. E., GOODWIN, F. K., MURPHY, D. L., The “switch process” in manic-depressive illness. 3. Theoretical implications. *Arch. Gen. Psychiatry* **1972**, 27, 312–331.
- 60 BUNNEY JR., W. E., MURPHY, D. L., GOODWIN, F. K., BORGE, G. F., The “switch process” in manic-depressive illness. I. A systematic study of sequential behavioral changes. *Arch. Gen. Psychiatry* **1972**, 7, 295–302.
- 61 BUNNEY JR., W. E., GOODWIN, F. K., MURPHY, D. L., HOUSE, K. M., GORDON, E. K., The “switch process” in manic-depressive illness. II. Relationship to catecholamines, REM sleep, and drugs. *Arch. Gen. Psychiatry* **1972**, 27, 304–309.
- 62 PAUL, M. I., CRAMER, H., BUNNEY JR., W. E., Urinary adenosine 3',5'-monophosphate in the switch process from depression to mania. *Science* **1971**, 171, 300–303.
- 63 BUNNEY JR., W. E., MURPHY, D. L., GOODWIN, F. K., BORGE, G. F., The switch process from depression to mania: relationship to drugs which alter brain amines. *Lancet* **1970**, i, 1022–1027.
- 64 YOUNG, D. M., Psychiatric morbidity in travelers to Honolulu, Hawaii. *Compr. Psychiatry* **1995**, 36, 224–228.
- 65 BUNNEY, W. E., BUNNEY, B. G., Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. *Neuropsychopharmacology* **2000**, 22, 335–345.
- 66 FELDMAN-NAIM, S., TURNER, E. H., LEIBENLUFT, E., Diurnal variation in the direction of mood switches in patients with rapid-cycling bipolar disorder. *J. Clin. Psychiatry* **1997**, 58, 79–84.
- 67 WEHR, T. A., DUNCAN JR., W. C., SHER, L., et al., A circadian signal of change of season in patients with seasonal affective disorder. *Arch. Gen. Psychiatry* **2001**, 58, 1108–1114.
- 68 FAEDDA, G. L., TONDO, L., TEICHER, M. H., BALDESSARINI, R. J., GELBARD, H. A., FLORIS, G. F., Seasonal mood disorders. Patterns of seasonal recurrence in mania and depression. *Arch. Gen. Psychiatry* **1993**, 50, 17–23.
- 69 SHER, L., Genetics of seasonal affective disorder. *Lancet* **2002**, 359, 893–894.
- 70 POTKIN, S. G., ZETIN, M., STAMENKOVIC, V., KRIPKE, D., BUNNEY JR., W. E., Seasonal affective disorder: prevalence varies with latitude and climate. *Clin. Neuropharmacol.* **1986**, 9 (Suppl. 4), 181–183.
- 71 ROSENTHAL, N. E., *Winter Blues: Seasonal Affective Disorder*. New York: Guilford Press, **1993**.
- 72 ROSEN, L., KNUDSON, K. H., FANCHER, P., Prevalence of seasonal affective disorder among U.S. Army soldiers in Alaska. *Mil. Med.* **2002**, 167, 581–584.

- 73 LEPPAMAKI, S., PARTONEN, T., VAKKURI, O., LONNQVIST, J., PARTINEN, M., LAUDON, M., Effect of controlled-release melatonin on sleep quality, mood, and quality of life in subjects with seasonal or weather-associated changes in mood and behaviour. *Eur. Neuropsychopharmacol.* **2003**, *13*, 137–145.
- 74 GOEL, N., TERMAN, M., TERMAN, J. S., Depressive symptomatology differentiates subgroups of patients with seasonal affective disorder. *Depress. Anxiety* **2002**, *15*, 34–41.
- 75 SCHAFFER, A., LEVITT, A. J., BOYLE, M., Influence of season and latitude in a community sample of subjects with bipolar disorder. *Can. J. Psychiatry* **2003**, *48*, 277–280.
- 76 AVASTHI, A., SHARMA, A., GUPTA, N., et al., Seasonality and affective disorders: a report from North India. *J. Affect Disord.* **2001**, *64*, 145–154.
- 77 MULDER, R. T., COSGRIFF, J. P., SMITH, A. M., JOYCE, P. R., Seasonality of mania in New Zealand. *Aust. N. Z. J. Psychiatry* **1990**, *24*, 187–190.
- 78 CLARKE, M., MORAN, P., KEOGH, F., et al., Seasonal influences on admissions for affective disorder and schizophrenia in Ireland: a comparison of first and readmissions. *Eur. Psychiatry* **1999**, *14*, 251–255.
- 79 LEE, H. J., KIM, L., JOE, S. H., SUH, K. Y., Effects of season and climate on the first manic episode of bipolar affective disorder in Korea. *Psychiatry Res.* **2002**, *113*, 151–159.
- 80 DANIELS, B. A., KIRKBY, K. C., MITCHELL, P., HAY, D., MOWRY, B., Seasonal variation in hospital admission for bipolar disorder, depression and schizophrenia in Tasmania. *Acta Psychiatr. Scand.* **2000**, *102*, 38–43.
- 81 WHITNEY, D. K., SHARMA, V., KUENEMAN, K., Seasonality of manic depressive illness in Canada. *J. Affect Disord.* **1999**, *55*, 99–105.
- 82 GRAW, P., KRAUCHI, K., WIRZ-JUSTICE, A., POLDINGER, W., Diurnal variation of symptoms in seasonal affective disorder. *Psychiatry Res.* **1991**, *37*, 105–111.
- 83 AVERY, D. H., DAHL, K., SAVAGE, M. V., et al., Circadian temperature and cortisol rhythms during a constant routine are phase-delayed in hypersomnic winter depression. *Biol. Psychiatry* **1997**, *41*, 1109–1123.
- 84 DUNCAN JR., W. C., Circadian rhythms and the pharmacology of affective illness. *Pharmacol. Ther.* **1996**, *71*, 253–312.
- 85 MURRAY, G., ALLEN, N. B., TRINDER, J., Seasonality and circadian phase delay: prospective evidence that winter lowering of mood is associated with a shift towards Eveningness. *J. Affect Disord.* **2003**, *76*, 15–22.
- 86 MAGNUSSON, A., BOIVIN, D., Seasonal affective disorder: an overview. *Chronobiol. Int.* **2003**, *20*, 189–207.
- 87 KARADOTTIR, R., AXELSSON, J., Melatonin secretion in SAD patients and healthy subjects matched with respect to age and sex. *Int. J. Circumpolar Health* **2001**, *60*, 548–551.
- 88 DOGANAY, Z., SUNTER, A. T., GUZ, H., et al., Climatic and diurnal variation in suicide attempts in the ED. *Am. J. Emerg. Med.* **2003**, *21*, 271–275.
- 89 LAMBERT, G., REID, C., KAYE, D., JENNINGS, G., ESLER, M., Increased suicide rate in the middle-aged and its association with hours of sunlight. *Am. J. Psychiatry* **2003**, *160*, 793–795.
- 90 AVERY, D. H., EDER, D. N., BOLTE, M. A., et al., Dawn simulation and bright light in the treatment of SAD: a controlled study. *Biol. Psychiatry* **2001**, *50*, 205–216.
- 91 LEWY, A. J., BAUER, V. K., CUTLER, N. L., et al., Morning vs evening light treatment of patients with winter depression. *Arch. Gen. Psychiatry* **1998**, *55*, 890–896.
- 92 GRAW, P., HAUG, H. J., LEONHARDT, G., WIRZ-JUSTICE, A., Sleep deprivation response in seasonal affective disorder during a 40-h constant routine. *J. Affect Disord.* **1998**, *48*, 69–74.
- 93 FRITZSCHE, M., HELLER, R., HILL, H., KICK, H., Sleep deprivation as a predictor of response to light therapy in major depression. *J. Affect Disord.* **2001**, *62*, 207–215.
- 94 WEHR, T. A., ROSENTHAL, N. E., SACK, D. A., GILLIN, J. C., Antidepressant effects of sleep deprivation in bright and dim light. *Acta Psychiatr. Scand.* **1985**, *72*, 161–165.
- 95 SOKOLSKI, K. N., REIST, C., CHEN, C. C., DEMET, E. M., Antidepressant responses

- and changes in visual adaptation after sleep deprivation. *Psychiatry Res.* **1995**, *57*, 197–207.
- 96 SEGGIE, J., CARNEY, P. A., PARKER, J., GROF, E., GROF, P., Effect of chronic lithium on sensitivity to light in male and female bipolar patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1989**, *13*, 543–549.
 - 97 CARNEY, P. A., SEGGIE, J., VOJTECHOVSKY, M., PARKER, J., GROF, E., GROF, P., Bipolar patients taking lithium have increased dark adaptation threshold compared with controls. *Pharmacopsychiatry* **1988**, *21*, 117–120.
 - 98 HARRINGTON, M. E., RUSAK, B., Luminance coding properties of intergeniculate leaflet neurons in the golden hamster and the effects of chronic clorgyline. *Brain Res.* **1991**, *554*, 95–104.
 - 99 DUNCAN JR, W. C., JOHNSON, K. A., WEHR, T. A., Decreased sensitivity to light of the photic entrainment pathway during chronic clorgyline and lithium treatments. *J. Biol. Rhythms* **1998**, *13*, 330–346.
 - 100 LAM, R. W., ALLAIN, S., SULLIVAN, K., BEATTIE, C. W., REMICK, R. A., ZIS, A. P., Effects of chronic lithium treatment on retinal electrophysiologic function. *Biol. Psychiatry* **1997**, *41*, 737–742.
 - 101 MURPHY, D. G., MURPHY, D. M., ABBAS, M., et al., Seasonal affective disorder: response to light as measured by electroencephalogram, melatonin suppression, and cerebral blood flow. *Br. J. Psychiatry* **1993**, *163*, 327–331, 335–337.
 - 102 BENCA, R. M., OBERMEYER, W. H., THISTED, R. A., GILLIN, J. C., Sleep and psychiatric disorders. A meta-analysis. *Arch. Gen. Psychiatry* **1992**, *49*, 651–668; discussion 669–670.
 - 103 BUNNEY JR, W. E., HARTMANN, E. L., MASON, J. W., Study of a patient with 48-Hour manic-depressive cycles. II. Strong positive correlation between endocrine factors and manic defense patterns. *Arch. Gen. Psychiatry* **1965**, *12*, 619–625.
 - 104 PAPOLOS, D. F., VEIT, S., FAEDDA, G. L., SAITO, T., LACHMAN, H. M., Ultra-ultra rapid cycling bipolar disorder is associated with the low activity catecholamine-O-methyltransferase allele. *Mol. Psychiatry* **1998**, *3*, 346–349.
 - 105 SOUETRE, E., SALVATI, E., BELUGOU, J. L., et al., Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res.* **1989**, *28*, 263–278.
 - 106 SOUETRE, E., SALVATI, E., WEHR, T. A., SACK, D. A., KREBS, B., DARCOURT, G., Twenty-four-hour profiles of body temperature and plasma TSH in bipolar patients during depression and during remission and in normal control subjects. *Am. J. Psychiatry* **1988**, *145*, 1133–1137.
 - 107 AVERY, D. H., WILDSCHIODTZ, G., RAFAELSEN, O. J., Nocturnal temperature in affective disorder. *J. Affect Disord.* **1982**, *4*, 61–71.
 - 108 SZUBA, M. P., GUZE, B. H., BAXTER JR, L. R., Electroconvulsive therapy increases circadian amplitude and lowers core body temperature in depressed subjects. *Biol. Psychiatry* **1997**, *42*, 1130–1137.
 - 109 GOETZE, U., TOLLE, R., Circadian rhythm of free urinary cortisol, temperature and heart rate in endogenous depressives and under antidepressant therapy. *Neuropsychobiology* **1987**, *18*, 175–184.
 - 110 TOLLE, R., GOETZE, U., On the daily rhythm of depression symptomatology. *Psychopathology* **1987**, *20*, 237–249.
 - 111 WEHR, T. A., MUSCETTOLO, G., GOODWIN, F. K., Urinary 3-methoxy-4-hydroxy-phenylglycol circadian rhythm. Early timing (phase-advance) in manic-depressives compared with normal subjects. *Arch. Gen. Psychiatry* **1980**, *37*, 257–263.
 - 112 ATKINSON, M., KRIPKE, D. F., WOLF, S. R., Autorhythmometry in manic-depressives. *Chronobiologia* **1975**, *2*, 325–335.
 - 113 PARRY, B. L., MENDELSON, W. B., DUNCAN, W. C., SACK, D. A., WEHR, T. A., Longitudinal sleep EEG, temperature, and activity measurements across the menstrual cycle in patients with premenstrual depression and in age-matched controls. *Psychiatry Res.* **1989**, *30*, 285–303.
 - 114 PFLUG, B., ERIKSON, R., JOHNSON, A., Depression and daily temperature. A long-term study. *Acta Psychiatr. Scand.* **1976**, *54*, 254–266.

- 115 VON ZERSSEN, D., DIRLICH, G., DOERR, P., EMRICH, H. M., LUND, R., PLOOG, D., Are biological rhythms disturbed in depression? *Acta Psychiatr. Belg.* **1985**, *85*, 624–635.
- 116 BUYSSE, D. J., MONK, T. H., KUPFER, D. J., FRANK, E., STAPF, D., Circadian patterns of unintended sleep episodes during a constant routine in remitted depressed patients. *J. Psychiatr. Res.* **1995**, *29*, 407–416.
- 117 CARPENTER JR., W. T., BUNNEY JR., W. E., Adrenal cortical activity in depressive illness. *Am. J. Psychiatry* **1971**, *128*, 31–40.
- 118 BRANCHEY, L., WEINBERG, U., BRANCHEY, M., LINKOWSKI, P., MENDLEWICZ, J., Simultaneous study of 24-hour patterns of melatonin and cortisol secretion in depressed patients. *Neuropsychobiology* **1982**, *8*, 225–232.
- 119 JARRETT, D. B., COBLE, P. A., KUPFER, D. J., Reduced cortisol latency in depressive illness. *Arch. Gen. Psychiatry* **1983**, *40*, 506–511.
- 120 LINKOWSKI, P., Neuroendocrine profiles in mood disorders. *Int. J. Neuropsychopharmacol.* **2003**, *6*, 191–197.
- 121 CARROLL, B. J., CURTIS, G. C., MENDELS, J., Cerebrospinal fluid and plasma free cortisol concentrations in depression. *Psychol. Med.* **1976**, *6*, 235–244.
- 122 HALBREICH, U., ASNIS, G. M., SHINDLEDECKER, R., ZUMOFF, B., NATHAN, R. S., Cortisol secretion in endogenous depression. II. Time-related functions. *Arch. Gen. Psychiatry* **1985**, *42*, 909–914.
- 123 LINKOWSKI, P., MENDLEWICZ, J., LECLERCQ, R., et al., The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. *J. Clin. Endocrinol. Metab.* **1985**, *61*, 429–438.
- 124 STEIGER, A., HOLSBOER, F., Nocturnal secretion of prolactin and cortisol and the sleep EEG in patients with major endogenous depression during an acute episode and after full remission. *Psychiatry Res.* **1997**, *72*, 81–88.
- 125 GILLIN, J. C., DUNCAN, W., PETTIGREW, K. D., FRANKEL, B. L., SNYDER, F., Successful separation of depressed, normal, and insomniac subjects by EEG sleep data. *Arch. Gen. Psychiatry* **1979**, *36*, 85–90.
- 126 RIEMANN, D., VODERHOLZER, U., BERGER, M., Sleep and sleep-wake manipulations in bipolar depression. *Neuropsychobiology* **2002**, *45* (Suppl. 1), 7–12.
- 127 BENEDETTI, F., BARBINI, B., COLOMBO, C., CAMPORI, E., SMERALDI, E., Circadian mood fluctuations during a Major Depressive episode. *J. Affect Disord.* **1996**, *41*, 81–87.
- 128 KASPER, S., WEHR, T. A., The role of sleep and wakefulness in the genesis of depression and mania. *Encephale* **1992**, *18*, Spec. No. 1, 45–50.
- 129 CERVANTES, P., GELBER, S., KIN, F. N., NAIR, V. N., SCHWARTZ, G., Circadian secretion of cortisol in bipolar disorder. *J. Psychiatry Neurosci.* **2001**, *26*, 411–416.
- 130 KENNEDY, S. H., KUTCHER, S. P., RALEVSKI, E., BROWN, G. M., Nocturnal melatonin and 24-hour 6-sulphatoxy-melatonin levels in various phases of bipolar affective disorder. *Psychiatry Res.* **1996**, *63*, 219–222.
- 131 REIST, C., CHEN, C. C., CHHOEU, A., BERRY, R. B., BUNNEY JR., W. E., Effects of sleep on the antidepressant response to sleep deprivation. *Biol. Psychiatry* **1994**, *35*, 794–797.
- 132 SILVERSTONE, P. H., SILVERSTONE, T., A review of acute treatments for bipolar depression. *Int. Clin. Psychopharmacol.* **2004**, *19*, 113–124.
- 133 ALTSHULER, L. L., FRYE, M. A., GITLIN, M. J., Acceleration and augmentation strategies for treating bipolar depression. *Biol. Psychiatry* **2003**, *53*, 691–700.
- 134 WU, J. C., GILLIN, J. C., BUCHSBAUM, M. S., HERSHEY, T., JOHNSON, J. C., BUNNEY JR., W. E., Effect of sleep deprivation on brain metabolism of depressed patients. *Am. J. Psychiatry* **1992**, *149*, 538–543.
- 135 WU, J., BUCHSBAUM, M. S., GILLIN, J. C., et al., Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am. J. Psychiatry* **1999**, *156*, 1149–1158.
- 136 GERNER, R. H., POST, R. M., GILLIN, J. C., BUNNEY JR., W. E., Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. *J. Psychiatr. Res.* **1979**, *15*, 21–40.
- 137 JIMERSON, D. C., LYNCH, H. J., POST, R. M., WURTMAN, R. J., BUNNEY JR.,

- W. E., Urinary melatonin rhythms during sleep deprivation in depressed patients and normals. *Life Sci.* **1977**, *20*, 1501–1508.
- 138 SZUBA, M. P., BAXTER JR., L. R., FAIRBANKS, L. A., GUZE, B. H., SCHWARTZ, J. M., Effects of partial sleep deprivation on the diurnal variation of mood and motor activity in major depression. *Biol. Psychiatry* **1991**, *30*, 817–829.
 - 139 BARBINI, B., COLOMBO, C., BENEDETTI, F., CAMPORI, E., BELLODI, L., SMERALDI, E., The unipolar-bipolar dichotomy and the response to sleep deprivation. *Psychiatry Res.* **1998**, *79*, 43–50.
 - 140 WU, J. C., BUNNEY, W. E., The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am. J. Psychiatry* **1990**, *147*, 14–21.
 - 141 GIEDKE, H., SCHWARZLER, F., Therapeutic use of sleep deprivation in depression. *Sleep Med. Rev.* **2002**, *6*, 361–377.
 - 142 CHALLET, E., CALDELAS, I., GRAFF, C., PEVET, P., Synchronization of the molecular clockwork by light- and food-related cues in mammals. *Biol. Chem.* **2003**, *384*, 711–719.
 - 143 DIETZEL, M., Light treatment in depressive illness: polysomnographic, psychometric and neuroendocrinological findings. *Eur. Neurol.* **1986**, *25* (Suppl. 2), 93–103.
 - 144 KRIPKE, D. F., Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. *J. Affect Disord.* **1998**, *49*, 109–117.
 - 145 YAMADA, N., MARTIN-IVERSON, M. T., DAIMON, K., TSUJIMOTO, T., TAKAHASHI, S., Clinical and chronobiological effects of light therapy on nonseasonal affective disorders. *Biol. Psychiatry* **1995**, *37*, 866–873.
 - 146 LYNCH, H. J., JIMERSON, D. C., OZAKI, Y., POST, R. M., BUNNEY JR., W. E., WURTMAN, R. J., Entrainment of rhythmic melatonin secretion in man to a 12-hour phase shift in the light/dark cycle. *Life Sci.* **1978**, *23*, 1557–1563.
 - 147 WEHR, T. A., TURNER, E. H., SHIMADA, J. M., LOWE, C. H., BARKER, C., LEIBENLUFT, E., Treatment of rapidly cycling bipolar patient by using extended bed rest and darkness to stabilize the timing and duration of sleep. *Biol. Psychiatry* **1998**, *43*, 822–828.
 - 148 WIRZ-JUSTICE, A., QUINTO, C., CAJOCHEN, C., WERTH, E., HOCK, C., A rapid-cycling bipolar patient treated with long nights, bed rest, and light. *Biol. Psychiatry* **1999**, *45*, 1075–1077.
 - 149 BENEDETTI, F., COLOMBO, C., SERRETTI, A., et al., Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Biol. Psychiatry* **2003**, *54*, 687–692.
 - 150 WEHR, T. A., WIRZ-JUSTICE, A., GOODWIN, F. K., DUNCAN, W., GILLIN, J. C., Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science* **1979**, *206*, 710–713.
 - 151 SACK, D. A., NURNBERGER, J., ROSENTHAL, N. E., ASHBURN, E., WEHR, T. A., Potentiation of antidepressant medications by phase advance of the sleep-wake cycle. *Am. J. Psychiatry* **1985**, *142*, 606–608.
 - 152 RIEMANN, D., VOLLMANN, J., HOHAGEN, F., et al. (Treatment of depression with sleep deprivation and sleep phase advancement). *Fortschr. Neurol. Psychiatr.* **1995**, *63*, 270–276.
 - 153 RIEMANN, D., HOHAGEN, F., KONIG, A., et al., Advanced vs. normal sleep timing: effects on depressed mood after response to sleep deprivation in patients with a major depressive disorder. *J. Affect Disord.* **1996**, *37*, 121–128.
 - 154 VOLLMANN, J., BERGER, M., Sleep deprivation with consecutive sleep-phase advance therapy in patients with major depression: a pilot study. *Biol. Psychiatry* **1993**, *33*, 54–57.
 - 155 BERGER, M., VAN CALKER, D., RIEMANN, D., Sleep and manipulations of the sleep-wake rhythm in depression. *Acta Psychiatr. Scand. Suppl* **2003** (418), 83–91.
 - 156 BERGER, M., VOLLMANN, J., HOHAGEN, F., et al., Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. *Am. J. Psychiatry* **1997**, *154*, 870–872.
 - 157 RIEMANN, D., KONIG, A., HOHAGEN, F., et al., How to preserve the antidepressive effect of sleep deprivation: A comparison of sleep phase advance and sleep phase

- delay. *Eur. Arch. Psychiatry Clin. Neurosci.* **1999**, 249, 231–237.
- 158 VODERHOLZER, U., VALERIUS, G., SCHÄERER, L., et al., Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. *Eur. Arch. Psychiatry Clin. Neurosci.* **2003**, 253, 68–72.
 - 159 NEUMEISTER, A., GOESSLER, R., LUCHT, M., KAPITANY, T., BAMAS, C., KASPER, S., Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biol. Psychiatry* **1996**, 39, 16–21.
 - 160 BENEDETTI, F., BARBINI, B., CAMPORI, E., FULGOSI, M. C., PONTIGGIA, A., COLOMBO, C., Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? *J. Psychiatr. Res.* **2001**, 35, 323–329.
 - 161 BAXTER JR., L. R., LISTON, E. H., SCHWARTZ, J. M., et al., Prolongation of the antidepressant response to partial sleep deprivation by lithium. *Psychiatry Res.* **1986**, 19, 17–23.
 - 162 BAXTER JR., L. R., Can lithium carbonate prolong the antidepressant effect of sleep deprivation? *Arch. Gen. Psychiatry* **1985**, 42, 635.
 - 163 SZUBA, M. P., BAXTER JR., L. R., ALTSHULER, L. L., et al., Lithium sustains the acute antidepressant effects of sleep deprivation: preliminary findings from a controlled study. *Psychiatry Res.* **1994**, 51, 283–295.
 - 164 COLOMBO, C., BENEDETTI, F., BARBINI, B., CAMPORI, E., SMERALDI, E., Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Res.* **1999**, 86, 267–270.
 - 165 LABBATE, L. A., LAFER, B., THIBAUT, A., SACHS, G. S., Side effects induced by bright light treatment for seasonal affective disorder. *J. Clin. Psychiatry* **1994**, 55, 189–191.
 - 166 JAUHAR, P., WELLER, M. P., Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. *Br. J. Psychiatry* **1982**, 140, 231–235.
 - 167 REDDY, A. B., FIELD, M. D., MAYWOOD, E. S., HASTINGS, M. H., Differential resynchronisation of circadian clock gene expression within the suprachiasmatic nuclei of mice subjected to experimental jet lag. *J. Neurosci.* **2002**, 22, 7326–7330.
 - 168 ZHOU, J. N., RIEMERSMA, R. F., UNMEHOPA, U. A., et al., Alterations in arginine vasopressin neurons in the suprachiasmatic nucleus in depression. *Arch. Gen. Psychiatry* **2001**, 58, 655–662.
 - 169 KATZENBERG, D., YOUNG, T., FINN, L., et al., A CLOCK polymorphism associated with human diurnal preference. *Sleep* **1998**, 21, 569–576.
 - 170 SERRETTI, A., BENEDETTI, F., MANDELLI, L., et al., Genetic dissection of psychopathological symptoms: insomnia in mood disorders and CLOCK gene polymorphism. *Am. J. Med. Genet.* **2003**, 121B, 35–38.
 - 171 BENEDETTI, F., SERRETTI, A., COLOMBO, C., et al., Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am. J. Med. Genet.* **2003**, 123B, 23–26.
 - 172 DESAN, P. H., OREN, D. A., MALISON, R., et al., Genetic polymorphism at the CLOCK gene locus and major depression. *Am. J. Med. Genet.* **2000**, 96, 418–421.
 - 173 SHIINO, Y., NAKAJIMA, S., OZEKI, Y., ISONO, T., YAMADA, N., Mutation screening of the human period 2 gene in bipolar disorder. *Neurosci. Lett.* **2003**, 338, 82–84.
 - 174 SHEARMAN, L. P., JIN, X., LEE, C., REPPERT, S. M., WEAVER, D. R., Targeted disruption of the mPer3 gene: subtle effects on circadian clock function. *Mol. Cell Biol.* **2000**, 20, 6269–6275.
 - 175 YAMBE, Y., ARIMA, H., KAKIYA, S., MURASE, T., OISO, Y., Diurnal changes in arginine vasopressin gene transcription in the rat suprachiasmatic nucleus. *Brain Res. Mol. Brain Res.* **2002**, 104, 132–136.
 - 176 JAC, M., KISS, A., SUMOVA, A., ILLNEROVA, H., JEZOVA, D., Daily profiles of arginine vasopressin mRNA in the suprachiasmatic, supraoptic and paraventricular nuclei of the rat hypothalamus under various photoperiods. *Brain Res.* **2000**, 887, 472–476.
 - 177 HAUSER, J., LESZCZYNSKA, A., SAMOCHOWIEC, J., et al., Association analysis of the insertion/deletion polymorphism in serotonin transporter gene

- in patients with affective disorder. *Eur. Psychiatry* **2003**, *18*, 129–132.
- 178 LESCH, K. P., JATZKE, S., MEYER, J., et al., Mosaicism for a serotonin transporter gene promoter-associated deletion: decreased recombination in depression. *J. Neural Transm.* **1999**, *106*, 1223–1230.
- 179 LITTLE, K. Y., McLAUGHLIN, D. P., ZHANG, L., et al., Cocaine, ethanol, and genotype effects on human midbrain serotonin transporter binding sites and mRNA levels. *Am. J. Psychiatry* **1998**, *155*, 207–213.
- 180 NEUMEISTER, A., KONSTANTINIDIS, A., et al., Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression. *Arch. Gen. Psychiatry* **2002**, *59*, 613–620.
- 181 ROSENTHAL, N. E., MAZZANTI, C. M., BARNETT, R. L., et al., Role of serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. *Mol. Psychiatry* **1998**, *3*, 175–177.
- 182 BENEDETTI, F., SERRETTI, A., COLOMBO, C., et al., Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *Am. J. Psychiatry* **1999**, *156*, 1450–1452.
- 183 BAGHAI, T. C., SCHULE, C., ZWANZGER, P., et al., No Influence of a functional polymorphism within the serotonin transporter gene on partial sleep deprivation in major depression. *World J. Biol. Psychiatry* **2003**, *4*, 111–114.
- 184 LEVITAN, R. D., MASELLIS, M., BASILE, V. S., et al., Polymorphism of the serotonin-2A receptor gene (HTR2A) associated with childhood attention deficit hyperactivity disorder (ADHD) in adult women with seasonal affective disorder. *J. Affect Disord.* **2002**, *71*, 229–233.
- 185 ARIAS, B., GUTIERREZ, B., PINTOR, L., GASTO, C., FANANAS, L., Variability in the 5-HT(2A) receptor gene is associated with seasonal pattern in major depression. *Mol. Psychiatry* **2001**, *6*, 239–242.
- 186 JOHANSSON, C., SMEDH, C., PARTONEN, T., et al., Seasonal affective disorder and serotonin-related polymorphisms. *Neurobiol. Dis.* **2001**, *8*, 351–357.
- 187 NEUMEISTER, A., KONSTANTINIDIS, A., STASTNY, J., et al., Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression. *Arch. Gen. Psychiatry* **2002**, *59*, 613–620.
- 188 PREDA, A., MACLEAN, R. W., MAZURE, C. M., BOWERS JR., M. B., Antidepressant-associated mania and psychosis resulting in psychiatric admissions. *J. Clin. Psychiatry* **2001**, *62*, 30–33.
- 189 DUFFIELD, G. E., DNA microarray analyses of circadian timing: the genomic basis of biological time. *J. Neuroendocrinol.* **2003**, *15*, 991–1002.
- 190 YAMAGUCHI, S., ISEJIMA, H., MATSUO, T., et al., Synchronization of cellular clocks in the suprachiasmatic nucleus. *Science* **2003**, *302*, 1408–1412.

19

Neuropeptidergic Dysfunction in Depression

Garth Bissette

19.1

Introduction

19.1.1

Neuropeptide Neurobiology

Neuropeptides are defined by convention as proteins containing approximately 90 or fewer amino acids with a combined molecular weight of less than 10 000 Daltons. Over 100 distinct, biologically active neuropeptides have been discovered that occur in the central nervous systems of animals. Estimates are that there may be several hundred in total. A majority of these have specific receptors, but only a few have well-defined physiological roles.

Neuropeptides comprise a class of phylogenetically ancient signaling molecules that have often been conserved in both sequence and function across phyla to a remarkable degree. In fact, a yeast alpha-peptide mating factor shares a similar sequence of amino acids with the mammalian gonadotropin releasing hormone neuropeptide. Neuropeptides are produced by transcription of DNA and translation of RNA into a protein product. This precursor protein or pro-hormone contains one or more copies of the active neuropeptide which is cleaved from the precursor protein by specific processing enzymes acting on sites with tandem dibasic amino acids such as lysine or arginine during transport from the ribosome–Golgi complex to storage sites in synaptic vesicles. The active neuropeptide is then released into the synaptic gap and competes for access to the post-synaptic receptor. After binding to the receptor, the neuropeptide or its active fragment is either incorporated into the post-synaptic cell or dissociates from the receptor binding site.

Neuropeptide signaling is halted by degradation of the neuropeptide sequence into smaller fragments or individual amino acids that are then incorporated into the general metabolic amino acid pool. Several specific peptidase enzymes that recognize particular sequences of amino acids cleave the active peptide into fragments and eventually into single amino acids. No evidence has been described

for the re-uptake of intact neuropeptides by the pre-synaptic neuron as occurs for the biogenic amine neurotransmitters.

Because only a few amino acids within the complete peptide sequence are required for binding to the neuropeptide receptor, it is possible for neuropeptide metabolic fragments to have activity at the receptor or for specific receptors to exist for the fragment. Furthermore, many neuropeptide families are composed of peptides with homologous sequences of amino acids but with separate messenger RNA and genes (see Table 19.1). If a peptide receptor recognizes the sequences held in common by the neuropeptide family, then it is possible to have several ligands competing for the binding site, usually with slightly different affinities. All neuropeptide receptors characterized to date use G-protein coupled second messengers to transduce the signal at the post-synaptic membrane. Some neuropeptides, such as neurotensin (NT) or thyrotropin-releasing hormone (TRH), complex with a receptor that then is translocated from the neuronal membrane to the cell nucleus where specific regulatory effects on gene expression may ensue.

The physiological effects of neuropeptides continue for minutes to hours after binding to their receptors compared to the seconds or minutes for many of the classical chemical and amino acid neurotransmitters. These characteristics are the more remarkable because the concentrations of neuropeptides range from the picomolar (10^{-12}) to femtomolar (10^{-15}) relative to the nanomolar (10^{-9}) to micromolar (10^{-6}) concentrations of the classical chemical neurotransmitters or millimolar concentrations of certain amino acid neurotransmitters such as glutamic acid.

Thus neuropeptides possess unique ability to mediate chronic physiological effects such as psychiatric symptoms. Neuropeptides themselves, however, have major limitations as direct therapeutic agents. They usually cannot be orally delivered, as gut peptidases are designed to destroy them. Unless designed for a physiological role via the circulatory system, most neuropeptides have quite short half-lives in blood and few are capable of penetrating the blood-brain barrier. Thus much hope for direct manipulation of neuropeptide receptors rests in chemicals that have similar three-dimensional structures with the active amino acid sequence (epitope) of the neuropeptide of interest. Because the amino acids that compose the epitope recognized by the receptor are often not contiguous in the amino acid sequence, this task requires an understanding of tertiary protein structure in solution, which is a notoriously difficult problem. However, several pharmaceutical companies have developed chemical agonists or antagonists for proteins that bind to neuropeptides and a few of these are currently in clinical trials.

Most neuropeptides can only be directly measured by immunoassays, which use the unique ability of the immune system to recognize subtle differences in amino acid sequences of proteins. Radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISA) are principally used to quantitatively measure relative concentrations while immunohistochemistry reveals precise cellular anatomic location. The information gained from such assays has both strengths and weaknesses. Strengths of quantitative assays include an assessment of relative concentration that approximates the contributions of extracellular synaptic availability and vesicular content of the target neuropeptide. Weaknesses of immuno-

assays are the possible recognition of similar epitopes in fragments of the active peptide or related peptides with homologous sequences and the inability to determine functional meaning from concentration measures.

If the relative concentration of a neuropeptide differs across experimental groups, there are several mechanisms that could contribute to such changes. An increase in expression of the precursor protein product of the neuropeptide messenger RNA that is processed to the active neuropeptide in rates that exceed degradation by peptidases is one possibility. Other possible scenarios are decreased degradation relative to active peptide production, decreased release of the active peptide from vesicular stores with continued synthesis of new product and a combination of these. The reverse can be said for decreased neuropeptide concentrations. Without evidence of both releasability and evaluation of peptidase activity and mRNA expression, the turnover of a neuropeptide cannot be approximated. Having stated this, it must be said that one can come much closer to an understanding of synaptic availability with concentration evidence alone than one can with either mRNA content or peptidase activity alone. Knowledge of mRNA concentration alone is particularly limited as the expression level, mRNA degradation and synthesis rates and precursor processing rate all affect active neuropeptide concentrations. Neuropeptide receptor populations are subject to similar constraints, although in increase or decrease in receptor numbers can provide evidence for chronically decreased or increased release of their endogenous neuropeptide ligands, respectively.

19.1.2

Neuropeptides and Major Depression

When certain neuropeptide neurotransmitters are directly injected into the central nervous system, they have been shown to mediate some aspects of emotional and cognitive behaviors in laboratory animals and are believed to also do so in humans. Emotions such as rage and fear are widely believed to be shared by higher organisms, and almost certainly are shared among mammals as Panksepp [1] elegantly demonstrates comparing recent human imaging studies of brain regions activated by perceived social isolation with analogous regions in guinea pig brain that are activated by actual isolation. It is not surprising that a large component of the neuronal circuitry for such emotional changes would also be shared among species. This fortunate symmetry allows investigators of neurochemical alterations in psychiatric disease to attempt to model the disease in laboratory animals for development of rational pharmacotherapies aimed at ameliorating the pathological change underlying the mental illness. That very few diseases of the mind have had such pathological changes discovered is an indication of the various etiologies that may present as a certain type of mental illness. It is also an indictment of our forced reliance on psychiatric diagnoses that are often selected entirely by descriptive symptoms that can be further confounded by semantic ambiguities and cultural differences. Furthermore, individual variations in neurotransmitter concentrations approach an order of magnitude across a group of otherwise-unrelated humans,

which necessitates large populations to achieve the statistical power needed to discern differences in the face of such variance. Add to these difficulties, the limitations ethical research imposes on clinical investigations and one rapidly realizes how much effort and time it takes to actually conduct such research. Despite these limitations, real progress is now being made in the search for neurochemical substrates of mental illness and in the investigation of major depression in particular.

The current pharmacological treatment of major depressive disorder relies on a phenomenon that was discovered more than 30 years ago, i.e. that drugs blocking the pre-synaptic re-uptake of 5-hydroxy tryptamine (5-HT, serotonin) or norepinephrine (NE) can produce relief of depressive symptoms in approximately 70% of patients. However, symptom relief does not typically occur until treatment has continued for 3–6 weeks and there have been few confirmed observations of abnormalities in either 5-HT or NE in post-mortem brain of untreated patients with depressive symptoms at the time of death. Many patients do not respond adequately to the first antidepressant drug that they are prescribed and about 30% do not respond to any of the several antidepressant drugs that they may have tried. The goal of current research into the endogenous alterations that produce major depression is to determine which substances in which brain regions are altered during depressive symptom presence and discover new ways to normalize these changes in order to relieve such symptoms. Realization of such a goal would lead to a more immediate response to antidepressant pharmacologic intervention and would include those patients that now cannot obtain relief with the currently the available antidepressant drugs.

When investigating putative alterations in endogenous substances during mental illness, one is confronted by several serious potential confounds. The first is that the diagnosis is obtained through observation and communication rather than by an empirical biologic test and may or may not be reliable depending upon the skill of the physician and the cooperation of the patient. The second limitation is the biological compartment that may be sampled. Measurement of substances in urine, blood or cerebrospinal fluid (CSF) do not localize the region of the central nervous system that is contributing to the changes observed in these communal compartments and peripheral sources of certain substances may confound interpretation of such changes in blood and urine. Post-mortem brain has the potential confounds of individual differences in length and intensity of the agonal state, amount of post-mortem degradation, prior treatment with licit or illicit drugs and the usual diagnostic issues. Also, post-mortem tissue represents but one instance in time, a snapshot of the brain at death, rather than an indication of the dynamic processes occurring during life and consciousness. Imaging techniques have not matured yet to the point where specific alterations in major depression have been confirmed and for the most part do not provide real-time information about endogenous compounds of interest in depression research.

The ideal study design for identification of “state” markers of major depressive illness which are present only when depressive symptoms are present, would be a longitudinal approach with multiple samples from the same individual, because “state” alterations may actually mediate certain symptoms. In such a hypothetical

Table 19.1 Structures of neuropeptides implicated in major depressive disorder

Adrenocorticotropin (ACTH)	Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asn-Gly-Ala-Glu-Asp-Glu-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe-OH
Vasopressin (VP)	Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH ₂
Substance P (SP)	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH ₂
Beta-endorphin (BE)	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu-OH
Leu-enkephalin (LEK)	Tyr-Gly-Gly-Phe-Leu-OH
Met-enkephalin (MEK)	Tyr-Gly-Gly-Phe-Met-OH
Dynorphin A	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln-OH
Dynorphin B	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr-OH
Galanin (GAL)	Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-His-Ala-Val-Gly-Asn-His-Arg-Ser-Phe-Ser-Asp-Lys-Asn-Gly-Leu-Thr-Ser-OH
Thyrotropin-releasing hormone (TRH)	pGlu-His-Pro-NH ₂
Somatostatin (SRIF)	Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH
Corticotropin-releasing factor (CRF)	Ser-Gln-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-Asn-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH ₂
Cholecystokinin (CCK-8S)	Asp-Tyr(SO ₃ H)-Met-Gly-Trp-Met-Asp-Phe-OH
Calcitonin	Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly-Thr-Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH ₂
Calcitonin gene-related peptide (CGRP)	Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH ₂
Neuropeptide Y	Tyr-Pro-Ser-Lys-Pro-Asp-Asn-Pro-Gly-Glu-Asp-Ala-Pro-Ala-Glu-Asp-Met-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH ₂

study, a subject with major depressive illness would be examined upon initial diagnosis with blood and spinal fluid samples while depressive symptoms were present and then sampled again after significant relief of depressive symptoms from either pharmacotherapy or spontaneous remission. For post-mortem tissue studies, a group of subjects without antidepressant drugs in their systems and who were depressed at the time of death according to their friends and family, would be compared to subjects dying under the same circumstances who were age and sex matched to the depressed subjects and who did not have depressive symptoms at death. These rigorous conditions have only been successfully fulfilled in a handful of published papers in the literature on major depression while the large majority of studies have compared single blood, urine or CSF samples from depressed subjects to single samples from controls that were psychiatrically normal. The large overlap in the individual subject's values for the measure being taken among the groups allows only an average change to be discerned which does not allow informed application to any individual subject.

This chapter will encompass peer-reviewed research articles measuring neuropeptide changes in major depressive disorder and will not include the growing data from work with animal models of depressive symptoms or their use in developing new antidepressant drugs unless they are particularly relevant to the alterations in humans under discussion. Due to the limitations of space, we will confine our review to approximately the last 10 years unless the work preceding this period remains the only evidence for changes in a particular peptide during symptoms of major depression (for a more detailed discussion of neuropeptide neurobiology see [2, 3]).

19.2

Corticotropin-Releasing Factor (CRF)

The neuropeptide that has been most extensively investigated for a role in major depressive disorder is corticotropin-releasing factor (CRF). Since the discovery of CRF by Vale and colleagues in 1979, the behavioral role of CRF in mediating fear and arousal responses, in addition to its physiological endocrine role in regulating release of adrenocorticotropin (ACTH) and other pro-opiomelanocortin (POMC) products from the anterior pituitary, has been firmly established in a variety of laboratory animals, including primates. Infusion of synthetic CRF into specific brain regions of several animal species elicits behaviors similar to fear and anxiety [4–6] and alteration of endogenous CRF concentrations has been demonstrated in several brain regions after chronic or acute exposure of laboratory animals to stressful stimuli that result in behavioral responses associated with fear and anxiety [7]. An animal model of antidepressant drug effects, the olfactory bulbectomized rat, exhibits behavioral changes that are specifically reversed by antidepressant drug treatment [8] which normalized hypothalamic CRF alterations produced by the model. CRF responses are mediated by two types of receptor, type 1 (CRF-R1) and type 2 (CRF-R2), both of which stimulate adenylate cyclase.

There is an extensive literature encompassing hypothalamic–pituitary–adrenal (HPA) axis responses to major depressive disorder symptoms and their treatment that will not be reviewed here as this subject is discussed in Chapter 17 of this volume. Briefly, major depressive disorder (MDD) was first shown to involve the peripheral components of the hypothalamic–pituitary–adrenal (HPA) axis when Sachar and colleagues [9] demonstrated increased serum cortisol at all hours of the circadian rhythm in endogenously depressed compared to non-depressed subjects. The realization that alteration of the HPA endocrine axis occurs in stressful states began with the observation by Hans Selye [10] of increased adrenal weight in rats subjected to stressful stimuli. Thus, the finding of increased cortisol in depressed humans was quickly recognized as an endocrine attempt to cope with a perceived stressor and further investigation confirmed that all levels of the HPA axis are involved in this response in patients with major depressive disorder. Carroll and co-workers [11] extended this finding to include early escape from suppression of pituitary secretion of adrenocorticotropin (ACTH) in two-thirds of melancholic subjects after suppression of the HPA axis by acute administration of the synthetic glucocorticoid, dexamethasone. Holsboer and his collaborators demonstrated that CRF receptors at the pituitary were less sensitive to stimulation with synthetic CRF in depressed subjects than those in non-depressed subjects or after relief of depressive symptoms [12]. Thus the pituitary and adrenal components of the HPA axis often act as if they were subject to increased stimulation by CRF during depression and these alterations are largely normalized by treatments that produce remission of depressive symptoms. A recent paper by Galard et al. [13] demonstrated decreased plasma concentrations of CRF after dexamethasone in depressed subjects ($n = 14$) compared to controls ($n = 12$), which indicates that hypothalamic CRF release is more sensitive to cortisol feedback in depression, although with a half-life of only several minutes in blood, plasma CRF may not have diagnostic potential without such stimulation.

Direct assessment of CRF in human central nervous system compartments has been necessarily limited to CSF and post-mortem brain examinations. A four-fold increase in numbers of CRF mRNA-expressing neurons in the paraventricular hypothalamic nucleus of post-mortem brain from depressed subjects relative to normal controls has been reported [14]. Several reports of increased levels of CRF in lumbar CSF of depressed subjects have been published to date and have generally agreed that CRF is elevated during depressive episodes [15–18], although CSF obtained from the subarachnoid space over several hours has been reported to exhibit decreased CRF concentrations in eucortisolemic depressed subjects relative to controls [19]. Two published studies [20, 21] where pre- and post-treatment lumbar CSF samples from depressed subjects were obtained before and after electroconvulsive therapy (ECT) both reported decreased post-ECT levels of CRF in most subjects. The two published studies using this paired CSF sample design after chronic treatment with fluoxetine [22] and amitriptyline [23] have also demonstrated normalization of CRF levels in CSF after depressive symptom relief. Strong evidence for the involvement of CRF circuits in the production of depressive symptoms is also found in reports of CRF receptor antagonists having antidepressant effects [24].

That some of the CSF origin of CRF is due to hypothalamic contributions has always been presumed based upon the endocrine evidence, but evidence for other brain regions that might contribute to the CSF CRF signal have been rare. At present, the best direct evidence for a non-hypothalamic brain region with alterations of CRF in human major depressive disorder is the locus coeruleus (LC). This mesencephalic nucleus contains noradrenergic neuronal cell bodies that communicate with hypothalamic, limbic and cortical targets and receive excitatory input from CRF post-synaptic terminals, among others. Recently however, the LC has been demonstrated to have increased levels of CRF in post-mortem brain from depressed subjects by independent studies using both immunohistochemical and RIA techniques. Austin et al. [25] reported immunohistochemical evidence for a 30% increase in CRF in the LC and a 39 and 45% increase in the median raphe and caudal dorsal raphe respectively in post-mortem brains from 11 men who had committed suicide relative to matched controls. Bissette et al [26] reported a 20% increase in CRF content of the LC by RIA in micropunched sections from post-mortem brain of subjects with depressive symptoms at the time of death and without antidepressant drug treatment at the time of death ($n = 10$) relative to matched controls without depressive symptoms ($n = 10$).

Electrophysiological evidence has established that CRF-containing nerve terminals synapse with LC neurons and microiontophoretic application of CRF increases the firing rate of the LC neurons [27–29]. The ability of CRF to induce behavioral correlates of fear and anxiety (defensive withdrawal) after intraventricular delivery is potentiated by infusion into the LC region [5] and 2 weeks of chronic, unpredictable stress produces increased concentrations of CRF in the LC of laboratory rats [7]. A CRF receptor antagonist applied to the LC attenuates the defensive withdrawal induced by prior immobilization [30]. Thus, it may be argued that the increased concentrations of CRF in the LC of depressed patients may be due to the stressful aspects of depressive symptoms and, by extension, that some of the symptoms of depression may be due to CRF overdrive of these LC neurons. These conclusions presume that the increased concentrations of CRF in the LC of these depressed subjects are due to increased release of CRF onto LC neurons, which is not without alternative explanation, such as increased storage. However, the behavioral and physiological literature findings make a strong case for such an interpretation. Increased concentrations of CRF in the post-mortem LC of patients with depressive symptoms at death provides validation for laboratory animal models of chronic stress as surrogates for at least some of the neurochemical changes now confirmed in humans. Clear evidence of congruence between human and animal responses in CRF circuits innervating the LC and hypothalamus have now provided a way to assess the relevance of animal models to human major depressive disorder, at least for CRF.

While CRF levels in lumbar CSF from depressed patients [15, 16] or completed suicides [31] has been repeatedly demonstrated to be elevated, CRF concentrations in lumbar CSF from subjects with a prior suicide attempt have been reported either to be decreased [32, 33], or unchanged [34], possibly due to the absence of depressive symptoms at the time of CSF withdrawal. Interestingly, pituitaries from completed

suicides also indicate hypersecretion of hypothalamic CRF with elevated mRNA levels of pro-opiomelanocortin and glucocorticoid receptors [35] and a shift in the ratio of CRF 1 versus CRF 2 receptors [36]. Thus a case can now be made for hypersecretion of CRF in both the LC and hypothalamus of depressed patients potentially contributing to elevated lumbar CSF levels of CRF.

Further evidence supporting such central CRF hypersecretion may be found in receptor responses to chronic stimulation by the receptor ligand. Increased regional concentrations of a neuropeptide can be due to increased synthesis that exceeds physiological release and degradation or, alternatively, can be due to decreased release and/or degradation relative to synthesis and storage. In the former case, CRF mRNA levels should also increase and, if release is sustained, should be associated with locally reduced numbers of post-synaptic CRF receptors. This receptor “down-regulation” was originally reported for CRF receptors in the frontal cortex of suicides [37]. However, decreased numbers of CRF receptors were not confirmed in two later studies [38, 39], although in none of these studies were depressive symptoms documented at the time of death. In the hypothetical case of decreased release of CRF resulting in increased storage of pre-synaptic CRF, a regional increase in CRF binding protein and, eventually, increased numbers of CRF receptors might be expected, but no such evidence has been reported to date.

Preliminary evidence for an altered genetic component of CRF regulation in depressed subjects has recently been reported. A recent survey of subjects with unipolar major depression ($n = 89$) matched to controls ($n = 88$) for age, gender and ethnicity found two single nucleotide polymorphisms that are within the coding regions for the CRF binding protein in the depressed cohort relative to controls [40], although the effect of this polymorphism on endogenous CRF levels in brain remains unknown. Thus, the available evidence indicates that hypothalamic and midbrain CRF circuits in the brain that also contribute to lumbar CSF levels of CRF are apparently hyperactive during depressive symptom presence and it seems likely that at least some components of depressive symptoms may be caused by this putative hypersecretion of CRF.

19.3

Thyrotropin-Releasing Hormone (TRH)

This tripeptide regulates release of thyrotropin and prolactin from the anterior pituitary and is implicated in physiological regulation of body temperature (see [41] for a review). Pharmacologically, TRH reverses the effects of drugs that produce depression of CNS activity, such as alcohol and barbiturates and assists in neuronal recovery from damage through trophic effects. This arousal-like effect of TRH may be responsible for its beneficial effects in psychiatric disorders and TRH may be particularly useful in this regard as it produces CNS effects after peripheral administration.

19.3.1

TRH in Major Depressive Disorder

As the endocrine system is notoriously interdependent and regulated at multiple levels, it is not surprising that endocrine systems other than the adrenal axis are found to be altered in patients suffering from depression. These include the hypothalamic–pituitary–thyroid (HPT) axis, which has many of the same pathological features associated with depressive symptoms that were reviewed elsewhere for the HPA axis. While early reports that TRH possessed some antidepressant effects in women [42] were not widely replicated until recently [43], the hypothesis was not without feasibility, as TRH alone among the neuroendocrine releasing factors and hormones can cross the blood–brain barrier. A recent study involving a single intrathecal TRH (500 µg) administration to eight refractory depressed patients resulted in significant improvement in clinical rating scale scores in five patients [44]. The observation that groups of depressed patients have clear elevations in TRH concentrations in CSF has been almost exactly reproduced in two different populations of depressed patients by two different groups of investigators using different reagents [45, 46]. However, it is not observed in all populations of depressed patients in which CSF concentrations have been examined [47]. It is not known whether this is due to differences in severity of symptoms in different populations or due to differences in diagnostic criteria. However, other indications of the role of the HPT axis in depression include the high incidence of depressive symptoms in patients with thyroid disease, so high that a thyroid hormone disorder is one of the first medical causes sought for a presentation of depressive symptoms. A decrease in the circadian rhythm of TSH release into serum has been reported in groups of depressed patients relative to age- and sex-matched, non-depressed controls [48], which could be a response to hypersecretion of hypothalamic TRH. A further supporting finding is the apparent “down” regulation of TRH receptors or other mechanisms by which the injection of synthetic, exogenous TRH induces less release of thyrotropin (thyroid stimulating hormone, TSH) in a high proportion of depressed patients compared to age and sex-matched non-depressed controls [49] and which has been reported to normalize upon remission of the depressive symptoms [50]. The proportion of depressed patients with this “blunted” response to the TRH stimulation test is lower than the proportion of patients with blunted ACTH responses to CRF or with altered escape from dexamethasone suppression of ACTH and has been reported to be present in a relatively high proportion of alcoholics, thus making the TRH stimulation test of less potential use as an adjunct diagnostic indicator. However, the finding of alterations at the pituitary receptor level underscores the involvement of hypothalamic TRH release as being the most likely cause for the receptor response change, although extra-hypothalamic CNS sources of TRH are not excluded.

Animal studies have shown TRH to be altered in discrete brain regions by stressful stimuli (see [51] for a review), as well as CRF, and the role of the thyroid axis in responding to climatic changes is well known. The injection of pharmacologic doses of TRH peripherally or into discrete brain regions such as the anterior septum [52]

reverses the sedation and hypothermia produced by alcohol or barbiturates. This analeptic effect of TRH in reversing the effects of CNS depressant drugs is one of several indications that TRH can affect arousal mechanisms and lends further credence to the postulate that TRH systems in the CNS could play a role in endogenous depressive states. The further finding that TRH in the pre-optic anterior hypothalamus physiologically regulates thermoregulatory responses, as demonstrated by microiontophoretic application of TRH in physiological amounts causing an increase in the firing rate of cold-sensitive neurons and a decrease in the firing rate of cold-sensitive neurons in this region [53], led to the investigation of the role of TRH in producing the nocturnal hyperthermia and decreased circadian cycle of TSH secretion observed in bipolar affective disorder patients during the depressive stage of their illness and which is absent during remission of depressive symptoms [54].

There have been several reports of antidepressant drugs [55], and electroconvulsive shock [56] altering TRH concentrations, usually by increasing them, in discrete brain regions of laboratory rats. The 5-HT re-uptake inhibitor antidepressant, zimelidine, decreases TRH mRNA levels in medullary raphe neurons [57] where TRH is co-localized with 5-HT and where depletion of 5-HT increases TRH mRNA. TRH neurons of the paraventricular nucleus receive CRF and somatostatin terminals [58]. TRH is released from the median eminence by even brief restraint [59] or hemorrhage [60] stress and particularly by cold exposure, which may also cause release of CRF. TRH mRNA levels are also increased in the paraventricular nucleus of the hypothalamus by cold exposure [61] and antidepressant drug treatment inhibits cold-induced TRH release from the hypothalamus [62]. The concatenation of clinical and basic research on TRH indicates that TRH release is part of the stress response and thus might be expected to be secreted during the presence of depressive symptom, leading to altered concentrations in CSF. The response of human CSF levels of TRH to antidepressant drug treatment leading to depressive symptom remission remains unknown, although the data reviewed above would predict that concentrations would be reduced.

Post-mortem human studies using *in-situ* hybridization and autoradiography have measured decreased amounts of pre-pro-TRH mRNA in the paraventricular hypothalamic nucleus from post-mortem brain of depressed subjects ($n = 7$) relative to controls ($n = 7$) [63], which would suggest regulatory responses to the increased release of TRH.

Thus, hypersecretion of TRH in major depression apparently down-regulates pituitary TRH receptors mediating the release of TSH from the pituitary and contribute to increased CSF concentrations that are apparently state dependent as electroconvulsive therapy decreases CSF TRH [46]. This hypothesis has received further support from Staner et al. [64], who describe blunting of the TSH response to intravenous TRH in 113 depressed subjects. They administered TRH at 08.00 and 23.00 hours and found that 77% of subjects had a significantly decreased TSH response when the difference between the effects on TSH was compared for the two different times of administration of TRH. There was no relationship between the blunted TSH response and sleep EEG changes that were observed in these

subjects. Blunted TSH responses to TRH challenge were also reported by Duval et al. [65] in depressed patients ($n = 60$) compared to controls ($n = 20$) and they demonstrated that patients with such blunted responses had more normal endocrine response to d-fenfluramine challenge than depressed patients with more normal TSH responses to TRH. Such a finding indicates a possible distinction in the mechanisms of depression in subjects with HPA versus HPT alterations. Amsterdam et al. [66] reported no essential change in TSH responses to TRH after 6 weeks of fluoxetine treatment between subjects receiving relief of depressive symptoms and those with no improvement nor were such responses related to liability for relapse. French researchers [67] tested two groups of subjects ($n = 40$) that were treated with either maprotiline or fluvoxamine for 28 days and reported a decreased TSH response to TRH after the serotonin re-uptake inhibitor fluvoxamine, with an increased TSH response to TRH after the norepinephrine uptake inhibitor, maprotiline. In a study with impressive numbers of subjects Molchan et al. [68] reported that 28% of non-bipolar depressed subjects ($n = 280$) had a blunted TSH response to TRH, although correlations with severity of depression or sleep EEG disturbances were not sustained. Garbutt et al. [70] reported that depressed men ($n = 6$) responded to TRH stimulation with decreased TSH and prolactin responses compared to controls ($n = 7$), whereas alcoholic men ($n = 8$) only demonstrated decreased TSH responses to TRH challenge, differentiating these populations that both show blunted TSH responses.

The antidepressant drug, paroxetine, has been shown to decrease (11%) the serum levels of thyroxine (T4) in 25 severely depressed subjects [70], although a recent study of 101 subjects sampled before initial treatment of depression found no evidence for thyroid hormone levels being associated with treatment response to antidepressant drugs [71]. Molchan et al. [68] confirmed the blunted TSH response to TRH stimulation in elderly depressed subjects ($n = 18$) compared to normal controls ($n = 13$) and Alzheimer's disease (AD) subjects ($n = 40$).

Induction of TRH synthesis by electroconvulsive shock may mediate some of the therapeutic aspects of this treatment in reversing symptoms of major depression and this topic is reviewed by Sattin [73]. Kirkegaard [46] reported decreased CSF levels of TRH in depressed subjects after ECT but Hofmann et al. [74] did not find alterations in the TSH response to TRH in depressed subjects after several ECT treatments compared to their responses before ECT.

Taken together, the clinical data indicate increased secretion of hypothalamic TRH circuits during major depressive episodes that leads to decreased pituitary receptor responses to stimulation by TRH, and increased CSF levels of TRH. At present, there is no clinical evidence for the contribution of extra-hypothalamic TRH circuits to depressive symptom profiles, but the ability of TRH treatment to briefly ameliorate depressive symptoms would suggest that a TRH receptor agonist would be a promising antidepressant candidate.

19.4

Somatostatin (SRIF, Somatotropin-Release Inhibiting Factor)

Somatostatin is a neuropeptide that was originally isolated from the hypothalamus of sheep and pigs as a factor controlling the release of pituitary hormones (see [75, 76] for reviews). Somatostatin was shown to physiologically regulate the release of growth hormone and many other pituitary hormones by providing the inhibitory component of the dual regulation experienced by most of the anterior pituitary hormones. Upon further investigation, it was quickly realized that the distribution of SRIF outside of the hypothalamus was more indicative of a neurotransmitter role in addition to that as a hypothalamic releasing factor and application of SRIF to neurons consistently inhibited their firing rate. It was subsequently found to often be co-localized within neurons containing the inhibitory transmitter, gamma amino butyric acid (GABA), in the cortex and two active forms have been identified which are cleaved from a larger precursor molecule and contain either 14 or 28 amino acids. Five molecular subtypes of SRIF receptors have now been cloned and the specific peptidases contributing to the degradation of active SRIF have also been identified.

19.4.1

Somatostatin in Major Depressive Disorder

The pituitary hormone regulatory mechanism includes dual regulation by stimulatory hormones and releasing factors as well as inhibitory factors that prevent or decrease pituitary hormone release. The principal inhibitory agent is somatostatin which was named for the first inhibitory effect discovered for it, namely the inhibition of growth hormone (somatotropin) release. Somatostatin also inhibits the release of several other anterior pituitary hormones, including ACTH and TSH. Unlike TRH and CRF, the CSF concentration of SRIF is decreased, rather than increased, in groups of depressed patients ($n = 17$) compared to non-depressed control ($n = 10$) [77] and this is consistent with a general effect of increased secretion of the pituitary hormones during the depressive episode. However, just about any group of patients with cognitive disturbances have been reported to have reduced amounts of SRIF in CSF; these groups include such diverse populations as schizophrenic, Alzheimer disease, Huntington's disease, Parkinson's disease with dementia, multiple sclerosis with cognitive disturbances and otherwise cognitively normal patients during states of delirium (see [78] for a review). That these changes may be reflective of a reversible process when the delirious state is no longer present is indicated by the normalization of these CSF concentration deficits in somatostatin induced by delirium. At least one report has indicated that the reduction in somatostatin concentrations in CSF during depression is ameliorated after treatment with a regimen of ECT [20]. In the post-mortem brain of patients who died with a diagnosis of depression, somatostatin receptors do not appear to be changed, although the few subjects evaluated may not represent an adequate sample [79]. Thus, there is some reason to believe that SRIF in CSF may be a state marker for depressive symptoms, albeit a non-specific one.

Animal studies have reported increased releasability of SRIF from perfused median eminence of rats exposed to 2 h of immobilization stress for seven consecutive days, but did not find changes in pituitary receptors for SRIF mediating growth hormone release [80]. Some antidepressant drugs (clomipramine and zimelidine) have been shown to selectively decrease SRIF concentrations in various brain regions, while others (imipramine, maprotiline, mianserin, carbamazepine and zotepine) were without such effects after 10 days of twice daily intraperitoneal injections [81]. Desipramine has been reported to increase the numbers (B_{\max}) of SRIF receptors in the nucleus accumbens after chronic, but not acute, treatment [82]. These data indicate that SRIF systems in various CNS regions are targets of stress and antidepressant drug effects, but do not provide evidence for the relationship of these changes to behavioral states seen in major depression.

Widerlov et al. [83] reported increased CRF and decreased SRIF in 22 patients with major depression compared to 10 controls and although CRF correlated with catecholamine metabolites in CSF, SRIF did not exhibit such correlations. Although not statistically significant, SRIF was increased after a regimen of ECT in nine subjects with major depressive disorder and psychotic features, indicating a potential state marker response [20]. Molchan et al. [84] compared CSF SRIF in both elderly major depressed ($n = 18$) and Alzheimer's disease subjects ($n = 60$) against aged normal controls ($n = 12$) and correlated decreased SRIF with decreased serotonin metabolite content in both groups compared to controls. Evidence of an interaction between CRF and SRIF was reported by Molchan et al. [85] in a group of elderly depressed ($n = 18$) and Alzheimer's disease subjects ($n = 49$) compared to aged normal controls ($n = 13$). The CRF and SRIF levels in CSF of the AD subjects were significantly correlated and the correlation between the levels of these two neuropeptides in the CSF of the depressed group was also near significance. Both the Alzheimer's disease and depressed groups had decreased levels of SRIF in CSF compared to the controls. Kling et al. [86] compared CSF levels of SRIF and CRF in subjects with major depression ($n = 28$), Cushing's disease ($n = 11$) and normal controls ($n = 41$) and reported decreased SRIF in the depressed group relative to the controls with the Cushing's patients having even lower amounts of SRIF in CSF. Both the Cushing patients and the controls had significantly correlated SRIF and SRIF levels, but this relationship was not maintained in the depressed subjects. Such a finding may indicate that SRIF in the CNS is sensitive to cortisol levels in blood and CRF tone in the hypothalamus. Indirect evidence of possible SRIF alterations in adolescents and young adults with a major depressive episode after a neuroendocrine and sleep study 10 years prior was obtained by retrospectively examining the growth hormone (GH) secretion data from their adolescent sleep data. From the initial group of 77 subjects, those that later had a major depressive episode had a more rapid increase in the release of GH following sleep onset than did subjects who did not go on to have a later depressive episode. Abnormal sleep-related regulation of GH release at sleep onset may be the mechanism to explain such a finding and would suggest that decreased SRIF could be a trait marker of depression [87]. Westrin et al. [88] reported that the CSF levels of somatostatin of 16 subjects were increased from initial levels measured after a suicide attempt to

follow-up levels obtained after 5–7 months of treatment resulting in significant symptom relief, while CRF concentrations remained similar at both time-points. Blunted growth hormone responses to a growth hormone-releasing hormone (GHRH) stimulation test were reported in children at increased risk of affective disorder when compared to low-risk children [89].

Somatostatin may well be a state marker of depressive symptoms based upon data collected to date. However, pre- and post-treatment trials examining CSF SRIF would be helpful in establishing SRIF as a state marker in major depression.

19.5 Substance P (SP)

Substance P is an 11-amino acid member of the neurokinin peptide family with roles in pain perception and salivary secretion and has also been implicated in learning and memory functions in normal and lesioned laboratory animals (for reviews see [90, 91]). There are currently three known subtypes of neurokinin receptors (NK1, NK2 and NK3) distributed throughout the CNS and gut [92].

19.5.1 Substance P in Major Depression

Substance P (SP) has been implicated in MDD in a way that represents the reverse approach to finding endogenous agents that are altered by depressive symptoms. The original report [93] of elevated SP concentrations in CSF of depressed subjects ($n = 12$) compared to psychiatrically normal controls ($n = 15$) could not be replicated [94] using non-medicated unipolar depressed subjects ($n = 12$) compared to normal controls ($n = 6$). Another later study sought changes in CSF SP after 3 or 6 weeks of treatment with fluoxetine in hospitalized subjects with major depressive disorder ($n = 13$) but did not report significant differences due to treatment [95]. Thus, until recently, SP concentrations in CSF of depressed subjects did not seem to be reproducibly elevated during depression. However, indications of putative antidepressant activity in rats administered a neurokinin NK1 receptor antagonist (see [96] for a review) led to clinical trials that have been both positive and negative [97]. This salutary response led to a renewed interest in the search for alterations in endogenous ligands for tachykinin receptors in MDD. Bondy et al. [98] have reported increased serum levels of SP in depressed subjects ($n = 23$) relative to non-depressed controls ($n = 33$) and found that antidepressant treatment for 4 weeks decreased SP levels in 37% of patients and this decrease correlated with more effective relief of depressive symptoms by the drug treatment. Using post-mortem brain from subjects ($n = 11$) diagnosed as having depressive symptoms at the time of death ($n = 12$), Stockmeier et al. [99] reported decreased numbers of neurokinin-1 receptors throughout all cortical layers of the orbitofrontal cortex of the depressed subjects when compared to matched non-depressed controls. Such changes would be expected if SP synaptic availability is chronically increased in MDD. Burnet and

Harrison [100] found that NK1 receptors in the cingulate cortex of depressed ($n = 13$) or bipolar subjects ($n = 13$) and controls was not different in post-mortem brain but that in unipolar depressed subjects the difference between the number of receptors in the superficial versus deep layers of the cortex was small. A potential mechanism of NK1 receptor blockade in producing depressive symptom relief was demonstrated by Haddjeri and Blier [101] in rats treated with an NK1 antagonist for 14 days. Rats thus treated had enhanced firing of serotonin neurons of the dorsal raphe after disinhibition with a selective 5-HT1 antagonist that was enhanced in these rats when compared to rats treated for only 2 days, vehicle-treated rats or rats treated for 14 days with a similar compound without NK1 receptor effects.

Substance P is degraded by angiotensin-converting enzyme among other peptidases and there has been one report of an association of a polymorphism in the gene for this enzyme with dysregulation of the HPA axis in depression and with increased responses to antidepressant drugs [102], although these findings could not be replicated in a separate population [103]. Two additional CSF studies in depressed subjects have been reported in abstract form at the time when this chapter was written: one in which single CSF samples from untreated depressed ($n = 36$) and psychiatrically normal control subjects ($n = 49$) were compared and significant elevations in SP levels were described in the depressed subjects [104]; in another study, subjects with medicated treatment-resistant major depression ($n = 21$) were compared to normal controls ($n = 21$) and found to have decreased amounts of CSF SP [105]. If replicated, such a finding would indicate that SP levels increase during major depressive episodes and decrease after antidepressant drug treatment, although without achieving symptom relief as would be the case with a state marker of depression that normalizes upon symptom remission.

Thus, SP was assumed to be altered in major depression based upon activity of a receptor antagonist in an animal model screen (forced swim test) rather than initially reported as reproducibly changed in post-mortem brain or in CSF from living subjects. Although some evidence exists at present for such clinical alterations in SP the final word has not been written on the effectiveness of tachykinin receptor antagonists for relief of depressive symptoms. However, during the last week of preparation of this chapter, Merck Pharmaceuticals announced discontinuation of their SP receptor antagonist for use in the treatment of major depressive disorder.

19.6 Endogenous Opioids

The endogenous opioids comprise a family of neuropeptides that interact with one or more types of opioid receptors (for a review see [106]). One of the possible cleavage products of proopiomelanocortin (POMC) precursor protein is beta-endorphin (BE), which is released from the anterior pituitary by the actions of CRF, vasopressin or urocortin on POMC cells. The enkephalins (Met-enkephalin (MEK) and Leu-enkephalin (LEK) are derived by differential processing of the pro-enkephalin precursor protein and four different bioactive products can be obtained from the

pro-dynorphin precursor protein (dynorphin A and B and alpha- and beta-neoendorphin). The opioid receptors comprise three major subtypes, mu, delta and kappa opioid receptors. Unlike most neuropeptides, a chemical antagonist for opioid receptors, naloxone, has been known for some time. This panoply of possible agonists and multiple receptors provides a rich substrate for behavioral and physiological responses to painful stimuli. As perceptions of pain can be potentiated or suppressed in major depressive disorder, it is not surprising that the endogenous opioids have been investigated for a possible role in this disease.

19.6.1

Endogenous Opioids in Major Depression

del Campo et al. [107] treated depressed female subjects ($n = 7$) and normal matched controls ($n = 7$) with naloxone twice per day for 2 days and reported naloxone-induced elevations in plasma levels of cortisol, ACTH and luteinizing hormone (LH) along with subjective dysphoria in both groups, but greater dysphoria and blunted afternoon cortisol responses to naloxone in the depressed group. This finding may indicate increased sensitivity of endogenous opioid receptors to blockade in major depressive disorder.

Hurd [108] reported significantly decreased prodynorphin mRNA levels in two of four sub-nuclei of the amygdaloid complex using post-mortem brain from patients diagnosed with unipolar depression ($n = 14$) compared to psychiatrically normal controls ($n = 15$). Bipolar subjects ($n = 14$) also had decreased prodynorphin mRNA in these same regions, but the reductions were not as severe as in the depressed subjects. A previous study [109] reported no changes in prodynorphin or kappa opiate receptor mRNA in the prefrontal cortex or cingulate cortex of depressed subjects relative to controls.

Animal studies have shown decreased delta-opioid receptor numbers, with no change in affinity, in the frontal cortex of rats treated for 15 days, but not for 5 days, with the antidepressant drug clomipramine [110].

Using an animal model of depressive symptoms, the chronic mild stress rat, Dziedzicka-Wasylewska and Papp [111] reported that chronic imipramine treatment reversed the stress-induced decrease in met-enkephalin in the nucleus accumbens, while both stressed and control rats were reported to have decreased met-enkephalin in the ventral tegmental area after chronic imipramine treatment. This result argues that part of the therapeutic effect of tricyclic antidepressant drugs may involve the meso-limbic endogenous opioid circuitry.

19.7

Neuropeptide Y

The most abundant and highly conserved member of the pancreatic polypeptide family is neuropeptide Y (NPY). This 36-amino acid peptide has identical sequence homology in humans and rats and is widely distributed in the central nervous

system. There are currently three known receptors for NPY (see [112] for a review). Ordway et al. [113] reported no change in frontal cortex NPY protein content from suicide victims with depressive symptoms at the time of death, while a later study [114] confirmed this finding in major depression for NPY mRNA, although they reported a decrease in NPY mRNA in the prefrontal cortex of bipolar affective disorder subjects.

Caberlotto and Hurd [115] have measured mRNA for the Y1 and Y2 receptors for neuropeptide Y in the dorsolateral prefrontal cortex from post-mortem brain of subjects with major depression compared to normal controls and found no changes except for an elevation of Y2 mRNA in layer 4 of patients who died from suicide. A current history of marijuana use was associated with elevations in Y1 mRNA.

CSF concentrations of NPY have been reported to be decreased in major depressive disorder subjects in comparison to schizophrenic subjects or normal controls [116], a finding that supports decreased synaptic availability of NPY in major depressive disorder. Plasma levels of neuropeptide Y and CRF were reported to be low in patients who had recently attempted suicide compared to controls and NPY was lowest in those patients who had attempted suicide the highest number of times [117]. Another report of increased CRF in plasma of depressed ($n = 26$) and dysthymic ($n = 10$) subjects compared to normal controls ($n = 17$) found that severity of depression increased plasma CRF concentrations [118]. The plasma concentrations of NPY were reported to be decreased when platelets were removed and platelet NPY was reported to be elevated in depressed subjects compared to controls [119]. In a pilot study, plasma levels of NPY were found to be decreased in women ($n = 5$) after 2 weeks of a 4-week regimen of electroacupuncture treatment for depression [120].

Animal studies have documented that a 14-day regimen of electroconvulsive shock therapy increases the concentration of NPY protein in the frontal and parietal cortex and the hippocampus [121] and this was extended to include mRNA for NPY in the piriform cortex and dentate gyrus by Mikkelsen et al. [122].

19.8

Vasopressin and Oxytocin

Vasopressin (VP) and oxytocin (OXY) are posterior pituitary hormones released into the circulation from neuronal origins in magnocellular nuclei of the hypothalamus. Regulating osmotic balance and blood pressure, VP is an 11-amino acid neuropeptide, as is OXY, which regulates parturition, milk ejection, maternal behavior and social recognition (see [123] for a review). Vasopressin has a long history of association with major depressive disorder (see [124] for a review). Vasopressin potentiates corticotropin release from the anterior pituitary and is reported to be altered by major depressive disorder. Unlike many of the CNS neuropeptides, VP levels in blood may be reliably measured as it is released from the posterior pituitary gland into the circulatory system to produce its physiological effects of regulating osmolarity. Vasopressin also produces behavioral effects and

an analog of VP is marketed as a memory enhancing agent. Elevated VP levels in plasma from depressed subjects ($n = 34$) was reported to be associated with blunted TSH responses to TRH [125]. Swaab's group has reported an average 56% increase in VP neurons and a 23% increase in OXY neurons in the post-mortem paraventricular hypothalamic nucleus of unipolar depressed subjects ($n = 8$) matched to normal control ($n = 8$) subjects [126]. Pitts et al. [127] did not observe statistically significant differences in VP, OXY or CRF in CSF from drug-treated major depressive disorder subjects ($n = 19$) compared to controls ($n = 18$), but did report a significant correlation between VP and CRF in both groups confirming the close physiological association of these two hypophyseal regulators. van Londen et al. [128] reported increased levels of plasma VP in a large group of subjects with major depression ($n = 52$) compared to normal controls ($n = 37$) and associated this increase with daytime psychomotor retardation and night-time restlessness in a separate group of patients with major depression ($n = 48$) compared to healthy controls ($n = 30$) over a 5-day consecutive period [129]. Similar associations with OXY were not observed. In a study of 55 subjects with major depression receiving a course of ECT, plasma VP increased in subjects receiving a second ECT with current 150% above seizure threshold compared to lower-current ECT subjects, although no association with clinical improvement and amount of VP secretory surge was found at the second or ninth ECT session [130]. Thus, unlike CRF, elevated levels of VP do not seem to be a state marker of the presence of major depressive symptoms.

19.9 Cholecystokinin

Cholecystokinin (CCK) is a 33-amino acid neuropeptide that shares sequence similarity with the gut hormone, gastrin (see [131] for a review). There are two CCK receptors, CCKA and CCKB and the C-terminal eight-amino acid, sulfated fragment of CCK has activity at both receptor subtypes.

CCK concentrations in CSF from depressed subjects ($n = 10$) were not found to be different from normal controls ($n = 10$) using a 6-h, continuous sampling (10 min) protocol [132]. CCK and CRF concentrations in CSF are more highly correlated in depressed ($n = 10$) and abstinent alcoholic ($n = 5$) subjects than in normal controls ($n = 15$) during a continuous CSF withdrawal protocol that sampled CSF every 10 min for 6 h [133]. Thus the hypersecretion of CRF may also produce hypersecretion of CCK in major depressive disorder.

19.10**Delta Sleep-inducing Peptide**

Delta sleep-inducing peptide (DSIP) contains nine amino acids and is reported to induce sleep onset in mammals. As major depression often presents with sleep disturbances, it is not inconceivable that DSIP may be altered in this illness. Westrin et al. [134] have reported increased plasma levels of DSIP in patients who have attempted suicide ($n = 34$) compared to age- and sex-matched controls ($n = 34$) and found a disassociation between DSIP and the adrenal axis in the depressed subjects relative to the controls after dexamethasone administration.

19.11**Hypocretins/Orexins**

Orexins/hypocretins are peptides that affect appetite and sleep regulation (see [135] for a review). Orexin A contains 32 and orexin B contains 28 amino acid residues, with orexin A binding to the orexin receptor with approximately 10-fold higher affinity than orexin B. Found in brain within the hypothalamus, these peptides may be altered in major depressive disorder which often presents with disturbances in food intake and sleep rhythms.

Administration of synthetic orexin-A (hypocretin-1) to rats via an intracerebroventricular route slows their ability to learn a spatial memory task in a water maze and their subsequent retention of that memory in later trials and produces suppression of long-term potentiation in CA1 neurons of the hippocampus *in vitro* [136]. This putative mechanism may not be associated with major depressive disorder, because a decrease in CSF hypocretin is seen in depression and narcolepsy [137]. CSF concentrations of orexin-A (hypocretin-1) was reported to be decreased in depressed subjects ($n = 15$) compared to control ($n = 14$) subjects and was further decreased by 5 weeks of sertraline treatment [138], although no evidence of decreased food intake in the depressed subjects was mentioned.

19.12**Galanin**

Galanin (GAL) was originally purified from colon and pituitary and is a 30-amino acid neuropeptide that generally inhibits firing of neurons with which it communicates (see [139] for a review). Recently a third GAL receptor, GAL3, was cloned in rats and humans [140], joining the prior two GAL receptor subtypes to be described. In the only paper found that measured GAL in CSF of involuntarily depressed subjects, no differences from age and sex-matched controls was reported [141]. Therefore, it is not evident that GAL concentrations or synaptic availability is altered in major depressive disorder.

19.13

Calcitonin Gene-Related Peptide (CGRP)

Calcitonin and calcitonin gene-related peptide (CGRP) are 32- and 37-amino acid neuropeptides, respectively, that regulate calcium levels in blood and gastric acid secretion (see [142] for a review). Calcitonin gene-related peptide and calcitonin have been measured in CSF of patients with major depression ($n = 29$) and in normal controls ($n = 19$) and calcitonin was reported to be decreased in the depressed subjects while CGRP concentrations remained unchanged [143]. A previous report that measured CGRP in depressed patients ($n = 63$) compared to healthy controls ($n = 20$) found an increase in CSF concentrations of CGRP in the depressed group [144]. Thus the evidence for increased CGRP secretion in major depression is not confirmed at present.

19.14

Conclusions

Several neuropeptides have been demonstrated to be altered in major depressive disorder and among these CRF, TRH and somatostatin have been implicated as state markers of depression. Evidence for the involvement of other neuropeptides in this disorder is also accruing and it will be of major interest to observe how SP receptor antagonists develop as an antidepressant treatment. Other neuropeptides that are as yet undiscovered may prove to be intimately involved in emotional responses and to also be altered in major depression. Further development of animal models that reproduce the alterations seen in humans subjects with major depression are a critical part of the investigation into these agents in this disease and of the development of more rational treatments based upon reproducible clinical observations.

References

- 1 PANKSEPP, J., Feeling the pain of social loss. *Science* **2003**, *302*, 237–239.
- 2 OWENS, M. J., NEMEROFF, C. B., BISSETTE, G., Neuropeptides: Biology, regulation and role in neuropsychiatric disorders. In KAPLAN, H. I., SADDOCK, B. J. (Eds.), *The Comprehensive Textbook of Psychiatry*, VII, Vol. 1. Williams and Wilkins: Philadelphia, **2001**, 60–70.
- 3 HOKFELT, T. G. M., CASTEL, M. N., MORINO, P., ZHANG, X., DAGERLIND, A., General overview of neuropeptides. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 483–492.
- 4 KOOB, G., BRITTON, K., Behavioral effects of corticotropin-releasing factor. In DESOUSA, E. B., NEMEROFF, C. B. (Eds.), *Corticotropin-releasing Factor: Basic and Clinical Studies of a Neuropeptide*. Boca Raton, FL: CRC Press, **1990**, 253–265.
- 5 BUTLER, P. D., WEISS, J. M., STOUT, J. C., NEMEROFF, C. B., Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus coeruleus. *J. Neurosci.* **1990**, *10*, 176–183.

- 6 STROME, E. M., WHEELER, G. H., HIGLEY, J. D., LORIAUX, D. L., SUOMI, S. J., DOUDET, D. J., ICV CRF increases limbic glucose metabolism and has social context dependent behavioral effects in nonhuman primates. *Proc. Natl. Acad. Sci. USA* **2002**, 99, 15749–15754.
- 7 CHAPPELL, P. B., SMITH, M. K., KILTS, C. D., BISSETTE, G., RITCHIE, J., ANDERSON, C., NEMEROFF, C. B., Alterations in corticotropin-releasing factor-like immunoreactivity in discrete rat brain regions after acute and chronic stress. *J. Neurosci.* **1986**, 6, 2908–2914.
- 8 BISSETTE, G., Effects of sertraline on regional neuropeptide concentrations in olfactory bulbectomized rats. *Pharmacol. Biochem. Behav.* **2001**, 69, 1–13.
- 9 SACHAR, E. J., HELLMAN, L., ROFFWARG, H. P., HALPERN, F. S., FUKUSHIMA, D. K., GALLAGHER, T. F., Disrupted 24-hour patterns of cortisol secretion in psychotic depression. *Arch. Gen. Psychiatry* **1973**, 28, 19–24.
- 10 SELYE, H., A syndrome produced by diverse nocuous agents. *Nature (Lond.)* **1936**, 138, 32–36.
- 11 CARROLL, B. J., FEINBERG, M., GREDEN, J. F., TARIKA, J., ALBALA, A. A., HASKETT, R. F., JAMES, N. M., KRONFOL, Z., LOHR, N., STEINER, M., DEVIGNE, J. P., YOUNG, E., A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. *Arch. Gen. Psychiatry* **1981**, 38, 15–22.
- 12 HEUSER, I., YASSOURIDIS, A., HOLSBOER, F., The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *J. Psychiatr. Res.* **1994**, 28, 341–356.
- 13 GALARD, R., CATALAN, R., CASTELLANOS, J. M., GALLART, J. M., Plasma CRF in depressed patients before and after dexamethasone suppression test. *Biol. Psychiatry* **2002**, 51, 463–468.
- 14 RAADSHEER, F. C., HOOGENDIJK, W. J., STAM, F. C., TILDERS, F. J., SWAAB, D. F., Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology* **1994**, 60, 436–444.
- 15 NEMEROFF, C. B., WIDERLOV, E., BISSETTE, G., WALLEUS, H., KARLSSON, I., EKLUND, K., KILTS, C. D., LOOSEN, P. T., VALE, W. W., Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* **1984**, 226, 1342–1344.
- 16 BANKI, C. M., BISSETTE, G., ARATO, M., O'CONNOR, L., NEMEROFF, C. B., Cerebrospinal fluid corticotropin-releasing factor-like immunoreactivity in depression and schizophrenia. *Am. J. Psychiatry* **1987**, 144, 873–877.
- 17 KASCKOW, J. W., BAKER, D., GERACIOTI, T. D., Corticotropin-releasing hormone in depression and post-traumatic stress disorder. *Peptides* **2001**, 22, 845–851.
- 18 KECK, M. E., HOLSBOER, F., Hyperactivity of CRH neuronal circuits as a target for therapeutic interventions in affective disorders. *Peptides* **2001**, 22, 835–844.
- 19 GERACIOTI, T. D., LOOSEN, P. T., ORTH, D. N., Low cerebrospinal fluid corticotropin-releasing hormone concentrations in eucortisolemic depression. *Biol. Psychiatry* **1997**, 42, 165–174.
- 20 NEMEROFF, C. B., BISSETTE, G., AKIL, H., FINK, M., Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy: corticotropin-releasing factor, β -endorphin and somatostatin. *Brit. J. Psychiatry* **1991**, 158, 59–63.
- 21 KLING, M. A., GERACIOTI, T. D., LICINIO, J., MICHELSON, D., OLDFIELD, E. H., GOLD, P. W., Effects of electroconvulsive therapy on the CRH–ACTH–cortisol system in melancholic depression: preliminary findings. *Psychopharmacol. Bull.* **1994**, 30, 489–494.
- 22 DEBELLIS, M. D., GOLD, P. W., GERACIOTI, T. D., LISTWAK, S. J., KLING, M. A., Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *Am. J. Psychiatry* **1993**, 150, 656–657.
- 23 HEUSER, I., BISSETTE, G., DETTLING, M., SCHWEIGER, U., GOTTHARDT, U., SCHMIDER, J., LAMMERS, C. H., NEMEROFF, C. B., HOLSBOER, F., Cerebrospinal fluid concentrations of corticotropin-releasing hormone, vasopressin and somatostatin in depressed patients and healthy controls: response to

- amitriptyline treatment. *Depress. Anxiety* **1998**, *8*, 71–79.
- 24 ZOBEL, A. W., NICKEL, T., KUNZEL, H. E., ACKL, N., SONNTAG, A., ISING, M., HOLTSBOER, F., Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J. Psychiatr. Res.* **2000**, *34*, 171–181.
 - 25 AUSTIN, M. C., JANOSKY, J. E., MURPHY, H. A., H. A., Increased corticotropin-releasing hormone immunoreactivity in monoamine-containing pontine nuclei of depressed suicide men. *Mol. Psychiatry* **2003**, *8*, 324–332.
 - 26 BISSETTE, G., KLIMECK, V., PAN, J., STOCKMEIER, C., ORDWAY, G., Elevated concentrations of CRF in the locus coeruleus of depressed subjects. *Neuropsychopharmacology* **2003**, *28*, 1328–1335.
 - 27 FOOTE, S. L., ASTON-JONES, G. S., Pharmacology and physiology of central noradrenergic systems. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press: New York, **1995**, 335–346.
 - 28 VALENTINO, R. J., FOOTE, S. L., ASTON-JONES, G., Corticotropin-releasing factor activates noradrenergic neurons of the locus coeruleus. *Brain Res.* **1983**, *270*, 363–367.
 - 29 PAGE, M. E., ABERCROMBIE, E. D., Discrete local application of corticotropin-releasing factor increases locus coeruleus discharge and extracellular norepinephrine in rat hippocampus. *Synapse* **1999**, *33*, 304–313.
 - 30 SMAGIN, G. N., HARRIS, R. B., RYAN, D. H., Corticotropin-releasing factor receptor antagonist infused into the locus coeruleus attenuates immobilization stress-induced defensive withdrawal in rats. *Neurosci. Lett.* **1996**, *220*, 167–170.
 - 31 ARATO, M., BANKI, C. M., BISSETTE, G., NEMEROFF, C. B., Elevated CSF CRF in suicide victims. *Biol. Psychiatry* **1989**, *25*, 355–359.
 - 32 TRASKMAN-BENDZ, L., EKMAN, R., REGNELL, G., OHMAN, R., HPA-related CSF neuropeptides in suicide attempters. *Eur. Neuropsychopharmacol.* **1992**, *2*, 99–106.
 - 33 BRUNNER, J., STALLA, G. K., STALLA, J., UHR, M., GRABNER, A., WETTER, T. C., BRONISCH, T., Decreased corticotropin-releasing hormone (CRH) concentrations in the cerebrospinal fluid of eucortisolemic suicide attempters. *J. Psychiatr. Res.* **2001**, *35*, 1–9.
 - 34 WESTRIN, A., EKMAN, R. R., REGNELL, TRASKMAN-BENDZ, L., A follow-up study of suicide attempters: increase of CSF-somatostatin but no change in CSF-CRH. *Eur. J. Neuropsychopharmacol.* **2001**, *11*, 135–143.
 - 35 LOPEZ, J. F., PALKOVITS, M., ARATO, M., MANSOUR, A., AKIL, H., WATSON, S. J., Localization and quantification of pro-opiomelanocortin mRNA and glucocorticoid receptor mRNA in pituitaries of suicide victims. *Neuroendocrinology* **1992**, *56*, 491–501.
 - 36 HIROI, N., WONG, M. L., LICINIO, J., PARK, C., YOUNG, M., GOLD, P. W., CHROUSOS, G. P., BORNSTEIN, S. R., Expression of corticotropin releasing hormone receptors type I and type II in suicide victims and controls. *Mol. Psychiatry* **2001**, *6*, 540–546.
 - 37 NEMEROFF, C. B., OWENS, M. J., BISSETTE, G., ANDORN, A. C., STANLEY, M., Reduced corticotropin-releasing factor binding sites in the frontal cortex of suicide victims. *Arch. Gen. Psychiatry* **1988**, *45*, 577–579.
 - 38 LEAKE, A., PERRY, E. K., PERRY, R. H., FAIRBAIRN, A. F., FERRIER, I. N., Cortical concentrations of corticotropin-releasing hormone and its receptor in Alzheimer type dementia and major depression. *Biol. Psychiatry* **1990**, *28*, 603–608.
 - 39 HUCKS, D., LOWTHER, S., CROMPTON, M. R., KATONA, C. L., HORTON, R. W., Corticotropin-releasing factor binding sites in cortex of depressed suicides. *Psychopharmacology* **1997**, *134*, 174–178.
 - 40 CLAES, S., VILLAFUERTE, S., FORSGREN, T., SLUIJS, S., DEL-FAVERO, J., ADOLFSSON, R., VAN BROECKHOVEN, C., The CRH binding protein is associated with major depression in a population from northern Sweden. *Biol. Psychiatry* **2003**, *54*, 867–872.
 - 41 MASON, G. A., GARBUIT, J. C., PRANGE, A. J., Thyrotropin-releasing hormone – focus on basic neurobiology. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 493–503.

- 42 PRANGE, A. J., WILSON, I. C., LARA, P. P., ALLTOP, L. B., BREESE, G. R., Effects of TRH in depression. *Lancet* **1972**, 2, 999–1002.
- 43 BUNEVICIUS, R., MATULEVICIUS, V., Short-lasting behavioral effects of thyrotropin-releasing hormone in depressed women: results of placebo-controlled study. *Psychoneuroendocrinology* **1993**, 18, 445–449.
- 44 L. MARANGELL GEORGE, M. S., CALLAHAN, A. M., KETTER, T. A., PAZZAGLIA, P. J., L'HERROU, T. A., LEVERICH, G. S., POST, R. M., Effects of intrathecal TRH in refractory depressed patients. *Arch. Gen. Psychiatry* **1997** 54, 214–222.
- 45 BANKI, C. M., BISSETTE, G., ARATO, M., NEMEROFF, C. B., Elevation of immunoreactive CSF TRH in depressed patients. *Am. J. Psychiatry* **1988**, 145, 1526–1531.
- 46 KIRKEGAARD, C., FABER, J., HUMMER, L., ROGOWSKI, P., Increased levels of TRH in cerebrospinal fluid from patients with endogenous depression. *Psychoneuroendocrinology* **1979**, 4, 227–235.
- 47 ROY, A., BISSETTE, G., NEMEROFF, C. B., DEJONG, J., RAVITZ, B., ADINOFF, B., LINNOILA, M., Cerebrospinal fluid thyrotropin-releasing hormone concentrations in alcoholics and normal controls. *Biol. Psychiatry* **1990**, 28, 767–772.
- 48 BARTALENA, L., PLACIDI, G. F., MARTINO, E., FALCONE, M., PELLEGRINI, L., DELL'OSSO, L., PACCHIAROTTI, A., PINCHERA, A., Nocturnal serum thyrotropin (TSH) surge and the TSH response to TSH-releasing hormone: dissociated behavior in untreated depressives. *J. Clin. Endocrinol. Metab.* **1990**, 71, 650–655.
- 49 SCHLESSER, M. A., RUSH, A. J., FAIRCHILD, C., CROWLEY, G., ORSULAK, P., The thyrotropin-releasing hormone test: a methodological study. *Psychiat. Res.* **1983**, 9, 59–67.
- 50 SHELTON, R. C., WINN, S., EKHATORE, N., LOOSEN, P. T., The effects of antidepressants on the thyroid axis in depression. *Biol. Psychiatry* **1993**, 33, 120–126.
- 51 BISSETTE, G., Neuropeptides involved in stress and their distribution in the mammalian central nervous system. In McCUBBIN, J. A., KAUFMAN, P. G., NEMEROFF, C. B. (Eds.), *Stress, Neuropeptides and Systemic Disease*. Academic Press: San Diego, CA, **1991**, 55–72.
- 52 KALIVAS, P. W., HORITA, A., Involvement of the septohippocampal system in TRH antagonism of pentobarbital narcosis. In GRIFFITHS, E. C., BENNETT, G. W. (Eds.), *Thyrotropin-releasing Hormone*. Raven Press: New York, NY, **1983**, 283–290.
- 53 HORI, T., YAMASAKI, M., ASAMI, T., KOGA, H., KIYOHARA, T., Responses of anterior hypothalamic thermosensitive neurons to thyrotropin-releasing hormone and cyclo (His-Pro). *Neuropharmacology* **1988**, 9, 895–901.
- 54 SOUETRE, E., SALVATI, E., WEHR, T. A., SACK, D. A., KREBS, B., DARCOURT, G., Twenty-four hour profiles of body temperature and plasma TSH in bipolar patients during depression and during remission and in normal control subjects. *Am. J. Psychiatry* **1988**, 145, 1133–1137.
- 55 LIGHTON, C., BENNETT, G. W., MARSDEN, C. A., Increase in levels and *ex vivo* release of thyrotropin-releasing hormone (TRH) in specific regions of the CNS of the rat by chronic treatment with antidepressants. *Neuropharmacology* **1985**, 24, 401–406.
- 56 KUBEK, M. J., MEYERHOFF, J. L., HILL, T. G., NORTON, J. A., SATTIN, A., Effects of subconvulsive and repeated electroconvulsive shock on the thyrotropin-releasing hormone in rat brain. *Life Sciences* **1985**, 36, 315–320.
- 57 RILEY, L. A., JONAKIT, G. M., HART, R. P., Serotonin modulates the levels of mRNA's coding for thyrotropin-releasing hormone and preprotachykinin by different mechanisms in medullary raphe neurons. *Brain Res. Mol. Brain Res.* **1993**, 17, 251–257.
- 58 LIAO, N., VAUDRY, H., PELLETIER, G., Neuroanatomical connections between corticotropin-releasing factor (CRF) and somatostatin (SRIF) nerve endings and thyrotropin-releasing hormone (TRH) neurons in the paraventricular nucleus of the rat hypothalamus. *Peptides* **1992**, 13, 677–680.
- 59 TAKAYAMA, H., OTA, Z., OGAWA, N., Effect of immobilization stress on neuropeptides and their receptors in rat central nervous system. *Reg. Peptides* **1986**, 25, 239–248.

- 60 ONO, T., OGAWA, N., MORI, A., The effects of hemorrhagic shock on thyrotropin-releasing hormone and its receptors in discrete regions of rat brain. *Reg. Peptides* **1989**, 25, 215–222.
- 61 URIBE, R. M., REDONDO, J. L., CHARLI, J. L., JOSEPH-BRAVO, P., Suckling and cold stress rapidly and transiently increase TRH mRNA in the paraventricular nucleus. *Neuroendocrinology* **1993**, 58, 140–145.
- 62 BROQUA, P., BENYASSI, A., GROUSELLE, D., ARANCIBIA, S., Antidepressant/anxiolytic ipsapirone inhibits cold-induced hypothalamic TRH release. *Neuroreport* **1993**, 4, 1200–1202.
- 63 ALKEMADE, A., UNMEHOPA, U. A., BROUWER, J. P., HOOGENDIJK, W. J., WIERSINGA, W. M., SWAAB, D. F., FLIERS, E., Decreased TRH gene expression in the hypothalamic paraventricular nucleus of patients with major depression. *Mol. Psychiatry* **2003**, 8, 838–839.
- 64 STANER, L., DUVAL, F., CALVI-GRIES, F., MOKRANI, M. C., BAILEY, P., HODE, Y., TOUSSAINT, M., LUTHRINGER, R., MUZET, A., MACHER, J. P., Morning and evening TSH response to TRH and sleep EEG disturbance in major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2001**, 25, 535–547.
- 65 DUVAL, F., MOKRANI, M. C., BAILEY, P., CORREA, H., DIEP, T. S., CROCQ, M. A., MACHER, J. P., Thyroid axis activity and serotonin function in major depressive episode. *Psychoendocrinology*, **1999**, 24, 695–712.
- 66 AMSTERDAM, J. D., FAVA, M., MAISLIN, G., ROSENBAUM, J., HORNIG-ROHAN, M., TRH stimulation test as a predictor of acute and long-term antidepressant response in major depression. *J. Affect Disord.* **1996**, 38, 165–172.
- 67 DE MENDONCA LIMA, C. A., VANDEL, S., BONIN, B., BECHTEL, P., CARRON, R., Maprotiline versus fluvoxamine: comparison of their effects on the hypothalamo–hypophyseal–thyroid axis. *Encephale* **1997**, 23, 48–55.
- 68 MOLCHAN, S. E., LAWLOR, B. A., HILL, J. L., MELLOW, A. M., DAVIS, C. L., MARTINEZ, R. A., SUNDERLAND, T., The TRH stimulation test in AD and major depression: relationship to clinical and CSF measures. *Biol. Psychiatry* **1991**, 30, 567–576.
- 69 HUBAIN, P. P., STANER, L., DRAMAIX, M., KERKHOFS, M., VAN VEEREN, C., PAPADIMITRIOU, G., MENDLEWICZ, J., LINKOWSKI, P., TSH response to TRH and EEG sleep in non-bipolar major depression: a multivariate approach *Eur. Neuropsychopharmacol.* **1994**, 4, 517–525.
- 70 GARBUTT, J. C., MAYO, J. P., LITTLE, K. Y., GILLETTE, G. M., MASON, G. A., DEW, B., PRANGE JR., A. J., Dose-response studies with thyrotropin-releasing hormone: evidence for differential pituitary responses in men with major depression, alcoholism or no psychopathology. *Alcohol Clin. Exp. Res.* **1996**, 20, 717–722.
- 71 JOFFE, R. T., Peripheral thyroid hormone levels in treatment resistant depression. *Biol. Psychiatry* **1999**, 45, 1053–1055.
- 72 KONIG, F., HAUGER, B., VON HIPPEL, C., WOLFERSDORF, M., KASCHKA, W. P., Effect of paroxetine on thyroid hormone levels in severely depressed patients. *Neuropsychobiology* **2000**, 42, 135–138.
- 73 SATTIN, A., The role of TRH and related peptides in the mechanism of action of ECT. *J. ECT* **1999**, 15, 76–92.
- 74 HOFMANN, P., GANGADHAR, B. N., PROBST, C., KONIG, G., HATZINGER, R., TSH response to TRH and ECT. *J. Affect Disord.* **1994**, 32, 127–131.
- 75 EPELBAUM, J., DOURNAUD, P., FODOR, M., VIOLETT, C., The neurobiology of somatostatin. *Crit. Rev. Neurobiol.* **1994**, 8, 25–44.
- 76 RUBINOW, D. R., DAVIS, C. L., POST, R. M., Somatostatin in the central nervous system. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 553–562.
- 77 BISSETTE, G., WIDERLOV, E., WALLEUS, H., KARLSSON, I., EKLUND, K., FORSMAN, A., NEMEROFF, C. B., Alterations in cerebrospinal fluid concentrations of somatostatin-like immunoreactivity in neuropsychiatric disorders. *Arch. Gen. Psychiatry* **1986**, 43, 1148–1154.
- 78 BISSETTE, G., MYERS, B., Minireview: Somatostatin in Alzheimer's disease and depression. *Life Sci.* **1992**, 51, 1389–1410.
- 79 CHARLTON, B. G., LEAKE, A., WRIGHT, C., FAIRBAIRN, A. F., MCKEITH, I. G., CANDY, J. M., FERRIER, N., Somatostatin content

- and receptors in the cerebral cortex of depressed and control subjects. *J. Neurol.* **1988**, *41*, 19–21.
- 80 BENYASSI, A., ROUSSEL, J. P., ROUGEOT, C., GAVALDA, A., ASTIER, H., ARANCIBIA, S., Chronic stress affects *in vivo* hypothalamic somatostatin release but not *in vitro* GH responsiveness to somatostatin in rats. *Neurosci. Lett.* **1993**, *159*, 166–170.
 - 81 KAKIGI, T., MAEDA, K., KANEDA, H., CHIHARA, K., Repeated administration of antidepressant drugs reduces regional somatostatin concentrations in rat brain. *J. Affect Disord.* **1992**, *25*, 215–220.
 - 82 GHEORVASSAKI, E. G., THERMOS, K., LIAPAKIS, G., SPYRAKI, C., Effects of acute and chronic desipramine treatment on somatostatin receptors in brain. *Psychopharmacology* **1992**, *108*, 363–366.
 - 83 WIDERLOV, E., BISSETTE, G., NEMEROFF, C. B., Monoamine metabolites, corticotropin releasing factor and SRIF as CSF markers in depressed patients *J. Affect Disord.* **1988**, *14*, 99–107.
 - 84 MOLCHAN, S. E., LAWLOR, B. A., HILL, J. L., MARTINEZ, R. A., DAVIS, C. L., MELLOW, A. M., RUBINOW, D. R., SUNDERLAND, T., CSF monoamine metabolites and SRIF in AD and major depression *Biol. Psychiatry* **1991**, *29*, 1110–1118.
 - 85 MOLCHAN, S. E., HILL, J. L., MARTINEZ, R. A., LAWLOR, B. A., MELLOW, A. M., RUBINOW, D. R., BISSETTE, G., NEMEROFF, C. B., SUNDERLAND, T., CSF SRIF in AD and major depression: relationship to HPA axis and clinical measures. *Psychoneuroendocrinology* **1993**, *18*, 509–517.
 - 86 KLING, M. A., RUBINOW, D. R., DORAN, A. R., ROY, A., DAVIS, C. L., CALABRESE, J. R., NIEMAN, L. K., POST, R. M., CHROUSOS, G. P., GOLD, P. W., CSF immunoreactive SRIF concentrations in patients with Cushing's disease and major depression: relationship to indices of CRH and cortisol secretion. *Neuroendocrinology* **1993**, *57*, 79–88.
 - 87 COPLAN, J. D., WOLK, S. I., GOETZ, R. R., RYAN, N. D., DAHL, R. E., MANN, J. J., WEISSMAN, M. M., Nocturnal growth hormone secretion studies in adolescents with or without major depression re-examined: integration of adult clinical follow-up data. *Biol. Psychiatry* **2000**, *47*, 594–504.
 - 88 WESTRIN, A., EKMAN, R., REGNALL, G., TRASKMAN-BENDZ, L., A follow up study of suicide attempters: increase in CSF somatostatin but no change in CSF CRH. *Eur. Neuropsychopharmacology* **2001**, *11*, 135–143.
 - 89 BIRMAHER, B., DAHL, R. E., WILLIAMSON, D. E., PEREL, J. M., BRENT, D. A., AXELSON, D. A., KAUFMAN, J., DORN, L. D., STULL, S., RAO, U., RYAN, N. D., Growth hormone secretion in children and adolescents at high risk for major depressive disorder. *Arch. Gen. Psychiatry* **2000**, *57*, 867–872.
 - 90 MANTYH, P. W. L., Neurobiology of substance P. *J. Clin. Psychiatry* **2002**, *63*, 6–10.
 - 91 HUSTON, J. P., HASENORHL, R. U., The role of neuropeptides in learning: focus on the neurokinin substance P. *Behav. Brain Res.* **1995**, *66*, 117–127.
 - 92 SAFFROY, M., TORRENS, Y., GLOWINSKI, J., BEAUJOUAN, J. C., Autoradiographic distribution of tachykinin NK2 binding sites in the rat brain: comparison with NK1 and NK3 binding sites. *Neuroscience* **2003**, *116*, 761–773.
 - 93 RIMON, R., LE GREVES, P., NYBERG, F., HEIKKILA, L., SARMELA, L., TERENIUS, L., Elevation of Substance P-like peptides in the CSF of psychiatric patients. *Biol. Psychiatry* **1984**, *19*, 509–516.
 - 94 BERRETINNI, W. H., RUBINOW, D. R., NURNBERGER, J. I., SIMMONS-ALLING, S., POST, R. M., GERSHON, E. S., CSF substance P immunoreactivity in affective disorders *Biol. Psychiatry* **1985**, *20*, 965–970.
 - 95 MARTENSSON, B., NYBERG, S., TORESSON, G., BRODIN, E., BERTILSSON, L., Fluoxetine treatment of depression. *Acta Psychiatr. Scand.* **1989**, *79*, 586–596.
 - 96 RUPNIAK, B., Elucidating the antidepressant actions of substance P (NK1 receptor) antagonists. *Curr. Opin. Investig. Drugs* **2002**, *3*, 257–261.
 - 97 KRAMER, M. S., Update on Sub p (NK-1 receptor) antagonists in clinical trials for depression. *Neuropeptides* **2000**, *34*, 255.
 - 98 BONDY, B., BAGHAI, T. C., MINOV, C., SCHULE, C., SCHWARZ, M. J., ZWANZGER, P., RUPPRECHT, R., MOLLER, J. J., Substance P serum levels are increased in major depression: preliminary results. *Biol. Psychiatry* **2003**, *53*, 538–542.

- 99 STOCKMEIER, C. A., SHI, X., KONICK, L., OVERHOLSER, J. C., JURJUS, G., MELTZER, H. Y., FRIEDMAN, L., BLIER, P., RAJKOWSKA, G., Neurokinin-1 receptors are decreased in major depressive disorder. *Neuroreport* **2002**, *13*, 1223–1227.
- 100 BURNET, P. W., HARRISON, P. J., Substance P (NK1) receptors in the cingulate cortex in unipolar and bipolar mood disorder and schizophrenia. *Biol. Psychiatry* **2000**, *47*, 80–83.
- 101 HADDERJI, N., BLIER, P., Sustained blockade of neurokinin-1 receptors enhances serotonin neurotransmission. *Biol. Psychiatry*, **2001**, *50*, 191–199.
- 102 BAGHAI, T. C., SCHULE, C., ZWANZGER, P., MINOV, C., ZILL, P., ELLA, R., ESER, D., OEZER, S., BONDY, B., RUPPRECHT, R., HPA axis dysregulation in patients with major depression is influenced by the insertion/deletion polymorphism in the angiotensin 1-converting enzyme. *Neurosci. Lett.* **2002**, *328*, 299–303.
- 103 HONG, C. J., WANG, Y. C., TSAI, S. J., Association study of angiotensin I-converting enzyme polymorphism and symptomatology and antidepressant response in major depressive disorder. *J. Neural Transm.* **2002**, *109*, 1209–1214.
- 104 CARPENTER, L. L., PRICE, L. H., KINKEAD, B., CASSELL, T., SANACORA, G., OWENS, M. J., NEMEROFF, C. B., Elevated cerebrospinal fluid concentration of substance P in major depression. *American College of Neuropsychopharmacology 42nd Annual Meeting Abstracts*, **2003**, #71, 215.
- 105 KLING, M. A., CARPENTER, L. L., MORENO, F., PRICE, L. H., OWENS, M. J., KINKEAD, B., NEMEROFF, C. B., Decreased cerebrospinal fluid concentrations of substance P in medicated patients with treatment-resistant major depression. *American College of Neuropsychopharmacology 42nd Annual Meeting Abstracts*, **2003**, #101, 161.
- 106 WAGNER, J. J., CHAVKIN, C. I., Neuroparmacology of endogenous opioid peptides. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 519–529.
- 107 MARTIN DEL CAMPO, A. F., DOWSON, J. H., HERBERT, J., PAYKEL, E. S., Diurnal variations in endocrine and psychological responses to 0.2 mg/kg naloxone administration in patients with major depressive disorder and matched controls. *J. Affect. Disord.* **2000**, *57*, 37–47.
- 108 HURD, Y. L., Subjects with major depression or bipolar disorder show reduction of prodynorphin mRNA expression in discrete nuclei of the amygdaloid complexes. *Mol. Psychiatry* **2002**, *7*, 75–81.
- 109 PECKYS, D., HURD, Y. L., Prodynorphin and kappa opioid receptor mRNA expression in the cingulate and prefrontal cortices of subjects diagnosed with schizophrenia or affective disorders. *Brain Res. Bull.* **2001**, *55*, 619–624.
- 110 VARONA, A., GIL, J., SARACIBAR, G., MAZA, J. L., ECHEVARRIA, E., IRAZUSTA, J., Effects of imipramine treatment on delta-opioid receptors. *Arzneimittelforschung* **2003**, *53*, 21–25.
- 111 DZIEDZICKA-WASYLEWSKA, M., PAPP, M., Effect of chronic mild stress and prolonged treatment with imipramine on the levels of endogenous met-enkephalin in the rat dopaminergic mesolimbic system. *Pol. J. Pharmacol.* **1996**, *48*, 53–56.
- 112 WAHLESTEDT, C., HEILIG, M., Neuropeptide Y and related peptides. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 543–551.
- 113 ORDWAY, G. A., STOCKMEIER, C. A., MELTZER, H. Y., OVERHOLSER, J. C., JACONETTA, S., WIDDOWSON, P. S., Neuropeptide Y in frontal cortex is not altered in major depression. *J. Neurochem.* **1995**, *65*, 1646–1650.
- 114 CABERLETTI, L., HURD, Y. L., Reduced neuropeptide Y mRNA expression in the prefrontal cortex of subjects with bipolar disorder. *Neuroreport* **1999**, *10*, 1747–1750.
- 115 CABERLOTTO, L., HURD, Y. L., Neuropeptide Y Y1 and Y2 receptor mRNA expression in the prefrontal cortex of psychiatric subjects: Relationship of Y2 subtype to suicidal behavior. *Neuropsychopharmacology* **2001**, *25*, 91–97.
- 116 WIDERLOV, E., LINDSTROM, L. H., WAHLESTEDT, C., EKMAN, R., Neuropeptide Y and peptide YY as possible cerebrospinal fluid markers for major depression and schizophrenia, respectively. *J. Psychiatr. Res.* **1988**, *22*, 69–79.

- 117 WESTRIN, A., EKMAN, R., TRASKMAN-BENDZ, L., Alterations of CRH and NPY plasma levels in mood disorder patients with a recent suicide attempt. *Eur. Neuropsychopharmacol.* **1999**, 9, 205–211.
- 118 CATALAN, R., GALLART, J. M., CASTELLANOS, J. M., GALARD, R., Plasma CRF in depressive disorders. *Biol. Psychiatry* **1998**, 44, 15–20.
- 119 NILSSON, C., KARLSSON, G., BLENNOW, K., HEILIG, M., EKMAN, R., Differences in the neuropeptide Y-like immunoreactivity of the plasma and platelets of human = volunteers and depressed patients. *Peptides* **1996**, 17, 359–362.
- 120 POHL, A., NORDIN, C., Clinical and biochemical observations during treatment of depression with electroacupuncture: a pilot study. *Hum. Psychopharmacol.* **2002**, 17, 345–348.
- 121 WAHLESTEDT, C., BLENDY, J. A., KELLAR, K. J., HEILIG, M., WIDERLOV, E., EKMAN, R., Electroconvulsive shocks increase the concentration of neocortical and hippocampal neuropeptide Y like immunoreactivity in the rat. *Brain Res.* **1990**, 507, 65–68.
- 122 MIKKELSEN, J. D., WOLDBYE, D., KRAGH, J., LARSEN, P. J., BOLWIG, T. G., Electroconvulsive shocks increase the expression of neuropeptide Y mRNA in the piriform cortex and the dentate gyrus. *Brain Res. Mol. Brain Res.* **1994**, 23, 317–322.
- 123 RINAMAN, L., SHERMAN, T. G., STRICKER, E. M., Vasopressin and Oxytocin in the central nervous system. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 531–542.
- 124 DE WIED, D., SIGLING, H. O., Neuropeptides involved in the pathophysiology of schizophrenia and major depression. *Neurotox. Res.* **2002**, 4, 453–468.
- 125 LENZINGER, E., MESZAROS, K., HORNIK, K., PARZER, P., HOLLERER, E., LANGER, G., RESCH, F., LEGROS, J. J., Correlation between vasopressin baseline and TSH-blunting in depressives. *Biol. Psychiatry* **1996**, 39, 341–345.
- 126 PURBA, J. S., HOOGENDIJK, W. J., HOFMAN, M. A., SWAAB, D. F., Increased number of vasopressin- and oxytocin-neurons in the paraventricular nucleus of the hypothalamus in depression. *Arch. Gen. Psychiatry* **1996**, 53, 137–143.
- 127 PITTS, A. F., SAMUELSON, S. D., MELLER, W. H., BISSETTE, G., NEMEROFF, C. B., KATHOL, R. G., CSF CRF VP and oxytocin concentrations in treated patients with major depression and controls. *Biol. Psychiatry* **1995**, 38, 330–335.
- 128 VAN LONDEN, L., GOEKOOP, J. G., VAN KEMPEN, G. M., FRANKHUIJZEN-SIEREVOGEL, A. C., WIEGANT, V. M., VAN DER VELDE, E. A., DE WIED, D., Plasma levels of arginine vasopressin in patients with major depression. *Neuropsychopharmacology* **1997**, 17, 284–292.
- 129 VAN LONDEN, L., KERKHOF, G. A., VAN DEN BERG, G., GOEKOOP, J. G., ZWINDERMAN, K. H., FRANKHUIJZEN-SIEREVOGEL, A. C., WIEGANT, V. M., DE WIED, D., Plasma arginine vasopressin and motor activity in major depression. *Biol. Psychiatry* **1998**, 43, 196–204.
- 130 DEVANAND, D. P., LISANBY, S., LO, E. S., FITZSIMONS, L., COOPER, T. B., HALBREICH, U., SACKHEIM, H. A., Effects of ECT on plasma VP and OXY. *Biol. Psychiatry* **1998**, 44, 610–616.
- 131 BEINFELD, M. C., Cholecystokinin/Gastrin. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 585–594.
- 132 GERACIOTI, T. D., NICHOLSON, W. E., ORTH, D. N., EKHATOR, N. N., LOOSEN, P. T., Cholecystokinin in human cerebrospinal fluid: concentrations, dynamics, molecular forms and relationship to fasting and feeding in health, depression and alcoholism. *Brain Res.* **1993**, 629, 260–268.
- 133 GERACIOTI, T. D., EKHATOR, N. N., NICHOLSON, W. E., ARNDT, S., LOOSEN, P. T., ORTH, D. N., Intra- and inter-individual correlations between cholecystokinin and CRH concentration in human CSF. *Depress. Anxiety* **1999**, 10, 77–80.
- 134 WESTRIN, A., EKMAN, R., TRASKMAN-BENDZ, L., High DSIP immunoreactivity in plasma in suicidal patients with major depressive disorder. *Biol. Psychiatry*, **1998**, 43, 734–739.

- 135 TAHERI, S., HAFIZI, S., The orexins/hypocretins: hypothalamic peptides linked to sleep and appetite. *Psychol. Med.* **2002**, *32*, 955–958.
- 136 AOU, S., LI, X. L., OOMURA, Y., SHIRAIISHI, T., SASAKI, K., IMAMURA, T., WAYNER, M. J., Orexin-A (hypocretin-1) impairs Morris water maze performance and CA1-Schaffer collateral long-term potentiation in rats. *Neuroscience* **2003**, *119*, 1221–1228.
- 137 MIGNOT, E., LAMMERS, G. J., RIPLEY, B., OKUN, M., NEVSIMALOVA, S., OVERREEM, S., VANKOVA, J., BLACK, J., HARSH, J., BASSETTE, C., SCHRADER, H., NISHINO, S., The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch. Neurol.* **2002**, *59*, 1553–1562.
- 138 SALOMON, R. M., RIPLEY, B., KENNEDY, J. S., JOHNSON, B., SCHMIDT, D., ZEITZER, M. J., NISHINO, S., MIGNOT, E., Diurnal variation of CSF hypocretin-1 (Orexin-A) levels in control and depressed subjects. *Biol. Psychiatry* **2003**, *54*, 96–104.
- 139 BARTFEI, T., Galanin – a neuropeptide with important central nervous system actions. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, Ltd.: New York, **1995**, 563–571.
- 140 SMITH, K. E., WALKER, M. W., ARTYMYSHYN, R., BARD, J., BOROWSKY, B., TAMM, J. A., YAO, W. J., VAYSSE, P. J., BRANCHEK, T. A., GERALD, C., JONES, K. A., Cloned human and rat galanin GAL3 receptors. Pharmacology and activation of G-protein inwardly rectifying K⁺ channels. *J. Biol. Chem.* **1998**, *273*, 23321–23326.
- 141 BERETTINI, W. H., KAYE, W. H., SUNDERLAND, T., MAY, C., GWIRTSMAN, H. E., MELLOW, A., ALBRIGHT, A., Galanin immunoreactivity in human CSF: studies in eating disorders and Alzheimer's disease. *Neuropsychobiology* **1988**, *19*, 64–68.
- 142 VAN ROSSUM, D., HANISCH, U. K., QUIRION, R., Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. *Neurosci. Biobehav. Rev.* **1997**, *21*, 649–678.
- 143 MATHE, A. A., AGREN, H., WALLIN, A., BLENNOW, K., Calcitonin gene-related peptide and calcitonin in the CSF of patients with dementia and depression: possible disease markers. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, *26*, 41–48.
- 144 MATHE, A. A., AGREN, H., LINDSTROM, L., THEODORSSON, E., Increased concentration of calcitonin gene-related peptide in cerebrospinal fluid of depressed patients. A possible trait marker of major depressive disorder. *Neurosci. Lett.* **1994**, *182*, 138–142.

20

Depression, Mania, and Thyroid Function: A Story of Intimate Relationships

Peter C. Whybrow and Michael Bauer

Abstract

The evidence that thyroid hormones are essential to the normal development of the brain and the prevalence of behavioral and neuropsychiatric symptoms in thyroid disease, especially the disturbances of affect found in hypothyroidism, have long suggested an intimate relationship between thyroid hormone metabolism and mood disorder. Individuals who suffer mood disorder frequently have disturbed indices of peripheral thyroid function, and clinical studies extending over three decades suggest that thyroid hormones can modulate the expression of both unipolar and bipolar disease when used in conjunction with psychotropic agents. This chapter reviews these observations and clinical studies and explores the underlying mechanisms that may explain this set of intriguing relationships, including a review of evidence from recent brain-imaging studies. The chapter concludes with a guide to the use of thyroid hormones as adjunctive therapeutic agents in treatment-resistant depression and rapid-cycling bipolar illness.

20.1

Introduction

Since the early 19th century, physicians have recognized that the activity of the thyroid gland is essential for normal brain development and mental functioning. Observations of behavioral changes in patients suffering from myxoedema culminated in a classic report from the Clinical Society of London in 1888, describing a variety of mental disturbances including irritability, agoraphobia, dementia, and depression [1]. Nonetheless, it has been only during the past 50 years that technological progress and scientific understanding has illuminated the relationship between thyroid function and behavior.

Today, it is well established that in the mature brain significant disturbances of the thyroid economy may profoundly alter mental function, influencing cognition and emotion. In adult life both excess thyroid hormone activity (hyperthyroidism)

and inadequate production (hypothyroidism) are associated with changes in mood and intellectual performance, and severe hypothyroidism can mimic melancholic depression and dementia [2–4]. The neurocognitive impairments accompanying dysfunction of the thyroid axis usually reverse rapidly following return to euthyroid status, although there is evidence that severe hypothyroidism, if left untreated, may result in irreversible cognitive disability [5].

For the practicing psychiatrist these facts have been tantalizing. If disturbed behavior is present in patients who suffer from thyroid metabolic disorders, then is it possible that changes in the hypothalamic–pituitary–thyroid (HPT) axis play a role in the etiology of psychiatric disorder? And if so, might the thyroid hormones have value in the treatment of psychiatric illness, particularly affective illness? It is our purpose in this essay to review these questions and to offer guidelines regarding the use of thyroid hormones in psychiatric practice.

The use of thyroid hormones as therapeutic agents in psychiatry began in the 1930s when Norwegian physicians used hypermetabolic doses of desiccated sheep thyroid gland to successfully treat patients with periodic catatonia, a cyclic mood disorder similar to that now diagnosed as rapidly cycling bipolar disease [6]. Later, with the identification of triiodothyronine (T_3) and levothyroxine ($L-T_4$) as the predominant thyroid hormones in the 1950s and with their subsequent availability as pharmaceutical agents, the effects of synthetic thyroid hormones alone and in combination with traditional psychotropic drugs were investigated [7, 8].

20.2

Thyroid Hormones and the Treatment of Affective Illness

Efforts to employ thyroid hormones alone as therapeutic agents in mood disorder or in other psychiatric disability have rarely been successful [9, 10]. Nonetheless, since Prange's classic acceleration studies in the late 1960s using T_3 in association with the tricyclic antidepressant imipramine [11], a series of open and controlled clinical trials have confirmed the adjunctive therapeutic value of thyroid hormones. Specifically, there is good evidence that T_3 can accelerate the therapeutic response to tricyclic antidepressants, especially in women [12], and some double-blind studies suggest that T_3 may augment the response to tricyclic antidepressants in treatment-resistant depressed patients, although here the results have been inconsistent [7, 13]. Subsequently, in a series of open-label studies, adjunctive treatment with supra-physiological doses of $L-T_4$ have proven effective and well tolerated in the maintenance treatment of patients suffering the malignant phenotype of rapid cycling and in those with otherwise prophylaxis-resistant bipolar disorders [14–19].

Augmentation with supra-physiological doses of $L-T_4$ has also been reported to have immediate therapeutic value in antidepressant-resistant bipolar and unipolar depressed patients during a phase of refractory depression and also in patients with chronic depression [20, 21]. In these studies of severely ill and treatment-refractory patients, an aggregate of approximately 70% of individuals experience

remission from affective symptoms, and women benefit more from thyroid hormone supplementation than do men [12, 22].

20.3

Peripheral Thyroid Metabolism and the Clinical Course of Affective Illness

Based upon the clinical evidence that hypothyroidism can mimic depressive symptoms, the implicit hypothesis driving many of the acceleration and augmentation studies is that individuals who respond to adjunctive thyroid treatment have a failing thyroid economy or suffer subclinical thyroid disease. In fact, the vast majority of patients with primary affective disorders (greater than 90%) have thyroid hormone blood levels within the euthyroid range [23]. However, within that normal range the thyroid hormone economy appears to be predictive of therapeutic response, with growing evidence that thyroid hormone levels in the low-normal range or below the normal range (i.e., thyroid hypofunction) can result in a suboptimal treatment outcome. The most consistent finding in patients during the depressive phase of illness, compared to controls and healthy subjects, is an elevation of serum concentrations of total and free T_4 (with normal T_3 levels), which fall upon recovery and correlate with the speed at which that recovery occurs [24, 25]. Similarly, Frye et al. [26] have reported that within the 'normal' range, a low level of free thyroxin (fT_4) in patients with bipolar disorder is associated with more affective episodes and greater severity of depression during prophylactic lithium treatment. In another study, lower free thyroxin index (FTI) values and higher TSH values within the normal range were significantly associated with poorer treatment response in bipolar patients during the depressed phase [27]. Taken together, these observations suggest that higher serum levels of thyroxin are adaptive in depression – much as an increase in thyroid metabolism is an adaptive response to cold stress – and that a robust thyroid economy confers an advantage that promotes rapid recovery following antidepressant treatment. Thus, a working hypothesis in seeking to explain these clinical observations is that thyroid hormones modulate the severity and course of depression rather than play a specific pathogenic role.

The idea that thyroid hormones act as modulators in affective illness is further strengthened by studies of the relationship between thyroid function and the clinical course of *bipolar disorder*, especially that of the rapid-cycling variant. By definition, patients with a rapid-cycling course of disease (70%–90% of whom are women) suffer more than four episodes of illness per year [28]. Rapid-cycling patients have a much higher incidence (about 25%) of grade I hypothyroidism than do bipolar patients in general (2%–5%) or those taking lithium carbonate (9%) [28, 29]. As a group, rapid cyclers also appear to be more vulnerable to antithyroid challenge. Thus, when previously unmedicated patients with the rapid-cycling phenotype of bipolar disease were challenged with therapeutic doses of lithium (a drug with antithyroid properties [30]), they were found to have a significantly higher δ -TSH after TRH stimulation than did healthy controls [31]. These studies thus again provide support that changes in the thyroid economy may play a modulating role

in affective illness and specifically in the development of the rapid-cycling pattern of bipolar disorder. The evidence that high doses of L-T₄, when added to the established treatment regimen of patients with rapid-cycling bipolar disorder who are refractory to lithium and other psychotropic drugs, can reverse the rapid cycling pattern further supports the hypothesis of thyroid metabolism as a modulator in affective illness [15, 16].

20.4

Response to L-Thyroxin in the Absence of Peripheral Thyroid Disease

As we have gained more experience with the use of supraphysiological doses of L-T₄ in patients with malignant or refractory bipolar disease, however, it has become apparent that many patients who respond to the adjunctive treatment have serum thyroid hormone levels within normal limits and have no past history of peripheral thyroid disease. Furthermore, there is mounting evidence that these patients respond differently to high-dose thyroxin than do healthy control subjects. The doses of L-T₄ required to achieve the therapeutic effect in these patients are higher (250–600 $\mu\text{g d}^{-1}$) than those used in the treatment of primary thyroid disorders such as hypothyroidism (typically 75–150 $\mu\text{g d}^{-1}$) [32]. (However, it is well to remember here that when L-T₄ was first introduced into clinical practice in the late 1950s the recommended doses for thyroid hormone replacement in hypothyroidism were far higher (200–400 $\mu\text{g d}^{-1}$) [33] than those now recommended in endocrine practice. Also to be remembered is that supraphysiological doses of L-thyroxin (up to 1000 $\mu\text{g d}^{-1}$) or large amounts of desiccated thyroid extract have been administered for short periods of time to healthy control subjects without major adverse effects being reported [34–36].)

In our own practice we find that patients with treatment-refractory affective disorders tolerate high doses of L-T₄ surprisingly well, and in follow-up studies over an extended period we have observed few adverse effects from the induced hyperthyroxinemia [17, 18, 37–40]. This low incidence of harmful side effects, including effects on bone mineral density, and the high tolerability contrasts with the response typically seen in patients with primary thyroid disease who are receiving high-dose thyroid hormone therapy. For example, patients with thyroid carcinoma treated with high doses of L-T₄ to achieve suppression of TSH commonly complain of the symptoms of thyrotoxicosis. As part of an ongoing effort to define the efficacy and safety parameters of supraphysiological doses of L-T₄, we have also observed, under well controlled conditions, significant differences in the physiological responses of healthy control subjects and depressed patients [41]. The peripheral thyroid hormone indices (total T₄, free T₄, and total T₃) in our rapid-cycling and treatment-refractory depressed patients were less elevated in response to high doses of L-T₄ than is the case in healthy controls, and the patients suffered significantly fewer side effects [41], suggesting a syndrome of resistance to thyroid hormone [42]. Thus the possibility arises that, although some bipolar patients develop refractory illness and resistance to standard psychotropic agents because of

diminished CNS thyroid hormone availability secondary to peripheral thyroid disease (which is sometimes exacerbated by lithium carbonate treatment), others have a diminished central (i.e., brain) capacity to *utilize* thyroid hormones. In both instances the use of thyroxin in supraphysiological doses increases the availability of thyroxin substrate to the brain and improves the CNS thyroid economy: in those with peripheral thyroid dysfunction, by restoring a euthyroid state; and in those in whom no peripheral disturbance is evident, by overriding the putative central resistance to thyroid hormone metabolism.

20.5

Brain Imaging Studies of Thyroid Hormones and Brain Metabolism

So what evidence is there to support this conjecture of a central disturbance of brain–thyroid metabolism in some patients who suffer treatment-refractory affective illness? Despite the clinical evidence of a close relationship between thyroid status and behavioral disturbance, metabolic effects of thyroid hormones in the adult mammalian brain have rarely been investigated *in vivo*. In part, this lack of curiosity may be traced to reports in the 1950s and 1960s that suggested that oxygen consumption in the mature human brain did not change with thyroid status [43, 44]. But the absence of a technology capable of direct *in-vivo* measurement of brain thyroid metabolism is also responsible. That still does not exist, but the evaluation of cerebral blood flow and metabolism by functional brain imaging techniques is a starting point, and recent studies have provided promising insights into the thyroid–brain relationship [45, 46].

By way of background, in animal studies autoradiographic analysis has revealed significantly lower levels of [^{14}C]2-deoxyglucose uptake throughout the brain in hypothyroid adult rats than in euthyroid controls (except for the brainstem and pons), indicating that a general decline in metabolic and functional activity occurs during thyroid hormone deficiency [47]. In human studies patients who had undergone total thyroidectomy for thyroid carcinoma were examined by using positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) both when euthyroid and after thyroid hormone withdrawal, inducing severe hypothyroidism when brain activity was found to be globally reduced [48].

Most neuroimaging studies in patients with mood disorders have not considered thyroid status [49]. There is one study, however, of euthyroid patients with major depression in which serum TSH (putatively the best marker of thyroid status) was inversely related to both global and regional cerebral perfusion and glucose metabolism, indicating lower relative metabolic activity in the prefrontal cortex, particularly in the dorsolateral and medial areas [50].

Following the lead of our earlier clinical studies, we have recently investigated the effects of adjunctive supraphysiological doses of L-T_4 on relative brain activity as a surrogate index of cerebral glucose metabolism in euthyroid women with bipolar depression using PET with FDG. At baseline (pretreatment), bipolar depressed women had functional abnormalities in prefrontal and limbic brain areas compared

to healthy controls. Over seven weeks, the treatment with L-T₄ significantly improved mood and was accompanied by significant changes in relative brain activity. In particular, L-T₄ treatment was associated with a widespread relative deactivation of limbic and subcortical structures, including the amygdala, hippocampus, caudate nucleus, ventral striatum, thalamus, and cerebellar vermis [51]. The findings suggest that in these treatment-resistant patients L-T₄ produces mood improvement by actions on the specific limbic and subcortical circuits that have been implicated in the pathophysiology of mood disorders [49, 52–54].

These studies, which were the first to use PET technology to demonstrate the effects of treatment with levothyroxine on regional brain metabolism in patients with bipolar disorder, confirm that thyroid hormones are active in modulating metabolic function in the mature adult brain and provide some intriguing neuroanatomical clues as to the locus of that action.

20.6

Searching for a Brain–Thyroid Metabolic Deficit in Affective Illness

Where should we concentrate our efforts in the future investigation of a potential thyroid–brain metabolic deficit in those patients with treatment-resistant affective disorder? As a guide to future research it is important to consider the key steps of thyroid metabolism in the brain: uptake of thyroid hormones into the brain; production of the active hormone T₃; thyroid receptor activity; and the genetics that underpin these various functions.

Unlike other organs in the body, which predominantly take up their T₃ requirements directly from the bloodstream, the brain actively regulates its own thyroid economy. Thus, transthyretin (TTR) plays an important role in the specific transport and distribution of thyroid hormone into the CNS [55] (Figure 20.1), and lower TTR concentrations in CSF may alter thyroid-hormone homeostasis in the CNS. Indeed, reduced levels of TTR have been detected in the CSF of depressed patients [56], potentially disrupting delivery of thyroid hormones to regions inside the blood–brain barrier despite normal peripheral hormone levels and pituitary activation. Thus, it has been hypothesized that a lack of TTR might account for a relative ‘brain hypothyroidism’ in those patients with major depression who have normal peripheral (serum) thyroid hormone concentrations [56].

Once thyroxine is delivered, the brain exerts tight control over its own thyroid economy through the actions of a chain of specific enzymes, particularly type-2 deiodinase (D2), which metabolizes T₄ to the active hormone T₃ [55, 57, 58]. In patients with bipolar disorder receiving lithium this vital pathway may be impaired. Lithium is concentrated in the pituitary gland as well as in the hypothalamus and may interfere with cellular metabolism in these tissues, as is evidenced in the many cross-sectional studies that report an exaggerated TSH response to TRH stimulation in 50%–100% of lithium-treated patients (reviewed in [30]). St. Germain [59] was among the first to study the neuropharmacological effects of lithium on brain thyroid metabolism in murine neural and anterior pituitary tissue. That research clearly

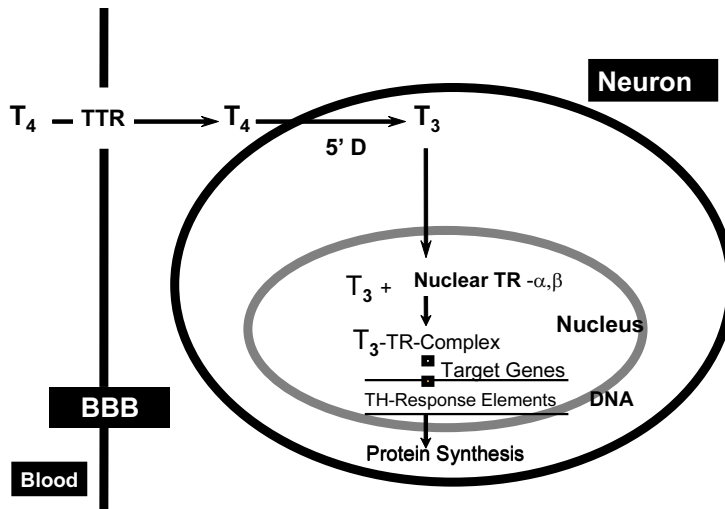


Figure 20.1 Thyroid hormone metabolism in the brain and candidate genes responsible for inter-individual variability in thyroid function (Abbreviations: BBB = blood–brain barrier; DNA = deoxyribonucleic acid; TH = thyroid hormone; T_3 = triiodothyronine; T_4 = thyroxine; TTR = transthyretin; TR = thyroid hormone receptor; 5' D = deiodinase)

demonstrated that lithium inhibits the activity of D2 in mouse neuroblastoma and rat GH3 pituitary cell lines in vitro. Later, Baumgartner et al. [60] showed that 14 days' administration of lithium in dosages employed in the prophylaxis of affective disorders significantly inhibited the D2 activity in various regions in rat brain, e.g., in the parieto-occipital cortex, septum, and hypothalamus. Lithium also modulates expression of the genes for thyroid hormone receptors in rat brain in vivo [61] and in rat pituitary GH3 and neuroblastoma B103 cell lines [62]. Hence, when used in patients with bipolar disorder, lithium may burden the thyroid economy of the brain, potentially creating a relative neuronal thyroid hormone deficiency in predisposed (vulnerable) individuals, thus stimulating an increase in pituitary TSH and possible up-regulation of pituitary TRH receptors, as we have found in our lithium challenge studies in rapid-cycling patients [31].

In the neuron the action of T_3 is mediated through nuclear thyroid hormone receptors that are widely distributed in the brain, with higher densities in the phylogenetically younger brain regions (e.g., amygdala and hippocampus) that are involved in mood regulation than in the older brain centers (the brain stem and cerebellum), where lower densities are found [63, 64]. (Thyroid hormone receptors belong to a nuclear superfamily of ligand-modulated transcription factors, which includes receptors for steroid hormones, vitamin D, and retinoic acid [55]. The T_3 receptor complex interacts with specific sequences in DNA regulatory regions, known as thyroid hormone-response elements, to modify the expression of target genes [65]. Molecular studies have demonstrated a growing number of genetic loci

that are responsive to thyroid hormones. For example, genes whose expression is controlled by thyroid hormones include genes that encode myelin, neurotrophins and their receptors, transcription factors, splicing regulators, and proteins involved in intracellular signaling pathways [55, 58, 66].)

Interactions of thyroid hormones and the long-track neurotransmitter systems of the brain, primarily norepinephrine and serotonin, which play a major role in the regulation of mood and behavior, are also important, although the specific mechanisms through which this influence occurs is unclear [67–69]. There is robust evidence, for example, particularly from animal studies, that the thyroid economy has a modulating impact on the serotonin system in the developing and mature brain. Thus, exogenously administered thyroid hormones may exert their modulatory effects in affective illness by fostering an increase in serotonergic neurotransmission, specifically by reducing the sensitivity of 5-HT_{1A} autoreceptors in the raphe nuclei, and by increasing 5-HT₂ receptor sensitivity [69]. Whether these 5-HT receptor modulations represent the final common pathway for behavioral change in the affective illness remains to be elucidated, but it is a potentially fruitful line of investigation.

20.7

Genetic Considerations

The genes involved in regulation of thyroid function are well characterized, and functional polymorphisms in some of these genes are known to be responsible for other clinical disorders. Could it be that genetic mechanisms play a significant role in persons having treatment-resistant affective illness that responds to high-dose L-T₄? Genetic factors, for example, may determine central thyroid dysfunction characterized by fast degradation of thyroxin, lower peripheral thyroxin levels, and minimal signs of hyperthyroidism after high-dose treatment with L-T₄ in patients with mood disorders.

The potential loci of candidate genes for inter-individual variability in thyroid function, and thereby for differences in response to L-T₄ treatment in mood disorders, are indicated in Figure 20.1. As outlined earlier, T₄ is transported across the blood–brain barrier via active transport by the TTR protein. TTR function has been extensively studied in amyloidosis, and many functional polymorphisms are known to alter activity of this transport molecule [70].

The genetics of the deiodinase enzymes is similarly pertinent; three isoenzymes (deiodinases 1, 2, and 3) are known [57]. Deiodinase type 1 probably has a more prominent role in the pituitary, thyroid, liver, and kidney; whereas T₃ production in the brain is mainly mediated by deiodinase type 2, which is located in astrocytes and tanycytes [55, 58, 71]. Deiodinase type 3 isoenzymes may be involved in cerebral metabolism of T₄ as well, since they were described as being located in neurons (in vivo) and astrocytes (in vitro) [55].

The thyroid hormone receptors present in brain have basically two forms, TR α and TR β , with the genes coding for them being located on chromosomes 17 and 3,

respectively. A mutation of the TR β thyroid hormone receptor has been described in patients with the syndrome of generalized hormone resistance [42], and although no patient syndrome has yet been associated with a TR α allele, mouse models lacking the TR α 1 receptor [72] or having a point mutation in the TR α 1 receptor locus originally found in the TR β gene [73] have a novel array of CNS defects.

Thus, although the genetic variability of TTR, the deiodinase enzymes, and the thyroid hormone receptors has not been investigated to date, there are a growing number of intriguing candidate genes that are worthy of study in patients having treatment-refractory mood disorders that respond to thyroid hormone treatment.

20.8

Conclusions

The adjunctive use of supraphysiological doses of L-T₄ appears to be a promising strategy in severely ill patients having treatment-refractory mood disorders, but it remains experimental. Additional research including randomized double-blind placebo-controlled trials in these severely ill patients is required. What is becoming clear, however, is that, without optimal thyroid function in the brain (which we suspect sometimes is suboptimal despite normal peripheral thyroid function), mood disturbances resistant to treatment may emerge. The use of L-T₄ in the malignant disorders of affect is comparable in concept to the use of steroids in severe inflammatory illness and frequently provides remission, without adverse physiological effects, when all else has failed. Thus, the evaluation of thyroid status is of vital concern to all physicians, especially psychiatrists, caring for those suffering from mood disorders.

20.9

Addendum: Practice Guidelines for the Use of Thyroid Hormones in the Clinical Setting

Supplementing standard treatment regimens with L-T₄ is a relatively novel therapeutic approach to treating affective disorders. Due to limited evidence from controlled experiments and to potential hazards, treatment with supraphysiological doses of L-T₄ should be reserved for patients with *refractory* mood disorder. Overall, there is more evidence on its efficacy in those who suffer malignant bipolar disorder, but there is also some evidence that it can be helpful in those with treatment-resistant unipolar depressive disorders. Specifically, *augmentation with L-T₄ is indicated in patients with:*

- rapid-cycling bipolar affective disorder who have failed to respond to standard pharmacotherapeutic intervention
- prophylaxis-resistant bipolar and unipolar affective disorders
- treatment-resistant major depressive episode (with or without a history of mania or hypomania)

Prophylaxis- and treatment-resistance to standard treatment is usually defined as failure to respond to two medication trials given at adequate dose and duration [18, 20]. Initiation of high-dose L-T₄ treatment, especially without mood stabilizers, is not recommended during a manic episode due to the potential risk of worsening the manic state [3]. (Although when, rarely, a manic state is associated with hypothyroidism [4], supplementation with thyroid hormone is indicated in addition to standard antimanic drug treatment.)

The experimental nature of supraphysiological L-T₄ treatment must be recognized. Careful examination of patients to identify potential hazards and exclude conditions that place a patient at predictable risk is required (Table 20.1). A series of investigations are recommended for baseline (pretreatment) medical evaluation of the patient

Table 20.1 Clinical applications of adjunctive treatment with supraphysiological doses of levothyroxine (L-T₄) in treatment-refractory mood disorders

Clinical indications	<ul style="list-style-type: none"> • Rapid-cycling bipolar disorders • Prophylaxis-resistant mood disorders • Treatment-refractory major depressive episodes (unipolar and bipolar)
Excluding conditions and states	<ul style="list-style-type: none"> • Thyroid (current hyperthyroidism, previous or current thyroid adenoma) • Cardiac factors (e.g., history of myocardial infarction, arrhythmia, insufficiency, malignant, unstable hypertension) • Pregnancy, breastfeeding • Postmenopausal women with evidence of osteopenia/osteoporosis and without concurrent protection for bone loss • Age > 70 years • Severe organic brain disorder (e.g., dementia)
Pretreatment screening and follow-up investigations^{a)}	<ul style="list-style-type: none"> • Psychiatric and medical history and status • Vital signs (blood pressure and pulse) • Body weight • Electrocardiogram (ECG)^{b)} • Bone mineral density (dual-energy X-ray absorptiometry, DXA) (only in patients who receive L-T₄ prophylactically ≥ 3 months) • Thyroid function tests (TSH, thyroid hormones^{c)}) • Routine laboratory evaluations • Consultation with endocrinologist/internist^{d)}
L-T₄ dosing regimen^{e,f)}	<ul style="list-style-type: none"> • Start dose: 100 µg day⁻¹ • Dose increase: 100 µg week⁻¹ • Target dose: 250–400 µg day⁻¹

^{a)} Consider additional radiological investigations in patients with history of or suspected thyroid disorder (e.g., sonography or scintigraphy of the thyroid gland).

^{b)} Consider 24-h ECG recording if history of arrhythmia.

^{c)} Total T₄, free T₄, and total T₃ levels; optional: free T₃ levels and thyroid (TPO) antibodies.

^{d)} Recommended if tolerability problems or adverse events occur.

^{e)} For euthyroid patients only; for patients with overt and subclinical hypothyroidism, see text.

^{f)} Single morning dose (30 min before breakfast).

and during treatment (Table 20.1). If pretreatment investigations show abnormal findings or if any medical problems arise during L-T₄ treatment, consultation with an endocrinologist or internist is recommended.

Many endocrinologists and internists either hesitate to use or resist the use of this approach in psychiatric patients. Experience has shown that it is wise to provide such consultants with reprints of reports on experiences with supraphysiological L-T₄ dosing in psychiatry, including observations of how unusually well patients with affective disorders tolerated this approach. In discussions with medical consultants, the suicide risk of a patient with treatment-refractory mood disorder must also be considered and weighed against the risks of L-T₄ treatment in a risk–benefit assessment.

Pretreatment thyroid status determines the dosing regimen (summarized in Table 20.1). The speed with which the L-T₄ dose can be increased varies with the patient's pretreatment thyroid status and tolerability to the agent during the initial treatment phase. Generally, the dose should be increased more slowly in patients with *overt* or *subclinical hypothyroidism*. In hypothyroid patients, the appropriate speed of increasing treatment depends on the duration and severity of hypothyroidism and the presence of other associated medical disorders. The initial dose may range from 25–50 µg d^{−1} to a full replacement dose based on age, weight, cardiac status, and severity of hypothyroidism [74]. Once a euthyroid state is established, we recommend a 'wait and see' approach for 4–8 weeks before deciding if additional supraphysiological L-T₄ treatment would be beneficial.

A faster speed of dosage increase is recommended for baseline *euthyroid* patients. If side effects occur (most often sweating or tremor), reducing the dose or slowing the speed of dosage increase usually helps. The target dose of L-T₄ is a matter of debate, but our experience suggests that 250–400 µg d^{−1} with suppression of TSH is the preferred range, depending on tolerability and response.

Duration of L-T₄ treatment is determined by clinical indication of use. In patients with treatment-resistant depression, augmentation with L-T₄ should be administered for at least 8 weeks, to allow assessment of the patient's response. This time period is necessary because, with a half life of one week, a steady state is not reached until approximately 3–4 weeks after the last dose increase. If the patient responds, L-T₄ should be continued as long as antidepressant medication is required.

The recommended minimum duration of treatment for patients with rapid-cycling bipolar disorder is 6 months, and it should be 12 months for patients with other prophylactic-resistant bipolar disorder. If the patient responds, prophylactic treatment may need to be continued for long periods (as long as no adverse physiological effects develop), but after clinical stability is achieved for several months, a reduction to bring the serum thyroid levels back within the normal range is recommended, to avoid the long-term risk of side effects with respect to cardiac function and bone metabolism.

Discontinuation of treatment is recommended if the patient does not respond to the intervention within the time frames outlined above. Due to the long half life of L-T₄, discontinuation can be performed over 1–2 weeks or even immediately (depending on the reason for discontinuation), without adverse effects.

References

- 1 Clinical Society of London: Report on myxedema. *Trans. Clin. Soc. Lond. (Suppl.)* **1888**, 21, 18.
- 2 WHYBROW, P. C., PRANGE JR., A. J., TREADWAY, C. R., Mental changes accompanying thyroid gland dysfunction. *Arch. Gen. Psychiatry* **1969**, 20, 48–63.
- 3 WHYBROW, P. C., BAUER, M., Behavioral and psychiatric aspects of thyrotoxicosis. In BRAVERMAN, L. E., UTIGER, R. D. (Eds.), *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, **2000**, 673–638.
- 4 WHYBROW, P. C., BAUER, M., Behavioral and psychiatric aspects of hypothyroidism. In BRAVERMAN, L. E., UTIGER, R. D. (Eds.), *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, **2000**, 837–842.
- 5 BAUER, M., SZUBA, M. P., WHYBROW, P. C., Psychiatric and behavioral manifestations of hyper- and hypothyroidism. In WOLKOWITZ, O. M., ROTHSCHILD, T. J. (Eds.), *Psychoneuroendocrinology: The Scientific Basis of Clinical Practice*. Washington, DC: American Psychiatric Press, **2003**, 419–444.
- 6 GJESSING, R., Disturbances of somatic function in catatonia with a periodic course and their compensation. *J. Ment. Sci.* **1938**, 84, 608–621.
- 7 BAUER, M., WHYBROW, P. C., Thyroid hormone, neural tissue and mood modulation. *World J. Biol. Psychiatr.* **2001**, 2, 57–67.
- 8 BAUER, M., WHYBROW, P. C., Thyroid hormone, brain, and behavior. In PFAFF, D. W., ARNOLD, A. P., ETGEN, A. M., FAHRBACH, S. E., RUBIN, R. T. (Eds.), *Hormones, Brain and Behavior*. San Diego: Academic Press, **2002**, 238–264.
- 9 FLACH, F. F., CELIAN, C. I., RAWSON, R. W., Treatment of psychiatric disorders with triiodothyronine. *Am. J. Psychiatry* **1958**, 114, 841–842.
- 10 WILSON, I. C., PRANGE JR., A. J., LARA, P. P., L-Triiodothyronine alone and with imipramine in the treatment of depressed women. In PRANGE JR., A. J. (Ed.), *The Thyroid Axis, Drugs, and Behavior*. New York: Raven Press, **1974**, 49–62.
- 11 PRANGE JR., A. J., WILSON, I. C., RABON, A. M., LIPTON, M. A., Enhancement of imipramine antidepressant activity by thyroid hormone. *Am. J. Psychiatry* **1969**, 126, 457–469.
- 12 ALTSHULER, L., BAUER, M., FRYE, M., GITLIN, M., MINTZ, J., SZUBA, M. P., LEIGHT, K. L., WHYBROW, P. C., Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am. J. Psychiatr.* **2001**, 158, 1617–1622.
- 13 ARONSON, R., OFFMAN, H. J., JOFFE, R. T., NAYLOR, D., Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch. Gen. Psychiatry* **1996**, 53, 842–848.
- 14 STANCER, H. C., PERSAD, E., Treatment of intractable rapid-cycling manic-depressive disorder with levothyroxine. *Arch. Gen. Psychiatr.* **1982**, 39, 311–312.
- 15 BAUER, M. S., WHYBROW, P. C., Rapid cycling bipolar affective disorders. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. *Arch. Gen. Psychiatr.* **1990**, 47, 435–440.
- 16 BAUMGARTNER, A., BAUER, M., HELLWEG, R., Treatment of intractable non-rapid cycling bipolar affective disorder with high-dose thyroxine: an open clinical trial. *Neuropsychopharmacol.* **1994**, 10, 183–189.
- 17 BAUER, M., PRIEBE, S., BERGHÖFER, A., BSCHOR, T., KIESSLINGER, K., WHYBROW, P. C., Subjective response to and tolerability of long-term supraphysiological doses of levothyroxine in refractory mood disorders. *J. Affect Disord.* **2001**, 64, 35–42.
- 18 BAUER, M., BERGHÖFER, A., BSCHOR, T., BAUMGARTNER, A., KIESSLINGER, U., HELLWEG, R., et al., Supraphysiological doses of L-thyroxine in the maintenance treatment of prophylaxis-resistant affective disorders. *Neuropsychopharmacol.* **2002**, 27, 620–628.
- 19 BAUER, M., ADLI, M., BSCHOR, T., HEINZ, A., RASGON, N., FRYE, M., et al., Clinical applications of levothyroxine in refractory mood disorders. *Clin. Appl. Bipolar Disord.* **2003**, 2, 49–56.

- 20 BAUER, M., HELLWEG, R., GRÄF, K. J., BAUMGARTNER, A., Treatment of refractory depression with high-dose thyroxine. *Neuropsychopharmacol.* **1998**, *18*, 444–455.
- 21 RUDAS, S., SCHMITZ, M., PICHLER, P., BAUMGARTNER, A., Treatment of refractory chronic depression and dysthymia with high-dose thyroxine. *Biol. Psychiatr.* **1999**, *2*, 229–233.
- 22 WHYBROW, P. C., Sex differences in thyroid axis function: relevance to affective disorder and its treatment. *Depression* **1995**, *3*, 33–42.
- 23 BAUMGARTNER, A., GRÄF, K. J., KÜRTE, I., MEINHOLD, H., The hypothalamic–pituitary–thyroid axis in psychiatric patients and healthy subjects: parts 1–4. *Psychiatry Res.* **1988**, *24*, 271–332.
- 24 WHYBROW, P. C., COPPEN, A., PRANGE JR., A. J., NOGUERA, R., BAILEY, J. E., Thyroid function and the response to liothyronine in depression. *Arch. Gen. Psychiatr.* **1972**, *26*, 242–245.
- 25 KIRKEGAARD, C., FABER, J., The role of thyroid hormones in depression. *Eur. J. Endocrinol.* **1998**, *138*, 1–9.
- 26 FRYE, M. A., DENICOFF, K. D., BRYAN, A. L., SMITH-JACKSON, E. E., ALI, S. O., LUCKENBAUGH, D., et al., Association between lower serum free T₄ and greater mood instability and depression in lithium-maintained bipolar patients. *Am. J. Psychiatr.* **1999**, *156*, 1909–1914.
- 27 COLE, D. P., THASE, M. E., MALLINGER, A. G., SOARES, J. C., LUTHER, J. F., KUPFER, D. J., et al., Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. *Am. J. Psychiatr.* **2002**, *159*, 116–121.
- 28 BAUER, M. S., WHYBROW, P. C., WINOKUR, A., Rapid cycling bipolar affective disorder. I. Association with grade I hypothyroidism. *Arch. Gen. Psychiatr.* **1990**, *47*, 427–432.
- 29 COWDRY, R. W., WEHR, T. A., ZIS, A. P., GOODWIN, F. K., Thyroid abnormalities associated with rapid-cycling bipolar illness. *Arch. Gen. Psychiatr.* **1983**, *40*, 414–420.
- 30 LAZARUS, J. H., The effects of lithium therapy on thyroid and thyrotropin-releasing hormone. *Thyroid* **1998**, *8*, 909–913.
- 31 GYULAI, L., BAUER, M., BAUER, M. S., GARCÍA-ESPAÑA, F., CNAAN, A., WHYBROW, P. C., Thyroid hypofunction in patients with rapid cycling bipolar disorder after lithium challenge. *Biol. Psychiatry* **2003**, *53*, 899–905.
- 32 TOFT, A. D., Thyroxine therapy. *N. Engl. J. Med.* **1994**, *331*, 174–180.
- 33 REICHLIN, S., UTIGER, R. D., Regulation of the pituitary–thyroid axis in man: relationship of TSH concentration to concentration of free and total thyroxine in plasma. *J. Clin. Endocrinol. Metab.* **1967**, *27*, 251–255.
- 34 BEIERWALTES, W. H., RUFF, G. E., Thyroxin and triiodothyronine in excessive dosage to euthyroid humans. *Arch. Intern. Med.* **1958**, *101*, 569–576.
- 35 BRAVERMAN, L. E., VAGENAKIS, A., DOWNS, P., FOSTER, A. E., STERLING, K., INGBAR, S. H., Effects of replacement doses of sodium l-thyroxine on the peripheral metabolism of thyroxine and triiodothyronine in man. *J. Clin. Invest.* **1973**, *52*, 1010–1017.
- 36 COHEN 3RD, J. H., INGBAR, S. H., BRAVERMAN, L. E., Thyrotoxicosis due to ingestion of excess thyroid hormone. *Endocr. Rev.* **1989**, *10*, 113–124.
- 37 BAUER, M., FAIRBANKS, L., BERGHÖFFER, A., HIERHOLZER, J., BSCHOR, T., RASGON, N., et al., No evidence of accelerated loss of bone density during maintenance treatment with supraphysiological doses of l-thyroxine in prophylaxis-resistant affective disorders. Manuscript submitted.
- 38 GYULAI, L., WHYBROW, P. C., JAGGI, J., BAUER, M. S., YOUNKIN, S., RUBIN, L., et al., Bone mineral density and l-thyroxine treatment in rapidly cycling bipolar disorder. *Biol. Psychiatry* **1997**, *41*, 503–506.
- 39 GYULAI, L., BAUER, M., ESPAÑA-GARCIA, F., HIERHOLZER, J., BAUMGARTNER, A., WHYBROW, P. C., Bone mineral density in pre- and post-menopausal women with affective disorder treated with long-term l-thyroxine augmentation. *J. Affect. Disord.* **2001**, *66*, 185–191.
- 40 WHYBROW, P. C., The therapeutic use of triiodothyronine and high-dose thyroxine in psychiatric disorder. *Acta Med. Austriaca* **1994**, *21*, 47–52.

- 41 BAUER, M., BAUR, H., BERGHÖFER, A., STRÖHLE, A., HELLWEG, R., MÜLLER-OERLINGHAUSEN, B., et al., Effects of supraphysiological thyroxine administration in healthy controls and patients with depressive disorders. *J. Affect Disord.* **2002**, *68*, 285–294.
- 42 REFETTOFF, S., Resistance to thyroid hormone. In BRAVERMAN, L. E., UTIGER, R. D. (Eds.), *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, **2000**, 1028–1043.
- 43 SOKOLOFF, L., WECHSLER, R. L., MANGOLD, R., BALLS, K., KETY, S. S., Cerebral blood flow and oxygen consumption in hyperthyroidism before and after treatment. *J. Clin. Invest.* **1953**, *32*, 202–208.
- 44 SENSENBACH, W., MADISON, L., EISENBERG, S., OCHS, L., The cerebral circulation and metabolism in hyperthyroidism and myxedema. *J. Clin. Invest.* **1954**, *33*, 1434–1440.
- 45 BAUER, M., MARSEILLE, D. M., GEIST, C. L., VAN HERLE, K., RASGON, N., MARTINEZ, D., et al., Effects of thyroid hormone replacement therapy on regional brain metabolism (abstract). *J. Nucl. Med.* **2002**, *43* (5 Suppl.), 254P.
- 46 SILVERMAN, D. H. S., GEIST, C. L., VAN HERLE, K., RASGON, N., MARTINEZ, D., MILLER, K. J., HASELRIG, T., et al., Abnormal regional brain metabolism in patients with hypothyroidism secondary to Hashimoto's disease (abstract). *J. Nucl. Med.* **2002**, *43* (5 Suppl.), 254P.
- 47 CALZA, L., ALOE, L., GIARDINO, L., Thyroid hormone-induced plasticity in the adult rat brain. *Brain Res. Bull.* **1997**, *44*, 549–557.
- 48 CONSTANT, E. L., DE VOLDER, A. G., IVANOIU, A., BOL, A., LABAR, D., SEGHERS, A., et al., Cerebral blood flow and glucose metabolism in hypothyroidism: a positron emission tomography study. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 3864–3870.
- 49 DREVETS, W. C., Neuroimaging studies of mood disorders. *Biol. Psychiatry.* **2000**, *48*, 813–829.
- 50 MARANGELL, L. B., KETTER, T. A., GEORGE, M. S., PAZZAGLIA, P. J., CALLAHAN, A. M., PAREKH, P., et al., Inverse relationship of peripheral thyrotropin-stimulating hormone levels to brain activity in mood disorders. *Am. J. Psychiatr.* **1997**, *154*, 224–230.
- 51 BAUER, M., LONDON, E. D., RASGON, N., BERMAN, S. M., FRYE, M. A., ALTSCHULER, L., et al., Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in women with bipolar depression. **2004**, Manuscript submitted.
- 52 DREVETS, W. C., PRICE, J. L., SIMPSON JR., J. R., TODD, R. D., REICH, T., VANNIER, M., et al., Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **1997**, *386*, 824–827.
- 53 BRODY, A. L., BARSOM, M. W., BOTA, R. G., SAXENA, S., Prefrontal-subcortical and limbic circuit mediation of major depressive disorder. *Semin. Clin. Neuropsychiatr.* **2001**, *6*, 102–112.
- 54 KETTER, T. A., KIMBRELL, T. A., GEORGE, M. S., DUNN, R. T., SPEER, A. M., BENSON, B. E., et al., Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol. Psychiatry.* **2001**, *49*, 97–109.
- 55 LECHAN, R. M., TONI, R., Thyroid hormones in neural tissue. In PFAFF, D. W., ARNOLD, A. P., ETGEN, A. M., FAHRBACH, S. E., RUBIN, R. T. (Eds.), *Hormones, Brain and Behavior*. San Diego: Academic Press, **2002**, 157–238.
- 56 SULLIVAN, G. M., HATTERER, J. A., HERBERT, J., CHEN, X., ROOSE, S. P., ATTIA, E., et al., Low levels of trans-thyretin in the CSF of depressed patients. *Am. J. Psychiatry* **1999**, *156*, 710–715.
- 57 ST GERMAIN, D. L., GALTON, V. A., The deiodinase family of selenoproteins. *Thyroid* **1997**, *7*, 655–668.
- 58 KÖHRLE, J., Thyroid hormone metabolism and action in the brain and pituitary. *Acta Med. Austriaca* **2000**, *27*, 1–7.
- 59 ST GERMAIN, D., Regulatory effect of lithium on thyroxine metabolism in murine neural and anterior pituitary tissue. *Endocrinology* **1987**, *120*, 1430–1438.
- 60 BAUMGARTNER, A., PINNA, G., HIEDRA, L., GAIO, U., HESSENIUS, C., CAMPOS-BARROS, A., et al., The effects of lithium and carbamazepine on thyroid hormone metabolism in rat brain. *Neuropsychopharmacol.* **1997**, *16*, 25–41.

- 61 HAHN, C. G., PAWLYK, A. C., WHYBROW, P. C., GYULAI, L., TEJANI-BUTT, S. M., Lithium administration affects gene expression of thyroid hormone receptors in rat brain. *Life Sci.* **1999**, *64*, 1793–1802.
- 62 HAHN, C. G., PAWLYK, A. C., WHYBROW, P. C., TEJANI-BUTT, S. M., Differential expression of thyroid hormone receptor isoforms by thyroid hormone and lithium in rat GH3 and B103 cells. *Biol. Psychiatr.* **1999**, *45*, 1004–1012.
- 63 RUEL, J., FAURE, R., DUSSAULT, J. H., Regional distribution of nuclear T3 receptors in rat brain and evidence for preferential localization in neurons. *J. Endocrinol. Invest.* **1985**, *8*, 343–348.
- 64 SCHWARTZ, H. L., OPPENHEIMER, J. H., Nuclear triiodothyronine receptor sites in brain: probable identity with hepatic receptors and regional distribution. *Endocrinol.* **1978**, *103*, 267–273.
- 65 ANDERSON, G. W., MARIASH, C. N., OPPENHEIMER, J. H., Molecular actions of thyroid hormone. In BRAVERMAN, L. E., UTIGER, R. D. (Eds.), *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, **2000**, 174–195.
- 66 BAUMGARTNER, A., Thyroxine and the treatment of affective disorders: an overview of the results of basic and clinical research. *Int. J. Neuropsychopharmacol.* **2000**, *3*, 149–165.
- 67 WHYBROW, P. C., PRANGE JR., A. J., A hypothesis of thyroid–catecholamine-receptor interaction. *Arch. Gen. Psychiatr.* **1981**, *38*, 106–113.
- 68 HENLEY, W. N., KOEHLNLE, T. J., Thyroid hormones and the treatment of depression: an examination of basic hormonal actions in the mature mammalian brain. *Synapse* **1997**, *27*, 36–44.
- 69 BAUER, M., HEINZ, A., WHYBROW, P. C., Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Mol. Psychiatr.* **2002**, *7*, 140–156.
- 70 ROBBINS, J., Transthyretin from discovery to now. *Clin. Chem. Lab. Med.* **2002**, *40*, 1183–1190.
- 71 LEONARD, J. L., KÖHRLE, J., Intracellular pathways of iodothyronine metabolism. In BRAVERMAN, L. E., UTIGER, R. D. (Eds.), *Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, **2000**, 136–171.
- 72 GUADANO-FERRAZ, A., BENAVIDES-PICCIONE, R., VENERO, C., LANCHI, C., VENNSTROM, B., SANDI, C., et al., Lack of thyroid hormone receptor alpha1 is associated with selective alterations in behavior and hippocampal circuits. *Mol. Psychiatry* **2003**, *8*, 30–38.
- 73 TINNIKOV, A., NORDSTROM, K., THOREN, P., KINDBLOM, J. M., MALIN, S., ROZELL, B., ADAMS, M., RAJANAYAGAM, O., PETTERSSON, S., OHLSSON, C., CHATTERJEE, K., VENNSTROM, B., Retardation of post-natal development caused by a negatively acting thyroid hormone receptor alpha1. *EMBO J.* **2002**, *21*, 5079–5087.
- 74 American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr. Practice* **2002**, *8*, 457–469.

21

Stress System Dysregulation in Depression: From Molecular Biology to New Treatment Opportunities

P. W. Gold

21.1

Introduction

This chapter reviews the mediators and circuitries of the stress system to lay the groundwork and place in context physiological and structural alterations in depression that may occur as a part of stress system dysfunction. The stress response and major depression share many features, both associated with a diminution of cognitive and affective flexibility, alterations in arousal, and perturbations in neuroendocrine and autonomic function.

Major depression affects approximately 8% of men and 15% of women [1]. Over 75% have recurrent and life-long depression, with repeated remissions and exacerbations [2]. Depression causes mental anguish and disrupts biological processes, contributing to premature coronary artery disease and osteoporosis and doubling the mortality in patients without regard to age or significant physical illness [reviewed in 2–6]. Childhood trauma, environmental stress, and internal conflict are some factors that lead to and influence the course and severity of major depression [7].

The DSM-IV lists two major divisions of depressive subtypes based on the phenomenology of recurrent affective episodes: bipolar affective illness (recurrent bouts of both major depression and mania or hypomania) and major depression (recurrent bouts of major depression alone). Bipolar affective illness affects 1%–2% of the population, men and women equally, whereas unipolar predominates in females (2 : 1 in comparison to males), affecting 12% of the population. Both conditions are heritable, involving multiple genes [8, 9].

An independent distinction of depression that the DSM-IV includes is based on the pattern of psychological and neurovegetative symptoms [10]. This clinical phenotype provides direction for appropriate antidepressant medication [11]. The first is melancholic depression, noted by a state of pathological and physiological hyperarousal. Intense anxiety about the self, as well as feelings of worthlessness and failure, explain the melancholic's dread concerning the future [reviewed in 12]. Physiologically, patients manifest hypercortisolism, suppression of the growth

hormone and reproductive axes, insomnia, and loss of appetite. There exists a diurnal variation in the severity of depressed mood, which is greatest in the morning [reviewed in 12]. Pure melancholic features are present in 25%–30% of major depressed patients. Another 15%–30% have the second syndrome, pure atypical depression, which is an antithesis of melancholia. Atypical features include a sense of disconnectedness and emptiness, resulting in avoiding others, believing that contact is too demanding and tiring. They may lament about a cognitive and mental weariness, as reflected by their neurovegetative state, being lethargic and fatigued. They sleep excessively, increase food intake, gain weight, and have worsening symptoms as the day progresses [13]. Findings show that those with pure symptomatic features, melancholia or atypical, have a more severe course of illness than those with mixed features [10].

21.2

The Stress Response

A response to danger consists of a stereotyped series of physiological (e.g., increase in heart rate) and behavioral (defensive or offensive) programs crucial for survival. An extensive circuitry has thus been developed for generating and modulating fear and response, to both stimulate appropriate behavior characterized by speed and simplicity and inhibit more complex, novel, and untested response [14, 15]. Consistently, affect is often confined to a distressed fearful mode, as mood shifts are inhibited. For our purpose, the core stress system consists of the CRH system and the locus ceruleus–norepinephrine (LC–NE) systems. These systems promote arousal, maintain the limbic system and the cortex state favoring survival, and serve as a homeostat modulating the intensity and duration of the stress response.

21.3

The CRH System

CRH plays many roles in the stress response. As the main hypothalamic hormone that causes the pituitary to release corticotropin (ACTH), it indirectly activates adrenocorticosteroid secretions (the HPA axis regulation). In rats, CRH is also involved in activating the locus ceruleus, sympathetic nervous system, and adrenal medulla and in inhibiting contrasting activities such as food intake or endocrine programs for growth and reproduction [reviewed in 16–18]. An extrahypothalamic system consists of CRH-containing neurons in the amygdala, which activates fear-related behavior while inhibiting exploration [reviewed in 16–18]. Thus, CRH is involved in behavioral, neuroendocrine, neurovegetative, and autonomic components of the stress response.

Although acute levels of CRH-mediated glucocorticoid secretions and cortisol have adaptive advantages during stress, chronic release of CRH is almost always deleterious. Acute activation of glucocorticoid receptors in the prefrontal cortex,

hippocampus, amygdala, and hypothalamus inhibits the HPA axis, but chronic activation damages such neurons in the hippocampus, possibly leading to more severe hypercortisolism [19]. Not all glucocorticoid receptors are inhibitory; those found in the central nucleus of the amygdala and in the bed nucleus of the stria terminalis actually increase CRH mRNA. This is true also of a distinct population of PVN neurons that send descending terminals to brainstem noradrenergic neurons [20].

In the brain, CRH receptor type 1 (CRHR-1) is widely distributed, and in mice, its knockout mutant shows decreased anxiety [21]. Perhaps the type 2 receptors counter-regulate CRHR-1. KO studies demonstrate its role in mediating diminished arousal, anxiety, and food intake [22, 23]. There is also a CRH binding protein that parallels CRH receptors in the brain and acts as an endogenous CRH antagonist to promote arousal and diminish feeding [24].

Recently, oral administration to rhesus macaques of a CRH type 1 receptor antagonist that can cross the blood–brain barrier, antalarmin, resulted in inhibition of stress-induced, anxiety-like responses. Antalarmin also appears to inhibit increases in plasma ACTH, NE, epinephrine, and cortisol [25]. In rodents, it blocked the expression, development, and consolidation of conditioned fear [26]. These data from rodents and primates suggest that, if they are applicable to humans, there is great potential for treatment with an CRH antagonist after an acute traumatic event and in preventing adverse secondary CNS changes that occur during chronic stress. Work has been directed to the development of such a ligand [27].

21.4

The Locus Ceruleus Norepinephrine System, Amygdala, and Prefrontal Cortex

The LC–NE system, in the mid-pons, contains the highest concentration of noradrenergic cell bodies in the brain, innervating many areas of the brain. Normal firing rates enhance responses to either excitatory or inhibitory stimuli by increasing the signal-to-noise ratio. But at higher rates, this general enhancement is decreased, and the LC becomes the brain's alarm system, stimulating the sympathetic nervous system and HPA axis while inhibiting the parasympathetic nervous system and neurovegetative functions [reviewed in 28]. The LC also enhances the amygdala and other structures encoding aversive memories, promoting survival during a crisis and preparing for the future. Finally, Arnsten et al. [29] recently discovered that the LC inhibits the prefrontal cortex to favor fast and simple responses.

The amygdala transforms experiences of being afraid into feeling, by providing good or bad information to working memory and by activating arousal centers (with the core stress system) to maintain focus upon danger [14]. It is responsible for acquiring and storing classic fear-conditioned responses and for transferring complex memories to the hippocampus and striatum for storage and retrieval [15, 30]. Similar to the core stress system, the amygdala stimulates hypothalamic CRH release and brainstem autonomic centers to increase HPA and LC activity while inhibiting the prefrontal cortex [15]. The amygdala, hypothalamus, and

brainstem noradrenergic neurons have multiple feed-forward loops that can result in a sustained and powerful stress response.

The prefrontal cortex and the stress system inhibit each other's activity [reviewed in 31–33]. The dorsolateral prefrontal cortex is involved in attention and cognition, and the ventromedial modulates affect, neuroendocrine, and autonomic activity [reviewed in 29, 31–33]. Thus, flexibility in cognition and affect requires an activated

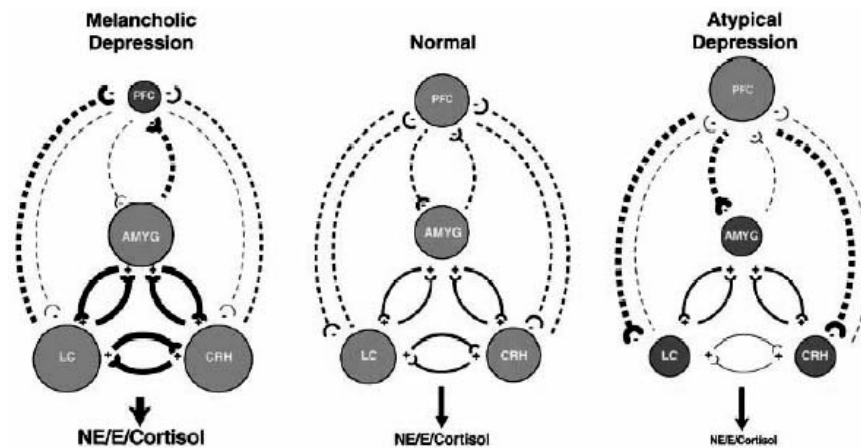


Figure 21.1 Schematic diagram of the interrelation of stress system mediators and circuitries in melancholic and atypical depression.

(middle) Normal. In the absence of stressful stimuli, the stress system is not quiescent, but rather resides in a dynamic state of bidirectional interactions among stress mediators. Such a homeostatic equilibrium can react flexibly to a range of different stimuli that may preferentially affect one component over another. Available data in primates suggest that under ordinary circumstances: (1) the prefrontal cortex inhibits the amygdala, HPA axis, and LC-NE system; (2) an activated amygdala inhibits the prefrontal cortex and stimulates both the HPA axis and the LC-NE. In the reverse direction; (3) the LC-NE activates the amygdala and HPA axis and inhibits the prefrontal cortex; (4) the HPA axis activates the LC-NE and the amygdala. Dotted lines inhibitory, solid lines excitatory. Schematically, in the normal state, the relative strength of each component is similar, denoted by circles of identical diameter. (left) Melancholic depression can be conceptualized as a prolonged and intensified stress response that does not yield to its

ordinary counter-regulatory restraints. The net effect is a pronounced shift in equilibrium with the following results: (1) diminished activity of the prefrontal cortex; (2) activation of the amygdala; (3) activation of the core stress system. The primary defect could arise from any of the structures pictured in the schematic diagram or circuits in which they participate. Note reciprocal relations between prefrontal cortex and subcortical stress components. Also note that the amygdala, LC, and CRH system are all excitatory to one another so that an increase in the activation of one component could set off a reverberate sequence of further activations unless overtaken by inhibitory stimuli. Similarly, the prefrontal cortex and the components of the stress system exhibit bidirectional inhibition on one another. (right) Atypical depression can be conceptualized as a state of stress system hypoactivity that has yielded too readily to its counter-regulatory restraints. The net effect is a pronounced shift in equilibrium with hypoactivity of each of the components of the stress system. Theoretically, the prefrontal cortex could be disinhibited or primarily hyperactive. Abbreviations: PFC, prefrontal cortex; AMYG, amygdala.

prefrontal cortex (and inhibited stress system). Humans and rats with cortex lesions often have exaggerated autonomic and endocrine responses in nonstressful situations, implying that the cortex inhibits the HPA axis and the sympathetic nervous system [33]. Further study in the rat led to the conclusion that the left infralimbic cortex (disinhibited core system when lesioned) inhibits the right (normal activity when lesioned) [34]. Figure 21.1 schematically illustrates the many potential positive-feedback loops that emerge during activation of the stress response in which each component activates the other.

21.5

Role of Stress System in Melancholic and Atypical Depression

Hypercortisolism in depression is common, and it is widely accepted that hypothalamic CRH is elevated in depression. Hypercortisolemic patients had significantly blunted plasma ACTH response to ovine CRH, indicating an appropriately restrained HPA axis (since the cortisol correctly provided negative feedback to the pituitary) [35]. The problem with depression is therefore a central defect originating above the hypothalamus. This is substantiated and contrasted by evidence from studies of patients with Cushing's disease, whose hypercortisolism is due to a peripheral (pituitary) defect. Cushing's patients have high ACTH and cortisol responses to CRH. Although the pituitary itself was resistant to cortisol negative feedback, other studies reveal that the hypothalamus appears to respond normally to glucocorticoid negative feedback [36].

Other evidence for hypersecretion of CRH in the pathophysiology of hypercortisolism includes a reduced number of CRH receptors in the frontal cortex of postmortem samples from suicides and elevated CSF CRH levels in depressed patients, which decreased significantly after treatment [37, 38]. In our group, DeBellis discovered that fluoxetine significantly lowers CSF CRH levels when depressions remitted and that chronic administration of imipramine down-regulates the HPA axis [39]. In animals, chronic imipramine also reduces the CRH mRNA levels while increasing the glucocorticoid receptor type I in the hippocampus, which is believed to be important in HPA feedback inhibition [40].

A compatible finding of negative correlation between CSF CRH and plasma cortisol is exemplified in a study of the 30-h pattern of CSF CRH levels in severely depressed inpatient melancholic subjects and controls. Depressed patients demonstrated 'normal' CSF CRH concentrations, despite significant hypercortisolism and constant elevated CSF NE [41]. In comparison, matching degrees of hypercortisolism in patients with depression associated with Cushing's had very low CSF CRH levels, and patients with both major depression and Cushing's had higher CSF CRH levels [36]. This suggests that the normal CNS (Cushing's patients) was correctly suppressed by cortisol feedback whereas the abnormal CNS (major depression patients) was not suppressed by hypercortisolism. The latter failure can be explained either by a resistance to glucocorticoid negative feedback at several potential sites or by the more favored idea that an overdriven HPA axis overcomes normal

glucocorticoid feedback. However, the interpretation of CSF CRH levels in depression is complicated by other factors. Although the PVN–median eminence is restrained by glucocorticoid negative feedback, glucocorticoids increase CRH mRNA levels in the amygdala, the bed nucleus of the stria terminalis, and the PVN CRH descending pathway to brainstem noradrenergic neurons (as mentioned before). Lesion studies of PVN in rats suggest that CRH activations are neutralized by CRH suppression of the HPA axis by glucocorticoids. This information is by no means definitively substantiated, but merely supported by circumstantial evidence. A CRH type 1 antagonist may better expose the role of CRH in depression.

21.6

The Locus Ceruleus Norepinephrine System

Based on the antidepressive effect of both MAO inhibitors and NE-uptake inhibitors, which increase noradrenergic activity, and the induced-depression effect of depleting NE by adding reserpine, the catecholamine hypothesis states that depression can be caused by a deficiency of NE delivery to its receptors in the CNS, rather than by only psychological trauma or adverse events [42, 43]. However, this is challenged by studies that show decreased, normal, or increased NE delivery to CNS receptors [44–75]. Past studies of CSF NE or its metabolites at this point in depressed patients were done at single time points and did not classify patients on the basis of melancholic or atypical subtypes of depression. A careful review later revealed that patients with reserpine-induced depression may have experienced a neuroleptic-like syndrome.

So our group conducted a study of drug-free and severely depressed melancholic patients who had received electroconvulsive treatments (ECT) for depression. CSF CRH and NE were measured for 30 consecutive hours by use of an indwelling lumbar drain, and plasma ACTH and cortisol were measured every half hour. CSF NE, whose origin is debatable (although the work of Goldstein et al. with Shy-Drager patients indicated dissociation between plasma and CSF NE levels), were elevated around the clock, with significantly increased plasma cortisol levels [41]. Like the normal controls, melancholic patients showed diurnal rhythms of CSF NE and plasma cortisol levels that were virtually superimposable and positively correlated. This led to the idea that cortisol stimulates centrally directed NE, agreeing with our in-vitro finding that NE stimulates CRH from the hypothalamus [18, 76].

Radesheer et al. [77], in their study on postmortem brains of depressed patients who had committed suicide, found significant increases in hypothalamic neurons expressing CRH with descending projections to brainstem noradrenergic nuclei (Figure 21.2). This finding, plus the knowledge that glucocorticoids increase CRH mRNA levels in the CRH neurons of the PVN that descend to brainstem noradrenergic neurons (as noted before), suggests another pathway independent of the HPA axis that glucocorticoids can activate, which would then activate brainstem noradrenergic neurons, providing more mutual reverberatory loops between CRH, NE, and cortisol.

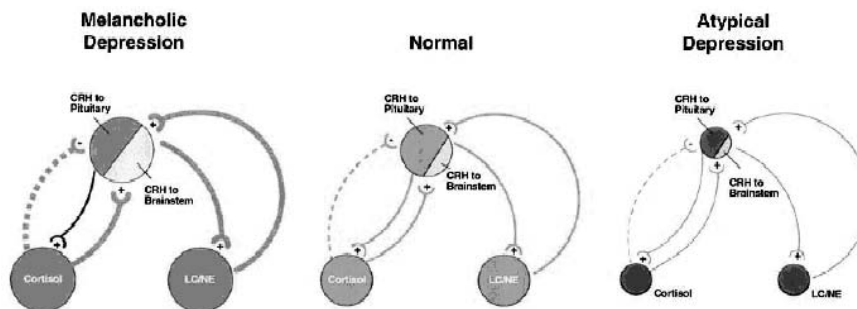


Figure 21.2 A specific PVN GRH pathway to brainstem noradrenergic nuclei independent of the HPA axis. Post mortem studies in patients who had been diagnosed with major depression reveal a significant increase in hypothalamic CRH-containing neurons. Surprisingly, this increase was much more pronounced in hypothalamic CRH-containing neurons that send descending projections to brainstem noradrenergic nuclei. The fact that glucocorticoids seem to activate rather than restrain this pathway introduces another context for a positive feedback loop in which an activated HPA axis leads to increased CRH

section, which in turn activates brainstem noradrenergic nuclei. This feedback loop may contribute to the pronounced hypernoradrenergic state seen in melancholic depression as well as the positive correlation we found between CSF NE and plasma cortisol levels seen in both patients and controls. The postulated activating effects of glucocorticoids upon hypothalamic CRH containing neurons that send descending fibers to brainstem noradrenergic nuclei establishes yet another positive feedback loop within the stress system and in melancholic depression.

To summarize the LC system, although scientists initially believed that NE-uptake blockers and MAO inhibitors enhanced noradrenergic activity by preserving NE, Weiss and others [42, 78] have shown that they actually decrease the firing rate of the LC during stress. We do not believe that all melancholics have activated noradrenergic secretion. The pathophysiology is complex and influenced by multiple genes. It is clear that norepinephrine is not the only nor the main neurotransmitter involved in major depression. In fact, serotonin-uptake inhibitors, like those of NE, also exert effects on both systems. More than a dozen 5HT receptors have been identified, some causing antithetical effects on cell firing. Effective antidepressants generally increase the release of 5HT and the density of post-synaptic 5HT 1a receptors and also decrease the density of 5HT 2a receptors [79, 80]. 5HT 1a receptors, which are reduced in brains of suicides, lower LC firing, whereas 5HT 2a receptors, which are increased in such brains, increase LC firing [81, 82].

All in all, the CRH and noradrenergic systems in depression, together with glucocorticoid hypersecretion, produce the hyperarousal and anxiety of melancholia. The two systems can activate one another, leading to glucocorticoid excess that positively feedbacks to the amygdala while inhibiting the prefrontal cortex to promote quick and simple behaviors. Excess glucocorticoid can also damage hippocampal neurons that would normally respond by restraining the HPA axis, activating the amygdala and extra-amygdala sites involved in conditional fear and declarative memories (more hypercortisolism), and descending CRH pathways to NE nuclei.

To illustrate the potent effect of glucocorticoid, administration of an antagonist (RU486) over several days reduced at least 50% of depressive symptoms in a majority of patients (Belanoff et al., in press).

21.7

Long-term Medical Consequences of Melancholia

The mortality rate of patients with major depression at any age is doubled regardless of suicide [4, 83]. A key cause for this is the increased risk of premature ischemic heart disease. Hypercortisolism and deficient sex steroids and growth hormone increases visceral fat mass, which leads to increased portal and peripheral fatty acids, and then insulin resistance, then hypertension, dyslipidemia, hypercoagulation, and enhanced endothelial inflammation [84, 85]. Increased NE also promotes insulin resistance, left ventricular hypertrophy, myocyte growth, and other cardiac problems [86–89].

Among our patients with very severe affective illness, about 40% of premenopausal women (~age 41) had peak bone density two standard deviations below their peak, or the usual level for women in their 60s [90]. For every 10% loss below peak density, the fracture rate is doubled [91]. Premature osteoporosis at the hip or spine is also severe, affecting 40% of women in their mid-to-late twenties, although our patients experienced more loss at the hip. [90]. Bone loss is due to hypercortisolism [92]. Patients given glucocorticoids experience maximal bone loss 3–4 months after treatment [93, 94]. Suppression of growth hormone and gonadal axes, as well as NE hypersecretion, which activates IL-6 which is responsible for postmenopausal osteoporosis, also contribute to bone loss.

21.8

Neuroimaging Studies

Changes at local synaptic sites, especially in the amygdala and prefrontal cortex, are crucial to the construction of models for depression and have been noted in neuroimaging studies. Increased cerebral blood flow and metabolism in activated amygdala correlate positively with depression severity and baseline plasma cortisol levels [95]. This is consistent with the amygdala activating the HPA axis, whose glucocorticoid then enhances the amygdala CRH system. Another finding demonstrates the covariation of neural activity in 5HT-related brain areas with both plasma tryptophan and ratings of depressed mood. Major depression is also characterized by hypoactivity of the dorsolateral prefrontal and hyperactivity of the ventral prefrontal and paralimbic structures associated with anxiety [96]. A loss of volume (40% in suicide patients) of the left subgenual prefrontal cortex has been well replicated [97]. This area aids in inhibiting the HPA axis and sympathetic nervous system of melancholic patients. Lateralization compatible with rat data is also found in patients, indicating that the left infralimbic region inhibits the right [34]. From

these data, we postulate that left-side defects in melancholia lead to hyperactivity of both the amygdala and core stress system. Atypical depression, in contrast, may have a hyperactive left prefrontal cortex, resulting in restraint and hypoactivity of the core stress system. These patients' primary defect may be on the right side.

What these decreases in volumes mean is not yet clear. Both glucocorticoids and CRH have been shown to be neurotoxic in animals. Thus, the degeneration of the core stress system can be due to abnormalities in growth factors and other intracellular mediators, according to the hypothesis of Nestler's group and Manji's work, and as supported by the fact that antidepressants such as lithium can cause a regrowth of this lost tissue [98, 99].

21.9 Atypical Depression

Studies in nonhuman primates that were abandoned or abused by their mothers have revealed that these animals had similar behavior to that of atypical-depression patients, having a virtual shutdown of their affective existence and hypoactivation of their HPA axis. Prompted by arousal symptoms of melancholia, we hypothesized many years ago that the lethargy, fatigue, and hypersomnia of atypical depression is associated with a reduction of stress system mediators [reviewed in 16–18]. Yahuda and colleagues recently published data suggestive of HPA axis hypoactivity in patients with post-traumatic disorder [100]. However, detecting a centrally mediated decrement in HPA axis has been difficult due to many factors, but we have developed an endocrine paradigm for differential diagnosis among adrenal, pituitary, and hypothalamic CRH-mediated hypoactivity of the HPA axis [101, 102].

Hypothalamic CRH deficiency is marked by low basal plasma ACTH and cortisol levels [103]. In response to synthetic CRH, patients show delayed plasma ACTH responses to CRH and very attenuated cortisol responses. My group postulated that the delay in ACTH response is due to the lack of priming of the ACTH-secreting pituitary cells by endogenous CRH. ACTH is made but is kept in a secondary releasable pool and thus more slowly released. Blunted cortisol response can be explained by adrenal hypostimulation. Patients given repeated priming pulses of CRH had significantly increased response to CRH [104]. Unlike hypothalamic CRH deficiency, primary adrenal insufficiency involves normal hypothalamus and pituitary. However, the adrenals are unable to produce adequate cortisol, resulting in high ACTH response to CRH but with little cortisol.

We review how patients with melancholia have high levels of cortisol that appropriately restrained pituitary cells from secreting more ACTH. So the response to synthetic CRH is a blunted ACTH and a very robust cortisol response due to hyper-responsive adrenals (which is further due to hyperactive hypothalamic CRH neurons). Unlike the situation in melancholia, the hypercortisolism of Cushing's disease stems from exaggerated ACTH responses (since the pituitary is not restrained) [102]. After surgery to remove the microadenoma, these patients are often adrenally insufficient. This low basal cortisol level and silent ACTH-secreting

cells reflect long-term suppression of either hypothalamic CRH or pituitary ACTH secretion from before surgery, which may last up to one year. Stimulation with CRH gave delayed and blunted ACTH and very reduced cortisol response, similar to the hypothalamic CRH deficiency pattern. But after many priming CRH doses, ACTH secretions were partially restored. This and the finding of suppressed CSF CRH levels support the idea that low ACTH secretion is due to longstanding hypercortisolism [105].

Other affective disorders we looked into to determine if atypical patients show evidence of a centrally mediated HPA axis hypoactivity are the depression in seasonal affective disorder, chronic fatigue syndrome, and postpartum depression [106–109]. All three showed the CRH deficiency phenotype of blunted, delayed plasma ACTH and cortisol responses. The patients with chronic fatigue syndrome, interestingly enough, had a bimodal ACTH/cortisol dose-dependent response [109]. A low dose of ACTH corresponded with exaggerated plasma levels, probably reflecting a type of increased sensitivity due to long-standing hypostimulation and adrenals that, though small and of low mass, could produce augmented cortisol responses to low ACTH. In contrast, a high dose of ACTH corresponded with attenuated cortisol response, indicating that the low understimulated adrenal mass failed to fully respond to high ACTH.

We also measured ACTH and cortisol levels every 3 min for 24 h in four atypical depressed patients and in four controls, to obtain a sampling of sufficient resolution to detect low-level pulses of ACTH and cortisol that would otherwise be missed. Atypical-depression patients had reduced plasma ACTH secretion (Licinio and Gold, unpublished findings). Since the pituitary and adrenal components of the HPA axis were normal, this further supports the hypothesis of a centrally mediated (hypothalamic) HPA axis deficiency. The atypical-depression patients' normal cortisol levels may be due to compensatory mechanisms, perhaps in the context of the unilateral adrenalectomy.

Only one study, meticulously done by Geraciotti et al. [110], reported reduced CSF CRH levels in patients with major depression. The authors noted that many, although not all, of the patients had features of atypical depression. They were also eucortisolemic, not surprising in the context of central CRH deficiency, given the multiple mechanisms for maintaining normal glucocorticoid secretion [102].

Optimal functioning of the CNS requires keeping the core stress system within a carefully maintained range. Deficits in CNS function occur in the context of either hyper- or hypoactive LC–NE and CRH systems. Glucocorticoids can prevent the immune response from overshooting by a negative feedback loop involving inflammatory mediators (e.g., IL-1) [111]. But if hypothalamic CRH neurons fail to respond adequately to cytokine stimulation, a hyperimmune state may lead to a range of autoimmune diseases dependent on the trigger administered, as found in rats. Thus, patients with chronic fatigue syndrome experience inflammatory symptoms as well as fatigue [112]. Hyperphagia is another characteristic of atypical depression, resulting in either obesity or a cycle of weight gain and loss throughout recurrent episodes of depression. Weight regained after weight loss is preferentially distributed as intra-abdominal fat, which could lead to adverse metabolic con-

sequences conducive to coronary artery. But our data from atypical patients having seasonal affective disorder suggest that bone mineral density is not reduced (Gold et al., unpublished findings).

21.10

Summary and Conclusions

Available data indicate concomitant activation of the CRH and LC–NE systems in melancholic depression with mutually reinforcing positive-feedback loops. CRH and NE can enhance the encoding of adverse memory and sensitize specific substrates so that future stress responses are intensified. Since CRH and glucocorticoids are neurotoxic, a progressive loss of critical tissue may theoretically occur.

Patients with major depression have increased susceptibility to premature onset of complex diseases common with age. Melancholia involves a dysregulation (hyperactivity) of the stress system with genetic, constitutional, and environmental components. On the other hand, lethargy, fatigue, apathy, hyperphagia, and hypersomnia are associated with down-regulation of the stress response. This difference in symptoms [1] is crucial, since they affect proper diagnosis and therapeutic intervention. The difference in biochemical phenotypes is also crucial to molecular genetic studies and the search for more long-term medical consequences. We have now gotten into the cell and have many mediators to understand, including CRHR-1, CRHR-2, their ligands, and CRH-binding protein.

Recently, a mutant line of *Drosophila* (*methuselah*) was discovered that has extended lifespan and enhanced resistance to various forms of stress [113]. Determination of the mutated gene's sequence indicated that its protein product would show homology to a well known family of receptors involved in neurotransmission, endocrine regulation, and metabolism. There is a close association between lifespan and stress, as has been exemplified in *C. elegans* [114]. Apparently, activation of the stress response not only comes with a high price, but also a higher price for those with an illness of long-term activation.

Emotional responses recruit various areas of the brain to function in integrating previous memories, assessing their significance and the present reality, and initiating a quick and simple plan of action involving reflexive physiological and metabolic changes [115]. Thus, depression is no longer seen as a disorder that merely affects mood, but rather as a systemic illness exerting enormous effects on the CNS and the periphery.

References

- 1 KESSLER, R. C., MCGONAGLE, K. A., ZHAO, S., et al., Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch. Gen. Psychiatry* **1994**, *51*, 8–19.
- 2 FRANK, E. T. M., Natural history and preventive treatment of recurrent mood disorders. *Annu. Rev. Med.* **1999**, *50*, 453–468.
- 3 GOLD, P. W., KLING, M. A., WHITFIELD, H. J., et al., The clinical implications of corticotropin-releasing hormone. *Adv. Exp. Med. Biol.* **1988**, *245*, 507–519.
- 4 BAREFOOT, J. C., SCHROLL, M., Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation* **1996**, *93*, 1976–1980.
- 5 PENNINX, B. W., GEERLINGS, S. W., DEEG, D. J., VAN EIJK, J. T., VAN TILBURG, W., BEEKMAN, A. T., Minor and major depression and the risk of death in older persons. *Arch. Gen. Psychiatry* **1999**, *56*, 889–895.
- 6 PRATT, L. A., FORD, D. E., CRUM, R. M., ARMENIAN, H. K., GALLO, J. J., EATON, W. W., Depression, psychotropic medication, and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. *Circulation* **1996**, *94*, 3123–3129.
- 7 KENDLER, K. S., KESSLER, R. C., WALTERS, E. E., et al., Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am. J. Psychiatry* **1995**, *152*, 833–842.
- 8 KENDLER, K. S., NEALE, M. C., KESSLER, R. C., HEATH, A. C., EAVES, L. J., The lifetime history of major depression in women: reliability of diagnosis and heritability. *Arch. Gen. Psychiatry* **1993**, *50*, 863–870.
- 9 KENDLER, K. S., GARDNER, C. O., NEALE, M. C., PRESCOTT, C. A., Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? *Psychol. Med.* **2001**, *31*, 605–616.
- 10 LEVITAN, R. D., LESAGE, A., PARIKH, S. V., GOERING, P., KENNEDY, S. H., Reversed neurovegetative symptoms of depression: a community study of Ontario. *Am. J. Psychiatry* **1997**, *154*, 934–940.
- 11 QUITKIN, F. M., STEWART, J. W., McGRATH, P. J., et al., Columbia atypical depression: a subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. *Br. J. Psychiatry Suppl.* **1993**, 30–34.
- 12 GOLD, P. W., CHROUSOS, G. P., The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proc. Assoc. Am. Physicians* **1999**, *111*, 22–34.
- 13 HORWATH, E., JOHNSON, J., WEISSMAN, M. M., HORNIG, C. D., The validity of major depression with atypical features based on a community study. *J. Affect Disord.* **1992**, *26*, 117–125.
- 14 LEDOUX, J. E., Emotion: clues from the brain. *Annu Rev Psychol* **1995**, *46*, 209–235.
- 15 CAHILL, L., MCGAUGH, J. L., Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.* **1998**, *21*, 294–299.
- 16 GOLD, P. W., GOODWIN, F. K., CHROUSOS, G. P., Clinical and biochemical manifestations of depression: relation to the neurobiology of stress (2). *N. Engl. J. Med.* **1988**, *319*, 413–420.
- 17 GOLD, P. W., GOODWIN, F. K., CHROUSOS, G. P., Clinical and biochemical manifestations of depression: relation to the neurobiology of stress (1). *N. Engl. J. Med.* **1988**, *319*, 348–353.
- 18 CHROUSOS, G. P., GOLD, P. W., The concepts of stress and stress system disorders: overview of physical and behavioral homeostasis. *JAMA* **1992**, *267*, 1244–1252.
- 19 SAPOLSKY, R. M., Stress in the wild. *Sci. Am.* **1990**, *262*, 116–123.
- 20 MAKINO, S., SHIBASAKI, T., YAMAUCHI, N., et al., Psychological stress increased corticotropin-releasing hormone mRNA and content in the central nucleus of the amygdala but not in the hypothalamic paraventricular nucleus in the rat. *Brain Res.* **1999**, *850*, 136–143.
- 21 SMITH, G. W., AUBRY, J. M., DELLU, F., et al., Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress

- response, and aberrant neuroendocrine development. *Neuron* **1998**, *20*, 1093–1102.
- 22 KISHIMOTO, T., RADULOVIC, J., RADULOVIC, M., et al., Deletion of *crhr2* reveals an anxiolytic role for corticotropin-releasing hormone receptor-2. *Nat. Genet.* **2000**, *24*, 415–419.
 - 23 BALE, T. L., CONTARINO, A., SMITH, G. W., et al., Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. *Nat. Genet.* **2000**, *24*, 410–414.
 - 24 HEINRICHS, S. C., LAPANSKY, J., LOVENBERG, T. W., DE SOUZA, E. B., CHALMERS, D. T., Corticotropin-releasing factor CRF1, but not CRF2, receptors mediate anxiogenic-like behavior. *Regul. Pept.* **1997**, *71*, 15–21.
 - 25 HABIB, K. E., WELD, K. P., RICE, K. C., et al., Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 6079–6084.
 - 26 DEAK, T., NGUYEN, K. T., EHRLICH, A. L., et al., The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. *Endocrinology* **1999**, *140*, 79–86.
 - 27 TIAN, X., HSIN, L. W., WEBSTER, E. L., et al., The development of a potential single photon emission computed tomography (SPECT) imaging agent for the corticotropin-releasing hormone receptor type. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 331–333.
 - 28 ASTON-JONES, G., RAJKOWSKI, J., KUBIAK, P., VALENTINO, R. J., SHIPLEY, M. T., Role of the locus coeruleus in emotional activation. *Prog. Brain Res.* **1996**, *107*, 379–402.
 - 29 ARNSTEN, A. F., Through the looking glass: differential noradrenergic modulation of prefrontal cortical function. *Neural Plast.* **2000**, *7*, 133–146.
 - 30 PACKARD, M. G., CAHILL, L., MCGAUGH, J. L., Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 8477–8481.
 - 31 FUSTER, J. M., The prefrontal cortex, an update: time is of the essence. *Neuron* **2001**, *30*, 319–333.
 - 32 FUSTER, J. M., Memory networks in the prefrontal cortex. *Prog. Brain Res.* **2000**, *122*, 309–316.
 - 33 SMITH, E. E., JONIDES, J., Storage and executive processes in the frontal lobes. *Science* **1999**, *283*, 1657–1661.
 - 34 SULLIVAN, R. M., GRATTON, A., Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. *J. Neurosci.* **1999**, *19*, 2834–2840.
 - 35 GOLD, P. W., CHROUSOS, G., KELLNER, C., et al., Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am. J. Psychiatry* **1984**, *141*, 619–627.
 - 36 GOLD, P. W., LORIAUX, D. L., ROY, A., et al., Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease: pathophysiologic and diagnostic implications. *N. Engl. J. Med.* **1986**, *314*, 1329–1335.
 - 37 NEMEROFF, C. B., WIDERLOV, E., BISSETTE, G., et al., Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* **1984**, *226*, 1342–1344.
 - 38 NEMEROFF, C. B., OWENS, M. J., BISSETTE, G., ANDORN, A. C., STANLEY, M., Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Arch. Gen. Psychiatry* **1988**, *45*, 577–579.
 - 39 MICHELSON, D., GALLIVEN, E., HILL, L., DEMITRACK, M., CHROUSOS, G., GOLD, P., Chronic imipramine is associated with diminished hypothalamic–pituitary–adrenal axis responsivity in healthy humans. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 2601–2606.
 - 40 BRADY, L. S., WHITFIELD JR, H. J., FOX, R. J., GOLD, P. W., HERKENHAM, M., Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain: therapeutic implications. *J. Clin. Invest.* **1991**, *87*, 831–837.
 - 41 WONG, M. L., KLING, M. A., MUNSON, P. J., et al., Pronounced and sustained

- central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl. Acad. Sci. USA* **2000**, 97, 325–330.
- 42 AXELROD, J., WHITBY, L. G., HERTTING, G., Effect of psychotropic drugs on the uptake of H3-norepinephrine by tissues. *Science* **1961**, 133, 383–384.
 - 43 SCHILDKRAUT, J. J., The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am. J. Psychiatry* **1965**, 122, 509–522.
 - 44 BERMAN, R. M., NARASIMHAN, M., MILLER, H. L., et al., Transient depressive relapse induced by catecholamine depletion: potential phenotypic vulnerability marker? *Arch. Gen. Psychiatry* **1999**, 56, 395–403.
 - 45 LAMBERT, G., JOHANSSON, M., AGREN, H., FRIBERG, P., Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. *Arch. Gen. Psychiatry* **2000**, 57, 787–793.
 - 46 ZHU, M. Y., KLIMEK, V., DILLEY, G. E., et al., Elevated levels of tyrosine hydroxylase in the locus coeruleus in major depression. *Biol. Psychiatry* **1999**, 46, 1275–1286.
 - 47 ORDWAY, G. A., SMITH, K. S., HAYCOCK, J. W., Elevated tyrosine hydroxylase in the locus coeruleus of suicide victims. *J. Neurochem.* **1994**, 62, 680–685.
 - 48 MUSCETTOIA, G., POTTER, W. Z., PICKAR, D., GOODWIN, F. K., Urinary 3-methoxy-4-hydroxyphenylglycol and major affective disorders: a replication and new findings. *Arch. Gen. Psychiatry* **1984**, 41, 337–342.
 - 49 VEITH, R. C., RASKIND, M. A., BARNES, R. F., GUMBRECHT, G., RITCHIE, J. L., HALTER, J. B., Tricyclic antidepressants and supine, standing, and exercise plasma norepinephrine levels. *Clin. Pharmacol. Ther.* **1983**, 33, 763–769.
 - 50 KOSLOW, J. H., MAAS, J. W., BOWDEN, C. L., DAVIS, J. M., HANIN, I., JAVAID, J. L., Cerebrospinal fluid and urinary biogenic amines and metabolites in depression, mania, and healthy controls: a univariate analysis. *Arch. Gen. Psychiatry* **1983**, 40, 999–1010.
 - 51 DELEON-JONES, F., MAAS, J. W., DEKIRMENJIAN, H., SANCHEZ, J., Diagnostic subgroups of affective disorders and their urinary excretion of catecholamine metabolites. *Am. J. Psychiatry* **1975**, 132, 1141–1148.
 - 52 GOLDSTEIN, D. S., ZIMLICHMAN, R., KELLY, G. D., STULL, R., BACHER, J. D., KEISER, H. R., Effect of ganglion blockade on cerebrospinal fluid norepinephrine. *J. Neurochem.* **1987**, 49, 1484–1490.
 - 53 SIEVER, L. J., UHDE, T. W., JIMERSON, D. C., LAKE, C. R., KOPIN, I. J., MURPHY, D. L., Indices of noradrenergic output in depression. *Psychiatry Res.* **1986**, 19, 59–73.
 - 54 GERNER, R. H., FAIRBANKS, L., ANDERSON, G. M., et al., CSF neurochemistry in depressed, manic, and schizophrenic patients compared with that of normal controls. *Am. J. Psychiatry* **1984**, 141, 1533–1540.
 - 55 GJERRIS, A., RAFAESEN, O. J., Catecholamines and vasoactive intestinal polypeptide in cerebrospinal fluid in depression. *Adv. Biochem. Psychopharmacol.* **1984**, 39, 159–160.
 - 56 CHRISTENSEN, N. J., VESTERGAARD, P., SORENSEN, T., RAFAESEN, O. J., Cerebrospinal fluid adrenaline and noradrenaline in depressed patients. *Acta Psychiatr. Scand.* **1980**, 61, 178–182.
 - 57 ASBERG, M., RINGBERGER, V. A., SJOQVIST, F., THOREN, P., TRASKMAN, L., TUCK, J. R., Monoamine metabolites in cerebrospinal fluid and serotonin uptake inhibition during treatment with chlorimipramine. *Clin. Pharmacol. Ther.* **1977**, 21, 201–207.
 - 58 MAAS, J. W., FAWCETT, J., DEKIRMENJIAN, H., 3-Methoxy-4-hydroxy phenylglycol (MHPG) excretion in depressive states: a pilot study. *Arch. Gen. Psychiatry* **1968**, 19, 129–134.
 - 59 SHAW, D. M., O'KEEFFE, R., MACSWEENEY, D. A., BROOKSBANK, B. W., NOGUERA, R., COPPEN, A., 3-Methoxy-4-hydroxyphenylglycol in depression. *Psychol. Med.* **1973**, 3, 333–336.
 - 60 VEITH, R. C., LEWIS, N., LINARES, O. A., et al., Sympathetic nervous system activity in major depression: basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch. Gen. Psychiatry* **1994**, 51, 411–422.

- 61 KLIMEK, V., STOCKMEIER, C., OVERHOLSER, J., et al., Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. *J. Neurosci.* **1997**, *17*, 8451–8458.
- 62 BOURNE, H. R., BUNNEY JR., W. E., COLBURN, R. W., et al., Noradrenaline, 5-hydroxytryptamine, and 5-hydroxy-indoleacetic acid in hindbrains of suicidal patients. *Lancet* **1968**, *2*, 805–808.
- 63 ESLER, M., TURBOTT, J., SCHWARZ, R., et al., The peripheral kinetics of norepinephrine in depressive illness. *Arch. Gen. Psychiatry* **1982**, *39*, 295–300.
- 64 LAKE, C. R., PICKAR, D., ZIEGLER, M. G., LIPPER, S., SLATER, S., MURPHY, D. L., High plasma norepinephrine levels in patients with major affective disorder. *Am. J. Psychiatry* **1982**, *139*, 1315–1318.
- 65 WYATT, R. J., PORTNOY, B., KUPFER, D. J., SNYDER, F., ENGELMAN, K., Resting plasma catecholamine concentrations in patients with depression and anxiety. *Arch. Gen. Psychiatry* **1971**, *24*, 65–70.
- 66 NOFZINGER, E., KESHEVAN, M., et al., The neurobiology of sleep in relation to mental disorder. In CHARNEY, D., NESTLER, E., BUNNEY, B. (Eds.), *The Neurobiological Foundation of Mental Illness*. Oxford University Press, **1999**.
- 67 SCHATZBERG, A. F., ORSULAK, P. J., ROSENBAUM, A. H., et al., Toward a biochemical classification of depressive disorders. V. Heterogeneity of unipolar depressions. *Am. J. Psychiatry* **1982**, *139*, 471–475.
- 68 AGREN, H., Depressive symptom patterns and urinary MHPG excretion. *Psychiatry Res.* **1982**, *6*, 185–196.
- 69 COPPEN, A., RAMA RAO, V. A., RUTHVEN, C. R., GOODWIN, B. L., SANDLER, M., Urinary 4-hydroxy-3-methoxyphenylglycol is not a predictor for clinical response to amitriptyline in depressive illness. *Psychopharmacology (Berl.)* **1979**, *64*, 95–97.
- 70 EDWARDS, D. J., SPIKER, D. G., NEIL, J. F., KUPFER, D. J., RIZK, M., MHPG excretion in depression. *Psychiatry Res.* **1980**, *2*, 295–305.
- 71 TAUBE, S. L., KIRSTEIN, L. S., SWEENEY, D. R., HENINGER, G. R., MAAS, J. W., Urinary 3-methoxy-4-hydroxyphenylglycol and psychiatric diagnosis. *Am. J. Psychiatry* **1978**, *135*, 78–82.
- 72 VESTERGAARD, P., SORENSSEN, T., HOPPE, E., RAFAELSEN, O. J., YATES, C. M., NICOLAOU, N., Biogenic amine metabolites in cerebrospinal fluid of patients with affective disorders. *Acta Psychiatr. Scand.* **1978**, *58*, 88–96.
- 73 GARFINKEL, P. E., WARSH, J. J., STANCER, H. C., GODSE, D. D., CNS monoamine metabolism in bipolar affective disorder: evaluation using a peripheral decarboxylase inhibitor. *Arch. Gen. Psychiatry* **1977**, *34*, 735–739.
- 74 BESKOW, J., GOTTFRIES, C. G., ROOS, B. E., WINBLAD, B., Determination of monoamine and monoamine metabolites in the human brain: post mortem studies in a group of suicides and in a control group. *Acta Psychiatr. Scand.* **1976**, *53*, 7–20.
- 75 SUBRAHMANYAM, S., Role of biogenic amines in certain pathological conditions. *Brain Res.* **1975**, *87*, 355–362.
- 76 ITOI, K., HELMREICH, D. L., LOPEZ-FIGUEROA, M. O., WATSON, S. J., Differential regulation of corticotropin-releasing hormone and vasopressin gene transcription in the hypothalamus by norepinephrine. *J. Neurosci.* **1999**, *19*, 5464–5472.
- 77 RAADSHEER, F. C., VAN HEERIKHUIZE, J. J., LUCASSEN, P. J., HOOGENDIJK, W. J., TILDERS, F. J., SWAAB, D. F., Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *Am. J. Psychiatry* **1995**, *152*, 1372–1376.
- 78 WEISS, J. M., SIMSON, P. G., Depression in an animal model: focus on the locus ceruleus. *Ciba Found. Symp.* **1986**, *123*, 191–215.
- 79 MONGEAU, R., BLIER, P., DE MONTIGNY, C., The serotonergic and noradrenergic systems of the hippocampus: their interactions and the effects of antidepressant treatments. *Brain Res. Brain Res. Rev.* **1997**, *23*, 145–195.
- 80 HADDJERI, N., BLIER, P., DE MONTIGNY, C., Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT_{1A} receptors. *J. Neurosci.* **1998**, *18*, 10150–10156.
- 81 MANN, J. J., The neurobiology of suicide. *Nat. Med.* **1998**, *4*, 25–30.

- 82 CHIANG, C., ASTON-JONES, G.,
A 5-hydroxytryptamine-2 agonist
augments gamma-aminobutyric acid
and excitatory amino acid inputs to
noradrenergic locus coeruleus neurons.
Neuroscience **1993**, 54, 409–420.
- 83 ANDA, R., WILLIAMSON, D., JONES, D.,
et al., Depressed affect, hopelessness,
and the risk of ischemic heart disease in
a cohort of U.S. adults. *Epidemiology*
1993, 4, 285–294.
- 84 CHAMBERS, J. C., EDA, S., BASSETT, P.,
et al., C-reactive protein, insulin
resistance, central obesity, and coronary
heart disease risk in Indian Asians from
the United Kingdom compared with
European whites. *Circulation* **2001**, 104,
145–150.
- 85 YUDKIN, J. S., KUMARI, M., HUMPHRIES,
S. E., MOHAMED-ALI, V., Inflammation,
obesity, stress and coronary heart disease:
is interleukin-6 the link? *Atherosclerosis*
2000, 148, 209–214.
- 86 SEN, S., TARAZI, R. C., KHAIRALLAH, P. A.,
BUMPUS, F. M., Cardiac hypertrophy in
spontaneously hypertensive rats. *Circ.
Res.* **1974**, 35, 775–781.
- 87 DZAU, V. J., Contributions of neuro-
endocrine and local autocrine–paracrine
mechanisms to the pathophysiology and
pharmacology of congestive heart failure.
Am. J. Cardiol. **1988**, 62, 76E–81E.
- 88 COLUCCI, W. S., The effects of nor-
epinephrine on myocardial biology:
implications for the therapy of heart
failure. *Clin. Cardiol.* **1998**, 21, 120–124.
- 89 CHABABEL, A., CHIEN, S., Blood viscosity
in human hypertension. In LARAGH, J.,
BRENNER, F. (Eds.), *Hypertension:
Pathophysiology, Diagnosis, and Treatment*.
New York: Raven Press, **1995**, 365–376.
- 90 MICHELSON, D., STRATAKIS, C., HILL, L.,
et al., Bone mineral density in women
with depression. *N. Engl. J. Med.* **1996**,
335, 1176–1181.
- 91 MICHELSON, D., GOLD, P. W., Patho-
physiologic and somatic investigations
of hypothalamic–pituitary–adrenal axis
activation in patients with depression.
Ann. NY Acad. Sci. **1998**, 840, 717–722.
- 92 RAFF, H., RAFF, J. L., DUTHIE, E. H.,
et al., Elevated salivary cortisol in the
evening in healthy elderly men and
women: correlation with bone mineral
density. *J. Gerontol. A Biol. Sci. Med. Sci.*
1999, 54, M479–M483.
- 93 HUGHES-FULFORD, M., APPEL, R.,
KUMEGAWA, M., SCHMIDT, J., Effect of
dexamethasone on proliferating osteo-
blasts: inhibition of prostaglandin E2
synthesis, DNA synthesis, and alterations
in actin cytoskeleton. *Exp. Cell Res.* **1992**,
203, 150–156.
- 94 GENNARI, C., MARTINI, G., NUTI, R.,
Secondary osteoporosis. *Aging (Milano)*
1998, 10, 214–224.
- 95 DREVETS, W. C., Functional neuroimaging
studies of depression: the anatomy of
melancholia. *Annu. Rev. Med.* **1998**, 49,
341–361.
- 96 BENCH, C. J., FRISTON, K. J., BROWN,
R. G., FRACKOWIAK, R. S., DOLAN, R. J.,
Regional cerebral blood flow in
depression measured by positron
emission tomography: the relationship
with clinical dimensions. *Psychol. Med.*
1993, 23, 579–590.
- 97 BENCH, C. J., FRACKOWIAK, R. S., DOLAN,
R. J., Changes in regional cerebral blood
flow on recovery from depression.
Psychol. Med. **1995**, 25, 247–261.
- 98 MANJI, H. K., DREVETS, W. C., CHARNEY,
D. S., The cellular neurobiology of
depression. *Nat. Med.* **2001**, 7, 541–547.
- 99 DUMAN, R. S., HENINGER, G. R., NESTLER,
E. J., A molecular and cellular theory of
depression. *Arch. Gen. Psychiatry* **1997**,
54, 597–606.
- 100 YEHUDA, R., Biology of posttraumatic
stress disorder. *J. Clin. Psychiatry* **2001**,
62, Suppl. 17, 41–46.
- 101 GOLD, P. W., CALABRESE, J. R., KLING,
M. A., et al., Abnormal ACTH and
cortisol responses to ovine corticotropin
releasing factor in patients with primary
affective disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1986**, 10, 57–65.
- 102 GOLD, P. W., LICINIO, J., WONG, M. L.,
CHROUSOS, G. P., Corticotropin releasing
hormone in the pathophysiology of
melancholic and atypical depression and
in the mechanism of action of anti-
depressant drugs. *Ann. NY Acad. Sci.*
1995, 771, 716–729.
- 103 SCHULTE, H. M., CHROUSOS, G. P.,
AVGERINOS, P., et al., The corticotropin-
releasing hormone stimulation test:
a possible aid in the evaluation of patients

- with adrenal insufficiency. *J. Clin. Endocrinol. Metab.* **1984**, *58*, 1064–1067.
- 104 AVGERINOS, P. C., SCHURMEYER, T. H., GOLD, P. W., et al., Pulsatile administration of human corticotropin-releasing hormone in patients with secondary adrenal insufficiency: restoration of the normal cortisol secretory pattern. *J. Clin. Endocrinol. Metab.* **1986**, *62*, 816–821.
 - 105 KLING, M. A., ROY, A., DORAN, A. R., et al., Cerebrospinal fluid immunoreactive corticotropin-releasing hormone and adrenocorticotropin secretion in Cushing's disease and major depression: potential clinical implications. *J. Clin. Endocrinol. Metab.* **1991**, *72*, 260–271.
 - 106 NAGAYAMA, H., SASAKI, M., ICHII, S., et al., Atypical depressive symptoms possibly predict responsiveness to phototherapy in seasonal affective disorder. *J. Affect Disord.* **1991**, *23*, 185–189.
 - 107 STEWART, J. W., QUITKIN, F. M., TERMAN, M., TERMAN, J. S., Is seasonal affective disorder a variant of atypical depression? Differential response to light therapy. *Psychiatry Res.* **1990**, *33*, 121–128.
 - 108 JOSEPH-VANDERPOOL, J. R., ROSENTHAL, N. E., CHROUSOS, G. P., et al., Abnormal pituitary–adrenal responses to corticotropin-releasing hormone in patients with seasonal affective disorder: clinical and pathophysiological implications. *J. Clin. Endocrinol. Metab.* **1991**, *72*, 1382–1387.
 - 109 DEMITRACK, M. A., DALE, J. K., STRAUS, S. E., et al., Evidence for impaired activation of the hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. *J. Clin. Endocrinol. Metab.* **1991**, *73*, 1224–1234.
 - 110 GERACIOTI JR., T. D., LOOSEN, P. T., ORTH, D. N., Low cerebrospinal fluid corticotropin-releasing hormone concentrations in eucortisolemic depression. *Biol. Psychiatry* **1997**, *42*, 165–174.
 - 111 BESEDOVSKY, H. O., DEL REY, A., The cytokine–HPA axis feed-back circuit. *Z. Rheumatol.* **2000**, *59*, Suppl. 2, II/26–30.
 - 112 HICKIE, I., LLOYD, A., HADZI-PAVLOVIC, D., PARKER, G., BIRD, K., WAKEFIELD, D., Can the chronic fatigue syndrome be defined by distinct clinical features? *Psychol. Med.* **1995**, *25*, 925–935.
 - 113 LIN, Y. J., SEROUDE, L., BENZER, S., Extended life-span and stress resistance in the *Drosophila* mutant *methuselah*. *Science* **1998**, *282*, 943–946.
 - 114 FRIEDMAN, D. B., JOHNSON, T. E., A mutation in the *age-1* gene in *Caenorhabditis elegans* lengthens life and reduces hermaphrodite fertility. *Genetics* **1988**, *118*, 75–86.
 - 115 LEDOUX, J. E., Emotion and the amygdala. In AGGLETON, J. P. (Ed.), *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*. New York: Wiley-Liss, **1992**, 339–351.

22

Neuroimmune Mediators: Are Cytokines Mediators of Depression?

Renaud de Beaurepaire, Artur H. Swiergiel and Adrian J. Dunn

Abstract

It has recently been proposed that cytokines may cause or contribute to the pathogenesis of depression. This cytokine hypothesis of depression is based on the observations that: (1) cytokine treatment in humans can induce symptoms of depression; (2) immune activation is more common in depressed patients than in the general population; (3) depression is more common in medical conditions associated with immune activation than those that are not; (4) interleukin-1 (IL-1) administration induces behavioral responses in animals (sickness behavior) that resemble symptoms of depression; (5) certain cytokines can activate the hypothalamic–pituitary–adrenal (HPA) axis, and brain noradrenergic and serotonergic systems; and (6) there may be cross-sensitization between responses to stress and to cytokines. The evidence for this hypothesis is critically evaluated here. It is concluded that while cytokine administration or excess endogenous production of cytokines may induce depression in some patients, this is not the only cause of depression. Immune activation is indeed more common among depressed patients, but the underlying disease or the impact of its diagnosis may contribute directly to the depression without involving the immune system. IL-1 is the major cytokine that induces depression-like symptoms, and activation of the HPA axis and noradrenergic and serotonergic systems. However, there is little evidence for substantial elevation of IL-1 concentrations in depressed patients. The induction of IL-1 within the brain has the potential to induce depression and this mechanism is worthy of further investigation. The existing evidence however, does not provide a firm empirical basis for a cytokine network within the brain that causes depression.

22.1**Introduction**

Alterations of immune function occur frequently in depressed patients. Although this has been known for a very considerable time, the significance of these alterations

is poorly understood. Depression may result directly or indirectly from an underlying disease that is associated with immune activation, or an immune activation may be a consequence of depression itself, but it is also possible that the immune activation could be responsible for the depression. A recent major consequence of studies of immune dysregulation in depression has been the emergence of the cytokine hypothesis of depression. In this chapter, we will address the role of neuroimmune mediators in depression by analyzing the evidence for this hypothesis. Because much of the research carried out before the development of the cytokine hypothesis was inconsistent or inconclusive, that literature will be referred to only incidentally and briefly when appropriate.

The cytokine hypothesis of depression proposes that depression is caused by actions of cytokines. The proponents of the hypothesis cite evidence that appears to indicate that cytokines are causal determinants of depression, but they do not always discuss the possibilities that cytokines may be responsible only for certain aspects or certain forms of depression, nor that the cytokine abnormalities observed in a number of depressed patients may be a consequence rather than a cause of the depression. We will outline the arguments that support the hypothesis, and discuss the possible pitfalls. We remind the reader that depression is typically characterized by the following symptoms: depressed mood (sadness), anhedonia (the inability to feel pleasure), anorexia, insomnia, motor retardation, inability to concentrate, ideas of culpability, and suicidal thoughts.

Brain mechanisms of depression have been the subject of much discussion for more than half a century. For much of the recent past, attention has been focused on the relationship(s) between stress and depression. Depression is frequently, but not always, precipitated by stress. Moreover, the symptoms of depression are not unlike those of chronic stress, so that some have viewed depression as a chronic stress-like state. Stress is associated with activation of the hypothalamo–pituitary–adrenal (HPA) axis, and by a hyperactivity of the sympathetic nervous system and the adrenal medulla, as well as catecholamines in the central nervous system [1]. A large proportion of patients with major depression (50–70%) has elevated plasma concentrations of cortisol, and about half show a reduced susceptibility of the HPA axis to suppression by dexamethasone (the dexamethasone suppression test, see Chapter 11), and are hypo-responsive to corticotropin-releasing factor (CRF) administration (see Chapter 11). Abnormalities in brain catecholamine function have been postulated, but although an early hypothesis (the catecholamine hypothesis of affective disorders, see Chapter 5 and 6) postulated a hypo-activity of central catecholaminergic systems, studies of cerebrospinal fluid (CSF) concentrations of norepinephrine (NE) and its catabolites have in contrast, tended to suggest a hyperactivity of central noradrenergic systems in patients with major depression [2]. This noradrenergic activation parallels the known responses in stress in both human and animal studies [1]. More recent hypotheses have tended to focus on abnormalities of another brain amine, serotonin (5-hydroxytryptamine, 5-HT). The first generation antidepressant drugs (the tricyclic antidepressants), were determined to inhibit the reuptake of NE and/or 5-HT. The antidepressants used most commonly today selectively inhibit 5-HT reuptake, and are thus known as SSRIs

(serotonin-selective uptake inhibitors). Their efficacy has been taken to suggest that depression may result from a central deficiency in serotonin. However, there is no direct experimental evidence for this, although there is some evidence for changes in the activity of various 5-HT receptors in depressed patients [3]. The serotonin-selective reuptake inhibitors (SSRIs) and the NE-selective reuptake inhibitors are equally effective, and some of the antidepressants introduced most recently inhibit the reuptake of both 5-HT and NE (so-called SNRIs – serotonin-norepinephrine selective reuptake inhibitors).

More recently, CRF itself has been implicated, because it may be a central coordinator of stress responses [4, 5], and there is some evidence for CRF abnormalities in depressed patients (elevated CSF concentrations of CRF and down-regulation of CRF-receptors, see Chapter 11, 19 and 21). Interestingly, because NE has been shown to be involved in the regulation of CRF secretion which initiates the activation of the HPA axis, these hypotheses are not exclusive, and there may be a direct relationship between the hyperactivity of the HPA axis and the hyperactivity of noradrenergic systems observed in depressives. Thus, the two responses may be symptomatic of the same abnormality. Because serotonin has also been implicated in the regulation of CRF secretion, abnormalities in this neurotransmitter may also be associated with the same systems. Thus each of these chemical hypotheses may be related.

22.2

Outline of the Cytokine Hypothesis

The origins of the cytokine hypothesis of depression derive from both clinical and experimental observations. Cytokines are proteins or glycoproteins secreted by immune cells that function to coordinate immune responses; they are the hormones of the immune system. It is now known that cytokines have effects outside the immune system, and that many non-immune cells can synthesize and secrete cytokines. The first observations relating cytokines to depression were clinical and were made in patients treated with interferons (IFN) in the late 1970s and interleukin-2 (IL-2) in the early 1980s. Such patients were described as having several nonspecific neuropsychiatric symptoms, some characteristic of depression, such as anorexia and motor retardation. However, the interest was not initially focused on depression. Studies indicating immune abnormalities in depressed patients appeared in the late 1970s. Early studies indicated a tendency towards decreased immune function in depression, but the results were very variable and inconsistent (see review by Weisse [6]). Other studies showed that depressive states were more frequent in diseases having an immunological component [7]. The interest in immune abnormalities in depression was renewed during the late 1980s with the conjunction of two sets of observations, the effects of immune challenges in animals, and indications that some form of immune activation was present in many depressed patients. In animal experiments, it was found that endotoxin (lipopolysaccharide, LPS) and the cytokine, interleukin-1 (IL-1) induced a set of behavioral alterations, some of which had similarities with depression. The behavioral

syndrome induced by IL-1 and LPS has been called “sickness behavior” [8]. In depressed patients, immune function was depressed in some aspects, but activated in others, and there were reports of increases of certain cytokines in the blood of depressed patients. These observations led to the cytokine hypothesis of depression. The first formal formulation of the hypothesis was the “macrophage hypothesis of depression” by Smith [9], who suggested that increases in the secretion of cytokines (especially IL-1) by activated macrophages could induce depression. Smith noted that administration of IL-1 mimicked not only some of the characteristics of depression, but also activated the HPA axis. This hypothesis immediately attracted attention because it reconciled a number of earlier observations.

It is relevant that the cytokine hypothesis does not conflict with the earlier HPA axis hyperactivity, and noradrenergic hyperactivity hypotheses, because it was subsequently shown that IL-1 activated brain noradrenergic systems [10–12]. Moreover, CRF is involved in the HPA responses to IL-1, because antibodies to CRF [13, 14] can prevent IL-1-induced HPA activation, and HPA responses to IL-1 are minimal in CRF knockout mice [15, 16]. The cytokine hypothesis may also be consistent with a serotonin hypothesis, because IL-1, IL-6 and tumor necrosis factor- α (TNF α) have been shown to affect brain serotonergic transmission [10, 11, 17, 18]. However, IL-1, IL-6 and TNF α all activate brain serotonergic systems, and, if depression were associated with a deficiency in serotonergic neurotransmission, these cytokines should have antidepressant properties. However, chronic activity of cytokines may decrease brain serotonin synthesis, and it is not at all clear that any abnormalities in serotonergic neurotransmission in depressed patients are a simple deficiency of serotonin.

22.3

Rationale for the Hypothesis

In its simplest form the cytokine hypothesis of depression posits that the production of certain cytokines, reflecting activation of the immune system, is responsible for the symptoms of depression. The cytokine hypothesis of depression rests on the following observations:

1. Cytokine treatments in humans can produce depressive symptoms or syndromes
2. Certain forms of immune activation are observed in depressed patients, including elevated circulating concentrations of certain cytokines
3. Depression occurs more often in medical disorders associated with immune dysfunction, e.g. peripheral inflammatory syndromes
4. Activation of the immune system, and administration of LPS and IL-1 to animals induces sickness behavior, which resembles depression, and chronic treatment with antidepressants has been shown to inhibit sickness behavior responses to LPS
5. IL-1 and certain other cytokines (IL-6, TNF α) activate the HPA axis, an activation commonly observed in depressed patients

6. IL-1 activates cerebral noradrenergic systems, commonly observed in depressed patients
7. IL-1 and certain other cytokines (IL-6) activate brain serotonergic systems, which may be involved in depression
8. Cross-sensitization of responses in stress and to cytokines can occur, and may occur in depressed patients

22.3.1

Cytokine Treatment of Humans

Several cytokines are used in humans for the treatment of different medical conditions. Interferon alpha (IFN α), IFN β , IFN γ and IL-2 have been shown to be effective in the treatment of chronic hepatitis, leukemia, renal cell cancer, Kaposi's sarcoma, melanoma and myeloma (IFN α), multiple sclerosis (IFN β), some infections (IFN γ), and renal carcinoma or other forms of cancer (IL-2). Each of these cytokines has been reported to produce side-effects such as asthenia, myalgia, confusion and "flu-like" symptoms. Depression has been mostly reported during treatment with IFN α (up to 45%), sometimes with IFN β and IL-2, but not with IFN γ . In the early publications, the most commonly reported neuropsychiatric side-effects of IFN α and IL-2 were apathy, anxiety, anorexia, clumsiness, irritability, hypersomnia, disorientation, confusion and "flu-like" symptoms [19–21]. Major depressive disorders were reported later, but the reports are quite often contradictory. Wichers and Maes [22] reviewed the occurrence of major depression during IFN α and IL-2 therapy, selecting the studies where reliable evaluation instruments were used. Seven studies reported an increase of major depression during IFN α therapy [23–29], and one during IL-2 therapy [30]; two studies reported nonsignificant increases of depression scores during IFN α therapy [31, 32]; three studies reported no increase in depression with IFN α , [30, 33, 34], and two studies no increase in depression with IL-2 [35, 36]. Other neuropsychiatric disorders have been reported with the use of IFN α IL-2, including delirium [37], manic depressive illness [38, 39], and suicidal behavior [40, 41]. Cognitive worsening [24, 31] and abnormalities in brain activity (prefrontal hypometabolism) [32, 42] have also been observed during cytokine therapy. However, other studies reported no cognitive worsening during cytokine treatment [33, 43]. A recent study on major depression in IFN α -treated malignant melanoma patients showed that 45% of the treated patients displayed depressive symptoms [44]. From a pathophysiological point of view, it is interesting to note that, in cytokine-treated patients, antidepressants are effective for mood symptoms, but not for neurovegetative symptoms, such as anorexia, motor retardation and sleep disorders [44–46]; this renders the use of animal models particularly problematic.

A review of the literature shows that the prevalence of depression is highly variable from one study to another; from no significant increases in depression in some studies, to a prevalence of 45% [44]. Such discrepancies between studies may be related to methodological issues. The method of assessment of depression is important; the use of standardized rating scales is more reliable than subjective reports of the patients. The comparison group is also important. Patients treated

with cytokines usually suffer from severe and debilitating diseases, and studies of the prevalence of major depression or depressive symptoms in untreated patients have found high scores. Hunt et al. found high incidences of depressive states or symptoms in untreated patients suffering from hepatitis C [25]. Singh et al. found significantly higher depression scores on the Beck inventory in patients with hepatitis C awaiting transplantation compared to those who were uninfected [47]. Johnson et al. found a higher frequency of depression in drug-using patients suffering from hepatitis C compared to those who did not [48]. Another important issue is the duration of the cytokine treatment. For instance, McHutchinson et al. showed that after 24 weeks of IFN α treatment, 25% of the patients displayed depressive symptoms, while the percentage was 37% after 37 weeks [49]. Another possible cause of discrepancy is related to the dosage of cytokine used during the treatment, with many studies showing a dose-dependent increase in neuropsychiatric side-effects or cognitive worsening [35, 50]. Combination of cytokines (IL-2 and IFN α) also appears to increase the risk of depression [30]. Finally some patients are more prone to develop depression than others. One study found that patients who have a history of psychiatric illness or depression are more at risk for depression during cytokine therapy than others [30], and another found that patients who develop depressive symptoms during cytokine therapy have higher pretreatment scores on depression scales than those who do not develop depressive symptoms [51]. However, other studies have shown no increased risk for depression among patients with a history of psychiatric illness [28, 34], and that pretreatment scores did not predict the likelihood of depression following IFN therapy [52]. Maes et al. proposed that some biological measurements, such as the plasma levels of enzymes involved in inflammatory responses (prolylendopeptidase and dipeptidyl peptidase IV) may be predictors of the risk of neuropsychiatric side-effects during cytokine therapy [53]. Thus administration of certain cytokines (most notably IL-1 and IFN α) can induce symptoms of depression in patients, but such responses are quite variable depending on the treatment and the underlying disposition of the patient, as well as the choice of control groups.

22.3.2

Immune Activation in Depression

A relatively large number of studies since the late 1970s have provided evidence for immune alterations in depression. These studies have not been particularly consistent. However, meta-analyses of these studies have indicated a tendency towards decreased immune function in depressed patients [6, 54, 55]. In particular, the depressed patients appear to have decreased circulating lymphocytes and decreased natural killer (NK) cell activity. Several studies showed that the intensity of immunosuppression was correlated with the severity of depression and with age, and a longitudinal study showed that immune responses may increase with recovery from depression [56]. It has also been proposed that the decreased immune function in depressed patients resembled the decrease in immune function produced by chronic stress. However, Irwin et al. showed that depressed patients

that were not severely stressed had reductions in NK cell activity similar to those of depressed patients who were under stress [57].

More recent studies have indicated that some aspects of immune responses are activated in depressed patients: for example, acute-phase proteins and activation of cell-mediated production of cytokines. According to certain studies (reviewed by Maes [58] and Kronfol [7]) major depression is associated with increased plasma concentrations of positive acute-phase proteins (haptoglobin, ceruloplasmin, C-reactive protein, hemopexin, α_1 -antitrypsin, and α_1 -acid glycoprotein), and with lower plasma concentrations of negative acute-phase proteins (transferrin, albumin, retinol-binding protein). An increase of acute-phase proteins associated with a decrease in negative acute-phase proteins is an indicator of an inflammatory state. Other indicators of inflammation such as prostaglandins [59] and complement [60] have also been shown to be increased in depressed patients. In other words, chronic depression may be associated with a chronic inflammatory state. According to Maes, the chronic inflammatory state observed in depression could be explained by an increase in the production of cytokines by circulating monocytes and macrophages [58]. A number of studies have shown an activation of cell-mediated immunity. Kronfol [7] reviewed reports that have shown increases in circulating leukocytes [60], activated T-cells [61], and plasma concentrations of cytokines. Neopterin, a sensitive marker of activation of cell-mediated immunity, was found to be increased in the plasma and urine of depressed patients [62, 63]. However, most of the evidence for an activation of immune responses in depressed patients has not been confirmed.

A particular interest has focused on the production and function of cytokines in depressed patients. Cytokines IL-1 β , IL-6 and the IFNs have been reported to be increased in the plasma of depressed patients [64–66]. The finding of an increase in plasma IL-1 was replicated in some studies [67, 68], but not in another [69]. The latter study also failed to find increases in circulating IL-6 or TNF α in depressed patients. Musselman et al. found higher IL-6 concentrations in cancer patients with depression compared to healthy subjects and to cancer patients without depression [70]. Haack et al. found normal concentrations of circulating cytokines in 361 psychiatric patients (including 113 depressives) compared to 64 healthy controls [71]. Other authors have found no evidence for immune activation in depressed patients [72, 73]. Increased concentrations of soluble IL-2 receptors and soluble IL-6 receptors have also been reported [74]. Increases in soluble receptors (sometimes hundreds of times higher than the cytokines themselves) may occur to confine an immune response locally, by protecting the rest of the body from the potentially toxic effects of the released cytokines [75]. There are relatively few reports of altered CSF concentrations of cytokines in depressed patients, but a recent study indicated increases in IL-1 β and decreases in IL-6 [76]. The increase in IL-1 correlated with the severity of the depression.

Alterations in cytokine secretion have also been studied *in vitro* by measuring cytokine production by stimulated immune cells or whole blood cell cultures. Thus, Maes et al. observed increased production of IL-1, IL-6 and IFN α in leukocytes isolated from depressed patients [64, 65]. Anisman et al. observed no changes in

cytokine production in patients with major depression, but found an increase in IL-1 β and a decrease in IL-2 production in dysthymic patients [77]. Seidel et al. found an increase of IFN γ in depressed patients, but no changes in the production of other cytokines [78]. Weizman et al. found decreases in the production of IL-1, IL-2 and IL-3 in depressed patients (which were normalized by the antidepressant treatment) [79]. Rothermundt et al. found that the production of IL-1 β by mitogen-activated lymphocytes was similar in depressed patients and healthy controls [80]. The biological significance of these *in vitro* stimulations is not at all clear, and overall the results have not been very consistent.

In a recent meta-analysis of the clinical data on immune abnormalities in depressed patients, Zorrilla et al. [81] found that patients with major depression exhibited: (1) an overall leukocytosis, manifested as a relative neutrophilia and lymphopenia; (2) increased CD4/CD8 ratios; (3) increased circulating haptoglobin, prostaglandin E $_2$, and IL-6 concentrations; (4) reduced NK-cell cytotoxicity; and (5) a reduced lymphocyte proliferative response to mitogens. However, Zorrilla et al. commented that “the degree of heterogeneity of the studies’ results raises questions about their robustness”. They also noted that among these biological markers, only three were associated with chronic stress: increased CD4/CD8 ratios, reduced mitogen-induced proliferative responses, and reduced NK cell cytotoxicity [81].

In a recent review, Pollmacher et al. pointed out that: (1) certain cytokines (such as IL-1 β) are physiologically undetectable in humans in normal conditions as well as during experimental endotoxemia; (2) the physiological fluctuations in normal and pathological states of the detectable cytokines (IL-6 and TNF α) are very poorly characterized; and (3) the alterations of circulating cytokines observed in the depressed (as well as in immune-related medical conditions) are extremely modest compared to the concentrations of circulating cytokines that occur during cytokine treatments [82]. This raises the issue of whether low circulating concentrations of cytokines can significantly affect brain function. This is a major question for proponents of the cytokine hypothesis of depression.

22.3.3

Depression in Immune-Related Medical Conditions

If an immune activation is a direct cause of depression, as proposed in the cytokine hypothesis of depression, it should be possible to make clear correlations between depressive symptoms and the immune states in different medical or clinical conditions. The prevalence of depression should be much higher in patients who suffer from medical conditions associated with immune activation, and it should be possible to correlate symptoms of depression with biological evidence of an immune activation (and circulating cytokines) in these medical conditions. Because some forms of immunodeficiency have been observed in the depressed (lymphopenia, decreased NK activity), depressed patients should be more prone to develop medical illnesses related to a loss of immune defenses.

A high incidence of depression has been reported in non-infectious diseases associated with a chronic activation of the immune system, such as multiple sclerosis

[83], allergy [84], rheumatoid arthritis [85], and stroke [86]. It has also been shown that in these diseases, the immune dysregulation precedes the development of depression [87]. However, studies seeking correlations between depression and immune activation or increased circulating cytokines in patients with autoimmune diseases or chronic infections or inflammation are rare and conflicting, particularly in longitudinal investigations (for a review, see Pollmacher et al. [82]). Women exhibit higher levels of immune activation than men, which may be related to the higher incidence of depression in women. There is a correlation during the menstrual cycle between cytokine secretion and depression, and there are high circulating concentrations of cytokines during parturition which may cause post-partum depression [88]. According to Maes et al., plasma tryptophan is decreased during the puerperium. This decrease was related to immune activation, and there was a relationship between the decrease of kynurenine (a catabolite of tryptophan), and the occurrence of anxiety or depressive symptoms during the early puerperium [89]. Therefore, immune activation may be responsible for the development of depression during diseases associated with activation of the immune system, and in women in relation to the menstrual cycle and after parturition. However, there are few studies indicating significant correlations between depression and cytokine concentrations or other indices of immune activation, and many confounding factors (other than immune activation) may be involved in the development of depression.

Furthermore, depression may also have a higher prevalence in diseases characterized by a loss of immune defenses, although the loss of certain immune defense mechanisms in these diseases is often accompanied by an increase of other immune mechanisms, for example in asthma or in stroke. A classical hypothesis proposed that if depression is accompanied by the loss of some defense mechanisms, diseases that develop in relation to a loss of defenses should have a higher incidence in depressed patients. For example, a higher prevalence of infections or cancers should occur in depressed patients. Even though there is some epidemiological evidence showing that this is the case, the methodological problems are critical, and the consequences for biological mechanisms still very uncertain (for a review, see Kronfol [7]).

22.3.4

Immune-Related Animal Models of Depression

Immune stimulation has provided valuable models for the cytokine hypothesis of depression. Immune stress induces behavioral alterations in animals, and some types of stress induce immune activation. Cross-reactions or sensitizations have been observed between immune and other forms of stress (see below), suggesting that stress-related mechanisms may be involved in the pathophysiology of depression.

A series of behavioral alterations occurs in sick animals, that are now considered to be defensive [90, 91]. These behavioral alterations are now referred to as sickness behavior [8], which can be induced by a variety of immune challenges (immune

stress), as well as LPS and IL-1. Sickness behavior in animals shares similarities with human depressive symptoms. Sickness behavior is presented today as the prototype of an immune-related depression-like state, which has led to the hypothesis that depression is an immunologically initiated sickness behavior [88, 92]. The behavioral effects of immune stress in rodents include hypoactivity, anorexia, hypersomnia, motor retardation, anhedonia, reduced sexual activity, and deficits in learning and memory, and other cognitive functions. Thus, sickness behavior could be perceived as a phylogenetically determined coping strategy, expressing a particular state of motivation of the individual, a motivation to fight the infection. Indeed, it has been argued that during sickness behavior, there occurs immunologic (immune activation), endocrine (HPA axis activation), cognitive (deficits in learning) and neurochemical (brain NE and 5-HT) changes which share similarities with major depression [77, 93, 94].

However, the similarity of cytokine-induced responses with depression remains questionable for several reasons: behavioral, immune, endocrine, cognitive, and evolutionary (see review by de Beaurepaire [95]).

22.3.4.1 Behavioral Reasons

Immune stressors produce a hyperthermia, a hypersensitivity to pain and a hypersomnia; hyperthermia is not a characteristic of depression (although there is a trend to a nocturnal hyperthermia in depressed patients), depressed patients are not hypersensitive to pain (they are more likely to suffer hypo-algesia), and hypersomnia is not typical of depression (depressed patients are most often insomniacs). However, in the case of sleep, we have shown that microinjection of IL-1 β into certain parts of the brain can produce insomnia [96] which could reconcile the effect of immune stimulation and depression.

22.3.4.2 Immune Reasons

The substantial immune stimulation induced in animals by infection with pathogens or LPS or IL-1 does not resemble the modest immune activation seen in depressed patients.

22.3.4.3 Endocrine Reasons

IL-1 is a potent stimulator of the HPA axis, and certain other cytokines stimulate the axis, but activation of the HPA axis is not consistently observed in depressed patients. In 30–50% of cases there is no elevation of plasma cortisol.

22.3.4.4 Cognitive Reasons

A number of animal experiments has shown that cytokines have deleterious effects in the brain, particularly in brain areas involved in learning and memory [97]. Clinical research has shown that cytokine administration in cancer patients can deeply affect cognitive functions, with effects reminiscent of the dysfunctions observed in neurodegenerative diseases [98]. Conversely, the cognitive dysfunctions observed in the depressed are generally mild, often restricted to some cognitive bias, and may resolve with resolution of the depression [99].

22.3.4.5 Evolutionary Reasons

Depression in humans is a long-lasting disorder, autoactivated by thoughts of worthlessness and guilt, while cytokine-induced depression (in the sickness behavior model as well as during cytokine therapy in humans) tends to stop when cytokine administration ceases (although in some patients the depression persists [100]).

A newer version of this model posits a role for cytokines in the brain. According to this model, immune activation in the periphery can induce the synthesis or appearance of cytokines, their receptors and accessory proteins within the brain (in the parenchyma). This amounts to a local inflammation within the brain. The cytokines induced are then able to induce depressive symptoms from within brain tissue [101]. The major cytokine studied has been IL-1 along with the IL-1-receptor antagonist (IL-1ra), and IL-1-receptors. Most studies have involved peripheral administration of high doses of LPS, and occasionally IL-1. This is a novel and an intriguing idea, but solid data to support some of the basic tenets are lacking. Almost all the studies have only measured the presence of mRNA for these molecules [102–104], and most of those have used non-quantitative techniques. Demonstration of the presence of the mRNA only indicates the propensity for the synthesis of the proteins, and in the case of IL-1, only for the precursor of IL-1. Wong et al. used *in situ* hybridization to demonstrate the presence of mRNA for IL-1, IL-1ra, the IL-1 Type I receptor, IL-10, and IL-13 following intraperitoneal injection of 5 mg LPS in the rat [103, 104]. The mRNAs appeared mainly in the pituitary and in various areas of the brain that lack a blood–brain barrier (the circumventricular organs, CVOs). A subsequent study by Quan et al. confirmed this anatomical pattern and concluded that most of the IL-1-mRNA was present in microglia, probably microglia derived from macrophages that penetrated the endothelia and/or the CVOs [105]. However, Wong and Licinio [104] did note some mRNA for the IL-1 Type 1 receptor in the hippocampus, a region that has been implicated in depression [106], although hippocampal abnormalities are not universally present in imaging studies of depressed patients.

Whether or not active IL-1 can be induced in the brain is quite controversial. An early immunohistochemical study indicated the presence of IL-1 in post mortem human brain [107], and subsequently there have been limited reports of studies in the rat [108] and pig [109]. The anatomical patterns of the IL-1 expression were quite different among the individual human brains in the human study, and there was little concordance among the localizations observed in human, rat and pig. None of these studies clearly demonstrated the presence of IL-1 in neurons. Quan et al. [110] found IL-1 immunoreactivity in rat brain following i.p. administration of LPS at a relatively high dose (2.5 mg/kg), and several studies from Maier's group have made similar observations (see Watkins et al. [111]). None of these studies used any purification of the IL-1 prior to the assay, so there can be no certainty that the immunoreactivity truly reflected IL-1, although Quan et al. [112] used a bioassay to demonstrate the activity of partially purified IL-1 in the brains of untreated rats. The classical criteria for the identification of hormones and neurotransmitters require more rigorous techniques, involving purification of the IL-1, and demonstration of its identity using both immunological and bioassays. However to

date, not even a Western blot has been published to demonstrate the existence of IL-1 in the brain. Moreover, it cannot be excluded that the presence of the limited amounts of IL-1 in these experiments reflects local pathologies, and the IL-1-containing cells might well have been microglia involved in phagocytosis of dead cells or cellular components. Likewise, although an early study claimed widespread binding of IL-1 to slices of rat brain [113], subsequent studies have failed to confirm this. Careful studies by Haour et al. [114] and Takao et al. [115] found that the majority of IL-1 binding in the rat and the mouse was associated with the endothelia. Neither group found any evidence for binding in the rat parenchyma, although both observed limited binding in the hippocampus of the mouse. Needless to say, it is possible that the number of receptors is so limited that they cannot be detected by binding techniques. Other studies have identified mRNA for the IL-1 Type 1 receptor in the brain [103, 116, 117].

The major evidence cited to indicate a role for cytokines in the brain is based on the use of intracerebral injections of IL-1ra [118–120]. Such data are useful and indicative of a role for IL-1, but much more evidence will be needed to define and establish such a role for IL-1, not the least in depression.

22.3.4.6 The Effects of Antidepressants

Depression in humans is responsive to antidepressants, which may cure the illness, regardless of the type of antidepressant used. In a creative series of studies, Yirmiya showed that treatment of rats with LPS, which is a potent stimulator of the production and secretion of the pro-inflammatory cytokines (IL-1, IL-6, TNF α and IFN γ), decreased the frequency with which rats pressed a bar to obtain a saccharin solution [121]. This response was considered to reflect anhedonia, a cardinal symptom of depression. Yirmiya tested this hypothesis by treating the rats chronically (for 3–5 weeks) with the classic tricyclic antidepressant, imipramine, which inhibits the reuptake of both NE and 5-HT. This treatment prevented the induction by LPS of the “anhedonia” in the rats. Similar results were obtained by Shen et al. using desmethylimipramine [122], and by Yirmiya using the SSRI, fluoxetine, although the reversal was less complete [123]. However, Shen et al. observed no such effect of the SSRI, paroxetine, or of the SNRI, venlafaxine [122]. Thus the effect of antidepressants appears to be less evident with the SSRIs than with the tricyclic antidepressants [88, 122]. However, the atypical antidepressant, tianeptine worked [124]. We failed to observe any effect of chronic imipramine or venlafaxine, on the inhibitory effect on LPS on the drinking of sweetened milk in mice [125]. Yirmiya has also indicated a failure to observe an effect of antidepressants on “anhedonia” in mice [123]. The effect of chronic antidepressant treatment is observed most often with LPS, but is less evident with IL-1. There is also evidence that the antidepressants may affect the induction by LPS of cytokines [123, 126], and thus may reflect a peripheral rather than a central mechanism. Thus Yirmiya’s exciting initial observation has failed to provide robust support for an IL-1 hypothesis of depression.

In summary, there are many aspects in which the sickness behavior model of depression does not resemble the human depressive syndrome. Furthermore, it has been shown that in experimental endotoxemia, fever and corticosterone

responses occur at a time when there are no detectable increases in circulating cytokines or endotoxin, which suggests that cytokines are not necessary for the activation of the endocrine and sickness responses [127].

Other animal models of immune-related depression have been proposed. For the most part, such models have been built around the idea that depression is a stress-related disorder, more specifically a disorder related to chronic stress. According to these models, chronic stress activates the HPA axis, and glucocorticoids have deleterious effects on brain structures (such as the hippocampus) and inhibitory or disorganizing effects on neurotransmitter systems (especially 5-HT). Depression occurs when an additional event (a negative life event, a psychological stress, or increased secretion of cytokines?) disorganizes the activity of the brain, decreasing the activity of the prefrontal cortex, and increasing that of subcortical structures, such as the amygdala, thus disrupting the ability of the individual to cope with their environment. However, studies have shown that depressed people are not more stressed than non-depressed people [128], and clinical experience shows that in many cases, an individual becomes abruptly depressed after a single traumatic event, whereas nothing would lead one to suspect before that event that the individual would be unable to cope and would develop a depressive state. Therefore, the chronic stress theory of depression does not adequately account for the clinical aspects of depression, and other conceptual frameworks must be developed. In this respect, a major concept is that of sensitization.

22.3.5

HPA Axis Activation in Depression and Induction by Cytokines

The activation of the HPA axis in depressed patients is the most noted biological marker, yet it occurs in only 50–70% of patients. The potent ability of IL-1 to activate the HPA axis was an important lead for the proposal of a cytokine hypothesis of depression [9, 129]. The ability of IL-1 to activate the HPA axis is indeed profound and an important biological discovery, extending the concept of stress to immune stimulation. It is important that IL-1 activates the HPA axis by mechanisms like those of psychological and physical stressors, involving activation of CRF-containing neurons in the paraventricular nucleus of the hypothalamus, and anterior pituitary adrenocorticotropin hormone (ACTH), although there is evidence that IL-1 may activate the HPA axis by multiple mechanisms (see [130, 131]).

Although the HPA axis-activating effect of IL-1 is shared by other cytokines, most notably, IL-6 and TNF α , the latter are markedly less potent than IL-1, and may have limited physiological significance, except in the absence of IL-1 [130, 131]. Thus the cytokine hypothesis of depression is more akin to an interleukin-1 hypothesis of depression. IL-6 contributes only modestly to the elevation of plasma ACTH and corticosterone by LPS in mice [132], but because plasma concentrations of this cytokine can be dramatically elevated by infections and other pathologies in which the HPA axis is elevated, IL-6 may contribute to the HPA axis activation. Interestingly, there is little evidence for habituation (desensitization) of the HPA axis response to IL-1, although there is rapid tolerance to the responses to LPS.

Administration of IFN α and IFN γ , but not IFN β causes a marked activation of the HPA axis in man (e.g. [133, 134]) but, curiously, IFN γ elevates cortisol, but has little effect on ACTH [135]. There appear to be marked species differences, because administration of relatively high doses of IFN α to mice did not alter plasma corticosterone [11], whereas modest increases in ACTH and corticosterone were observed in rats [136].

The principal factors mitigating against an IL-1 hypothesis of HPA axis activation in depression is the failure to observe consistent elevations of IL-1 in depressed patients, and the fact that one-third or more of depressed patients do not exhibit HPA axis activation.

22.3.6

Brain Noradrenergic Activation in Depression and Induction by Cytokines

There is good evidence that central noradrenergic systems are markedly activated by IL-1 from classical studies of NE catabolites [10–12] and also from microdialysis studies [137]. These studies indicate that noradrenergic neurons throughout the brain are affected, although the activation of the ventral noradrenergic projection system (projecting primarily into the hypothalamus) is substantially higher than that to other regions of the brain. Consistent with this, reductions in the hypothalamic content of NE have also been observed in rats [138]. There is no evidence for noradrenergic activation associated with IL-6, although TNF α has such an effect in mice at higher doses, although this could be attributed to TNF α -induced IL-1 secretion.

As indicated above, many studies have indicated hypersecretion of brain NE in depression, principally assessed by increased CSF concentrations of the NE catabolite, MHPG (3-methoxy-4-hydroxyphenylethyleneglycol), but also by direct measurement of CSF NE [2]. Thus an IL-1-mediated elevation of cerebral NE function could be taken as evidence for a role of IL-1 in depression, although as in the case of the HPA axis activation, the failure to observe consistent elevations of plasma IL-1 in depressed patients tempers this evidence.

22.3.7

Depression, Serotonin and Cytokines

A prevailing hypothesis is that depression is caused by a deficiency in serotonergic neurotransmission, or some disorganization of certain brain serotonergic systems. This hypothesis is based largely on the fact that antidepressants affect serotonergic transmission. Antidepressants may normalize a defective brain serotonergic transmission through plastic or neurotrophic effects. A serotonergic hypothesis is also supported by the observation that depletion of tryptophan can trigger a depressive state in vulnerable individuals, and that serotonin receptor abnormalities are found in the brains of depressed patients (for reviews, see [3, 139]). IL-1, IL-6 and TNF α have been shown to activate brain serotonergic systems, increasing brain tryptophan concentrations and the metabolism of 5-HT as indicated by the

production of 5-HIAA [10–12, 17, 140], and apparent 5-HT release as indicated by microdialysis and *in vivo* chronoamperometry [18]. At face value, these effects appear to promote serotonergic activity, which could be considered to have an antidepressant effect. However, the effects of chronic administration of the cytokines on serotonin function have not been studied. Certain other cytokines, most notably, IFN γ and IL-2, markedly activate indoleamine 2,3-dioxygenase, which depletes tryptophan by converting it to kynurenine [89, 139, 141]. Over-activation of this enzyme by cytokines could reduce the synthesis of 5-HT in the brain, providing a mechanism by which cytokines could reduce brain 5-HT transmission. Cytokines also activate the serotonin transporter, which could decrease extracellular 5-HT [142]. Therefore, there are a number of hypothetical mechanisms by which cytokines could act on brain serotonergic systems and thus contribute to the pathophysiology of depression. However, relationships between these potential mechanisms and depression remain to be demonstrated in depressed patients.

Yet another way in which cytokines could alter serotonergic transmission in the brain is through their activity on the HPA axis. IL-1, IL-6 and TNF α activate the HPA axis [14, 131, 143]. This activation is not only acute, but sustained over time [144] and is dependent on CRF activation [14, 131]. Activation of the HPA axis occurs in many patients during depression, and correlations have been reported between activation of the HPA axis and increased IL-1 β production by monocytes from depressed patients [64]. Therefore, it is tempting to propose that the hypercortisolemia observed in depression is related to the activation of the HPA axis by cytokines. Chronic hypercortisolemia has been proposed to play a causal role in the pathophysiology of depression [5]. The mechanism for this is not understood, but it is reasonable to propose that it is because glucocorticoids have inhibitory effects on brain serotonergic systems, particularly by decreasing the number and functional activity of 5-HT $_{1A}$ receptors [145] which may play a crucial role in the pathophysiology of depression [146]. Moreover, stress appears to synergize with IL-1 β on brain serotonergic systems [147, 148]. Therefore, through their effects on the HPA axis, cytokines may alter 5-HT metabolism in the brain, with a decrease in 5-HT $_{1A}$ function, an effect that could favor the development of depression. Another hypothesis proposes that cytokines may be involved in depression because they induce glucocorticoid resistance [149]. Glucocorticoid resistance is often observed in depressed patients, probably related to chronic increases in circulating cortisol. According to the cytokine hypothesis, the glucocorticoid resistance in depressed patients would be related to an action of cytokines. However, the mechanism by which glucocorticoid resistance could contribute to the pathophysiology of depression has not been determined. Glucocorticoid resistance is not consistently observed in depressed patients, and the fact that antidepressants alter glucocorticoid function [150] is not sufficient evidence *per se* to maintain that glucocorticoid resistance determines depression.

22.3.8

Sensitization and Cross-Sensitization to Stress and Cytokines

Individuals do not react the same way when confronted with a stressful event. Such differences can be explained by many factors, for example, genetic factors, and also by the prior stress history of the individual. A history of trauma, including stressful prenatal events, can alter the responses to stress for an individual's entire life. Early stressful events can alter the development of the brain, particularly the development of neurotransmitter systems, and of the systems that control the HPA axis. The mechanisms by which such alterations take place are not well understood, but a well-known consequence of stress (early or otherwise) is the occurrence of sensitization. Sensitization is a process in which the reaction to a given stimulus increases with repetition of the stimulus (i.e. is the opposite of habituation). Two types of sensitization have been described, time-related sensitization, in which the effect of a stimulus increases over time, and cross-sensitization, where sensitization is initiated by interchangeable stimuli (psychological, pharmacological, or other). As previously mentioned, psychological stressors and cytokine treatments share several common effects, including neurochemical, endocrine and behavioral effects. Sensitization has been interpreted to be a mechanism of defense with adaptive value [151]. Cross-sensitization has been observed between psychological stress and cytokines. A single administration of IL-1 to rats enhances their responses to a psychological stress (foot-shock), as evaluated by plasma concentrations of ACTH and corticosterone [152]. Some similar effects may occur after administration of TNF α [153]. Therefore, previous exposure to an immune stress may alter, later in life, the responses to a psychological stress. However, this model is hypothetical, and many aspects are unknown. For example, can the delay between the immune stress and psychological stress be indefinitely long (for instance from childhood to adult life)? Is the reverse also the case of a sensitization (a psychological trauma in childhood, an immune stress in adulthood)? To what extent is this model applicable to depression or to a mood disorder? Nevertheless, the priming effect of an immune stress remains a very interesting model within the framework of the cytokine hypothesis of depression. For example, this model could explain (from a theoretical point of view) the vulnerability of some individuals to the administration of cytokines. In other words, those individuals who develop a depressive state after administration of a cytokine could be those who have experienced a psychological trauma in the past that has sensitized certain systems which favor the development of depression. Sensitization could also explain why it is not necessary to have a large increase of cytokine secretion to trigger a depressive state; a brief or modest increase in immune activation, or a cross-reaction in the case of a psychological stress, could have strong effects on sensitized brain systems. However, these considerations remain purely hypothetical, and much work remains to be done to determine whether the sensitization model has any real relationship to the pathophysiology of depression.

22.4

Conclusions

The evidence reviewed above indicates some associations between the production of cytokines and depression. However, no clear causal relationship has been established. Administration of certain cytokines to humans does indeed induce symptoms of depression in some patients, but such responses occur only in a minority of patients, and many other neuropsychiatric symptoms may also be induced. Immune activation does indeed appear more frequently in depressed patients, but is not observed in all depressed patients. The hypothesis that immune activation in the depressed is a consequence rather than a cause of depression has rarely been taken into account. Moreover, the immune activation may reflect other medical conditions which may directly or by diagnosis induce depression.

By no means do all depressed patients exhibit immune activation or elevated circulating concentrations of cytokines. Although IL-1 is the major cytokine known to induce depression-like symptoms, evidence for the elevation of levels of this cytokine in depressed patients is conspicuously sparse. The plasma cytokine most commonly elevated in depressed patients is IL-6; plasma concentrations of this cytokine are elevated in almost all infections and also during stress. However, administration of IL-6 in animal studies fails to induce sickness behavior.

Although drugs that inhibit serotonin reuptake are the most useful for the treatment of depression, there is no strong direct evidence that abnormalities of 5-HT cause depression. The serotonin hypothesis remains a hypothesis, and much research remains to be done on the effects of antidepressants on the immune system. Nevertheless, the association of abnormalities in tryptophan and serotonin with infection by pathogens, with immune activation, and with depression are significant, and require more careful investigation.

The analogies between sickness behavior and depression are striking, especially the behaviors induced by IL-1 and LPS in animal studies. Nevertheless, there are important differences, for example, in sleep patterns. It is probably premature to consider experimentally-induced sickness behavior as a fully validated model of depression, but if applied in a critical manner, certain aspects of depression can be studied. Experiments in which animals are treated chronically with antidepressant drugs have failed to provide strong support for the idea that these treatments work by antagonizing the actions of cytokines.

These observations do not exclude a role for cytokines in inducing depression. One certainly cannot exclude the possibility that increased cytokine production may induce depression in some patients, and certainly cytokines may contribute to a variety of neuropsychiatric symptoms in patients with a variety of diseases. Nevertheless, one can conclude with some confidence that the actions of cytokines cannot account for all, or even most, cases of depression. However, it is likely, that by their enhancement of HPA axis function and noradrenergic mechanisms, as well as their effects on tryptophan and serotonin, that cytokines may complement (or even synergize with) other factors that can induce depression.

References

- 1 DUNN, A. J., Stress Neurochemistry. In ADELMAN, G. (Ed.), *Encyclopedia of Neuroscience*, 3rd edn. Cambridge, MA: Birkhauser Boston, 2004.
- 2 WONG, M. L., KLING, M. A., MUNSON, P. J., et al., Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl. Acad. Sci. USA* 2000, 97, 325–330.
- 3 MANJI, H. K., DREVETS, W. C., CHARNEY, D. S., The cellular neurobiology of depression. *Nature Med.* 2001, 7, 541–547.
- 4 DUNN, A. J., BERRIDGE, C. W., Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res. Rev.* 1990, 15, 71–100.
- 5 OWENS, M. J., NEMEROFF, C. B., Physiology and pharmacology of corticotropin-releasing factor. *Pharmacol. Rev.* 1991, 43, 425–473.
- 6 WEISSE, C. S., Depression and immunocompetence, a review of the literature. *Psych. Bull.* 1992, 111, 475–489.
- 7 KRONFOL, Z., Immune dysregulation in major depression: A critical review of existing evidence. *Intl. J. Neuropsychopharmacol.* 2002, 5, 333–343.
- 8 KENT, S., BLUTHÉ, R.-M., KELLEY, K. W., DANTZER, R., Sickness behavior as a new target for drug development. *Trends Pharmacol. Sci.* 1992, 13, 24–28.
- 9 SMITH, R. S., The macrophage theory of depression. *Med. Hypotheses* 1991, 35, 298–306.
- 10 DUNN, A. J., Systemic interleukin-1 administration stimulates hypothalamic norepinephrine metabolism paralleling the increased plasma corticosterone. *Life Sci.* 1988, 43, 429–435.
- 11 DUNN, A. J., Effects of cytokines and infections on brain neurochemistry. In ADER, R., FELTEN, D. L., COHEN, N. (Eds.), *Psychoneuroimmunology*, 3rd edn. New York: Academic Press, 2001, 649–666.
- 12 KABERSCH, A., DEL REY, A., HONEGGER, C. G., BESEDOVSKY, H. O., Interleukin-1 induces changes in norepinephrine metabolism in the rat brain. *Brain Behav. Immun.* 1988, 2, 267–274.
- 13 DUNN, A. J., Role of cytokines in infection-induced stress. *Ann. NY Acad. Sci.* 1993, 697, 189–202.
- 14 TURNBULL, A. V., RIVIER, C., Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *Physiol. Rev.* 1999, 79, 1–71.
- 15 DUNN, A. J., SWIERGIEL, A. H., Behavioral responses to stress are intact in CRF-deficient mice. *Brain Res.* 1999, 845, 14–20.
- 16 MUGLIA, L. J., BETHIN, K. E., JACOBSON, L., VOGT, S. K., MAJZOUB, J. A., Pituitary-adrenal axis regulation in CRH-deficient mice. *Endocrine Res.* 2000, 26, 1057–1066.
- 17 ZALCMAN, S., GREEN-JOHNSON, J. M., MURRAY, L., et al., Cytokine-specific central monoamine alterations induced by interleukin-1, -2 and -6. *Brain Res.* 1994, 643, 40–49.
- 18 ZHANG, J.-J., TERRENI, L., DE SIMONI, M.-G., DUNN, A. J., Peripheral interleukin-6 administration increases extracellular concentrations of serotonin and the evoked release of serotonin in the rat striatum. *Neurochem. Intl.* 2001, 38, 303–308.
- 19 HERSH, E. M., MURRAY, J. L., HONG, W. K., et al., Phase I study of cancer therapy with recombinant interleukin-2 administered by intravenous bolus injection. *Biotherapy* 1989, 1, 215–226.
- 20 KRIGEL, R. L., PADAVIC-SHALLER, K. A., RUDOLPH, A. R., KONRAD, M., BRADLEY, E. C., COMIS, R. L., Renal cell carcinoma, treatment with recombinant interleukin-2 plus beta-interferon. *J. Clin. Oncol.* 1990, 8, 460–467.
- 21 PARDO, N., MARTI, F., FRAGA, G., et al., High-dose systemic interleukin-2 therapy in stage IV neuroblastoma for one year after autologous bone marrow transplantation, pilot study. *Med. Pediatr. Oncol.* 1996, 27, 534–539.
- 22 WICHES, M., MAES, M., The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. *Intl. J. Neuropsychopharmacol.* 2002, 5, 375–388.
- 23 RENAULT, P. F., HOOFNAGLE, J. H., PARK, Y., et al., Psychiatric complications of long-term interferon alpha therapy. *Arch. Int. Med.* 1987, 147, 1577–1580.

- 24 PAVOL, M. A., MEYERS, C. A., REXER, J. L., VALENTINE, A. D., MATTIS, P. J., TALPAZ, M., Pattern of neurobehavioral deficits associated with interferon alfa therapy for leukemia. *Neurology* **1995**, 45, 947–950.
- 25 HUNT, C. M., DOMINITZ, J. A., BUTE, B. P., WATERS, B., BLASI, U., WILLIAMS, D. M., Effect of interferon-alpha treatment of chronic hepatitis C on health-related quality of life. *Dig. Dis. Sci.* **1997**, 42, 2482–2486.
- 26 MALAGUARNERA, M., DI FAZIO, I., RESTUCCIA, S., PISTONE, G., FERLITO, L., RAMPOLLO, L., Interferon alpha-induced depression in chronic hepatitis C patients, comparison between different types of interferon alpha. *Neuropsychobiology* **1998**, 37, 93–97.
- 27 MALAGUARNERA, M., LAURINO, A., DI FAZIO, I., et al., Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C, *J. Interferon Cytokine Res.* **2001**, 21, 273–278.
- 28 PARIANTE, C. M., ORRU, M. G., BAITA, A., FARCI, M. G., CARPINIELLO, B., Treatment with interferon-alpha in patients with chronic hepatitis and mood or anxiety disorders. *Lancet* **1999**, 354, 131–132.
- 29 BONACCORSO, S., MARINO, V., PUZELLA, A., et al., Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J. Clin. Psychopharmacol.* **2002**, 22, 86–90.
- 30 CAPURON, L., RAVAUD, A., DANTZER, R., Early depressive symptoms in cancer patients receiving interleukin-2 and/or interferon alpha-2b therapy. *J. Clin. Oncol.* **2000**, 18, 2143–2151.
- 31 ADAMS, F., QUESADA, J. R., GUTTERMAN, J. U., Neuropsychiatric manifestations of human leukocyte interferon therapy in patients with cancer. *J. Am. Med. Assoc.* **1984**, 252, 938–941.
- 32 JUENGLING, F. D., EBERT, D., GUT, O., et al., Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology* **2000**, 152, 383–389.
- 33 MAPOU, R. L., LAW, W. A., WAGNER, K., MALONE, J. L., SKILLMAN, D. R., Neuropsychological effects of interferon alpha-n3 treatment in asymptomatic human immunodeficiency virus-1-infected individuals. *J. Neuropsychiat. Clin. Neurosci.* **1996**, 8, 74–81.
- 34 MULDER, R. T., ANG, M., CHAPMAN, B., ROSS, A., STEVENS, I. F., EDGAR, C., Interferon treatment is not associated with a worsening of psychiatric symptoms in patients with hepatitis C. *J. Gastroenterol. Hepatol.* **2000**, 15, 300–303.
- 35 DENICOFF, K. D., RUBINOW, D. R., PAPA, M. Z., et al., The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells. *Ann. Int. Med.* **1987**, 107, 293–300.
- 36 BUTER, J., DE VRIES, E. G., SLEIJFER, D. T., WILLEMSE, P. H., MULDER, N. H., Neuropsychiatric symptoms during treatment with interleukin-2. *Lancet* **1993**, 341, 628.
- 37 NOZAKI, O., TAKAGI, C., TAKAOKA, K., TAKATA, T., YOSHIDA, M., Psychiatric manifestations accompanying interferon therapy for patients with chronic hepatitis C, an overview of cases in Japan. *Psychiatr. Clin. Neurosci.* **1997**, 51, 175–180.
- 38 MONJI, A., YOSHIDA, I., TASHIRO, K., HAYASHI, Y., TASHIRO, N., A case of persistent manic depressive illness induced by interferon-alpha in the treatment of chronic hepatitis C. *Psychosomatics* **1998**, 39, 562–564.
- 39 STRITE, D., VALENTINE, A. D., MEYERS, C. A., Manic episodes in two patients treated with interferon alpha. *J. Neuropsychiat. Clin. Neurosci.* **1997**, 9, 273–276.
- 40 FUKUNISHI, K., TANAKA, H., MARUYAMA, J., et al., Burns in a suicide attempt related to psychiatric side effects of interferon. *Burns* **1998**, 24, 581–583.
- 41 JANSSEN, H. L., BROUWER, J. T., VAN DER MAST, R. C., SCHALM, S. W., Suicide associated with alpha-interferon therapy for chronic viral hepatitis. *J. Hepatol.* **1994**, 21, 241–243.
- 42 MEYERS, C. A., VALENTINE, A. D., WONG, F. C. L., LEEDS, N. E., Reversible neurotoxicity of interleukin-2 and tumor necrosis factor: correlation of SPECT with neuropsychological testing. *J. Neuropsychiat. Clin. Neurosci.* **1994**, 6, 285–288.
- 43 CARACENI, A., GANGERI, L., MARTINI, C., et al., Neurotoxicity of interferon-alpha in melanoma therapy, results from a

- randomized controlled trial. *Cancer* **1998**, 83, 482–489.
- 44 MUSSELMAN, D. L., LAWSON, D. H., GUMNICK, J. F., et al., Paroxetine for the prevention of depression induced by high-dose interferon alfa. *New Engl. J. Med.* **2001**, 344, 961–966.
 - 45 CAPURON, L., GUMNICK, J. F., MUSSELMAN, D. L., et al., Neurobehavioral effects of interferon- α in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* **2002**, 26, 643–652.
 - 46 MIYAOKA, H., OTSUBO, T., KAMIJIMA, K., ISHII, M., ONUKI, M., MITAMURA, K., Depression from interferon therapy in patients with hepatitis C. *Am. J. Psychiatry* **1999**, 156, 1120.
 - 47 SINGH, N., GAYOWSKI, T., WAGENER, M. M., MARINO, I. R., Vulnerability to psychologic distress and depression in patients with end-stage liver disease due to hepatitis C virus. *Clin. Transplant.* **1997**, 11, 406–411.
 - 48 JOHNSON, M. E., FISHER, D. G., FENAUGHTY, A., THENO, S. A., Hepatitis C virus and depression in drug users. *Am. J. Gastroenterol.* **1998**, 93, 785–789.
 - 49 MCHUTCHISON, J. G., GORDON, S. C., SCHIFF, E. R., et al., Interferon-alpha-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C, Hepatitis Interventional Therapy Group. *New Engl. J. Med.* **1998**, 339, 1485–1492.
 - 50 DUSHEIKO, G., Side effects of alpha interferon in chronic hepatitis C. *Hepatology* **1997**, 3, 112S–121S.
 - 51 CAPURON, L., RAVAUD, A., Prediction of the depressive effects of interferon-alfa therapy by the patient's initial affective state. *New Engl. J. Med.* **1999**, 340, 1370.
 - 52 SCHEIBEL, R. S., VALENTINE, A. D., O'BRIEN, S., MEYERS, C. A., Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. *J. Neuropsychiat. Clin. Neurosci.* **2004**, 16, 185–191.
 - 53 MAES, M., CAPURON, L., RAVAUD, A., et al., Lowered serum dipeptidyl peptidase IV activity is associated with depressive symptoms and cytokine production in cancer patients receiving interleukin-2-based immunotherapy. *Neuropsychopharmacology* **2001**, 24, 130–140.
 - 54 HERBERT, T. B., COHEN, S., Depression and immunity: a meta-analytic review. *Psych. Bull.* **1993**, 113, 472–486.
 - 55 STEIN, M., MILLER, A. H., TRESTMAN, R. L., Depression and the immune system. In ADER, R., FELTEN, D. L., COHEN, N. (Eds.), *Psychoneuro-immunology*, 2nd edn. San Diego: Academic Press, **1991**, 897–930.
 - 56 IRWIN, M., LACHER, U., CALDWELL, C., Depression and reduced natural killer cytotoxicity: a longitudinal study of depressed patients and control subjects. *Psychol. Med.* **1992**, 22, 1045–1050.
 - 57 IRWIN, M., PATTERSON, T., SMITH, T. L., et al., Reduction of immune function in life stress and depression. *Biol. Psychiatry* **1990**, 27, 22–30.
 - 58 MAES, M., Evidence for an immune response in major depression: a review and hypothesis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1995**, 19, 11–38.
 - 59 LIEB, J., KARMALI, R., HORROBIN, D., Elevated levels of prostaglandin E2 and thromboxane B2 in depression. *Prostaglandins Leukotriene Med.* **1983**, 10, 361–367.
 - 60 KRONFOL, Z., HOUSE, J. D., Lymphocyte mitogenesis, immunoglobulin and complement levels in depressed patients and normal controls. *Acta Psychiatr. Scand.* **1989**, 80, 142–147.
 - 61 MAES, M., LAMBRECHTS, J., BOSMANS, E., et al., Evidence for a systemic immune activation during depression, results of leukocyte enumeration by flow cytometry in conjunction with monoclonal antibody staining. *Psychol. Med.* **1992**, 22, 45–53.
 - 62 DUCH, D. S., WOOLF, J. H., NICHOL, C. A., DAVIDSON, J. R., GARBUTT, J. C., Urinary excretion of biopterin and neopterin in psychiatric disorders. *Psychiatr. Res.* **1984**, 11, 83–89.
 - 63 DUNBAR, P. R., HILL, J., NEALE, T. J., MELLISOP, G. W., Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression, but not with schizophrenia. *Psychol. Med.* **1992**, 22, 1051–1057.
 - 64 MAES, M., BOSMANS, E., MELTZER, H. Y., SCHARPÉ, S., SUY, E., Interleukin-1 β : a putative mediator of HPA axis hyperactivity in major depression? *Am. J. Psychiatry* **1993**, 150, 1189–1193.

- 65 MAES, M., SCHARPÉ, S., MELTZER, H., et al., Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. *Psychiat. Res.* **1993**, *49*, 11–27.
- 66 MAES, M., SCHARPÉ, S., MELTZER, H. Y., et al., Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression, further evidence for an immune response. *Psychiatr. Res.* **1994**, *54*, 143–160.
- 67 GRIFFITHS, J., RAVINDRAN, A. V., MERALI, Z., ANISMAN, H., Immune and behavioral correlates of typical and atypical depression. *Soc. Neurosci. Abstr.* **1996**, *22*, 1350.
- 68 OWEN, B. M., ECCLESTON, D., FERRIER, I. N., YOUNG, A. H., Raised levels of plasma interleukin-1 β in major and postviral depression. *Acta Psychiatr. Scand.* **2001**, *103*, 226–228.
- 69 BRAMBILLA, F., MAGGIONI, M., Blood levels of cytokines in elderly patients with major depressive disorder. *Acta Psychiatr. Scand.* **1998**, *97*, 309–313.
- 70 MUSSELMAN, D. L., MILLER, A. H., PORTER, M. R., et al., Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *Am. J. Psychiatry* **2001**, *158*, 1252–1257.
- 71 HAACK, M., HINZE-SELCH, D., FENZEL, T., et al., Plasma levels of cytokines and soluble cytokine receptors in psychiatric patients upon hospital admission: effects of confounding factors and diagnosis. *J. Psychiatr. Res.* **1999**, *33*, 407–418.
- 72 LANDMANN, R., SCHAUB, B., LINK, S., WACKER, H. R., Unaltered monocyte function in patients with major depression before and after three months of antidepressive therapy. *Biol. Psychiatry* **1997**, *15*, 675–681.
- 73 NATELSON, B. H., DENNY, T., ZHOU, X. D., et al., Is depression associated with immune activation? *J. Affect. Disorders* **1999**, *53*, 179–184.
- 74 MAES, M., BOSMANS, E., DE JONGH, R., KENIS, G., VANDOOALAECH, E., NEELS, H., Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* **1997**, *9*, 853–858.
- 75 TRACEY, K. J., BEUTLER, B., LOWRY, S. F., et al., Shock and tissue injury induced by recombinant human cachectin. *Science* **1986**, *234*, 470–474.
- 76 LEVINE, J., BARAK, Y., CHENGAPPA, K. N., RAPOPORT, A., REBEY, M., BARAK, V., Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology* **1999**, *40*, 171–176.
- 77 ANISMAN, H., MERALI, Z., Anhedonic and anxiogenic effects of cytokine exposure. *Adv. Exp. Med. Biol.* **1999**, *461*, 199–233.
- 78 SEIDEL, A., AROIT, V., HUNSTIGER, M., RINK, L., BEHNISCH, A., KIRCHNER, H., Cytokine production and serum proteins in depression. *Scand. J. Immunol.* **1995**, *41*, 534–538.
- 79 WEIZMAN, R., LAOR, N., PODLISZEWSKI, E., NOTTI, I., DJALDETTI, M., BESSLER, H., Cytokine production in major depressed patients before and after clomipramine treatment. *Biol. Psychiatry* **1994**, *35*, 42–47.
- 80 ROTHERMUNDT, M., AROIT, V., BAYER, T. A., Review of immunological and immunopathological findings in schizophrenia. *Brain Behav. Immun.* **2001**, *15*, 319–339.
- 81 ZORRILLA, E. P., LUBORSKY, L., MCKAY, J. R., et al., The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain Behav. Immun.* **2001**, *15*, 199–226.
- 82 POLLMÄCHER, T., HAACK, M., SCHULD, A., REICHENBERG, A., YIRMIYA, R., Low levels of circulating inflammatory cytokines – Do they affect human brain functions? *Brain Behav. Immun.* **2002**, *16*, 525–532.
- 83 MINDEN, S. L., SCHIFFER, R. B., Affective disorders in multiple sclerosis. Review and recommendations for clinical research. *Arch. Neurol.* **1990**, *47*, 98–104.
- 84 MARSHALL, P. S., Allergy and depression, a neurochemical threshold model of the relation between the illnesses. *Psychol. Bull.* **1993**, *113*, 23–43.
- 85 DICKENS, C., MCGOWAN, L., CLARK-CARTER, D., CREED, F., Depression in rheumatoid arthritis, a systematic review of the literature with meta-analysis. *Psychosom. Med.* **2002**, *64*, 52–60.
- 86 SCHWARTZ, J. A., SPEED, N. M., BRUNBERG, J. A., BREWER, T. L., BROWN, M., GREDEN,

- J. F., Depression in stroke rehabilitation. *Biol. Psychiatry* **1993**, 33, 694–699.
- 87 FOLEY, F. W., TRAUGOTT, U., LAROCCA, N. G., et al., A prospective study of depression and immune dysregulation in multiple sclerosis. *Arch. Neurol.* **1992**, 49, 238–244.
 - 88 YIRMIYA, R., WEIDENFELD, J., POLLAK, Y., et al., Cytokines, “Depression due to a general medical condition”, and antidepressant drugs. *Adv. Exp. Med. Biol.* **1999**, 461, 283–316.
 - 89 MAES, M., VERKERK, R., BONACCORSO, S., OMBELET, W., BOSMANS, E., SCHARPE, S., Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. *Life Sci.* **2002**, 71, 1837–1848.
 - 90 HART, B. L., Biological basis of the behavior of sick animals. *Neurosci. Biobehav. Rev.* **1988**, 12, 123–137.
 - 91 LARSON, S. J., DUNN, A. J., Behavioral mechanisms for defense against pathogens. In BERCI, I., SVENTIVANYI, A. (Eds.), *Natural Immunity*. New York: Elsevier, **2004** (in press).
 - 92 DANTZER, R., BLUTHÉ, R.-M., LAYÉ, S., BRET-DIBAT, J. L., PARNET, P., KELLEY, K. W., Cytokines and sickness behavior. *Ann. NY Acad. Sci.* **1998**, 840, 586–590.
 - 93 MAIER, S. F., WATKINS, L. R., Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psych. Rev.* **1998**, 1501, 83–107.
 - 94 ANISMAN, H., HAYLEY, S., TURRIN, N., MERALI, Z., Cytokines as a stressor: Implications for depressive illness. *Intl. J. Neuropsychopharmacol.* **2002**, 5, 357–373.
 - 95 DE BEAUREPAIRE, R., Questions raised by the cytokine hypothesis of depression. *Brain Behav. Immun.* **2002**, 16, 610–617.
 - 96 SLISLI, Y., DE BEAUREPAIRE, R., Interleukin-1 β and calcitonin, but not corticotropin-releasing factor, alter sleep cycles when injected into the rat hypothalamic lateral paraventricular area. *Neurosci. Letts.* **1999**, 265, 29–32.
 - 97 VEREKE, E., O'DONNELL, E., LYNCH, M. A., The inhibitory effect of interleukin-1 β on long-term potentiation is coupled with increased activity of stress-activated protein kinases. *J. Neurosci.* **2000**, 20, 6811–6819.
 - 98 MEYERS, C. A., Mood and cognitive disorders in cancer patients receiving cytokine therapy. *Adv. Exp. Med. Biol.* **1999**, 461, 75–81.
 - 99 MCKENNA, P. J., MCKAY, A. P., LAWS, K., *Memory in Functional Psychosis. Memory Disorders in Psychiatric Practice*. Cambridge: Cambridge University Press, **2000**.
 - 100 MEYERS, C. A., SCHEIBEL, R. S., FORMAN, A. D., Persistent neurotoxicity of systemically administered interferon-alpha. *Neurology* **1991**, 41, 672–676.
 - 101 LICINIO, J., WONG, M.-L., The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol. Psychiatry* **1999**, 4, 317–327.
 - 102 LAYÉ, S., PARNET, P., GOIJON, E., DANTZER, R., Peripheral administration of lipopolysaccharide induces the expression of cytokine transcripts in the brain and pituitary of mice. *Mol. Brain Res.* **1994**, 27, 157–162.
 - 103 WONG, M.-L., LICINIO, J., Localization of interleukin-1 type I receptor mRNA in rat brain. *Neuroimmunomodulation* **1994**, 1, 110–115.
 - 104 WONG, M.-L., BONGIORNO, P. B., RETTORI, V., MCCANN, S. M., LICINIO, J., Interleukin (IL) 1 β , IL-1 receptor antagonist, IL-10, and IL-13 gene expression in the central nervous system and anterior pituitary during systemic inflammation: pathophysiological implications. *Proc. Natl. Acad. Sci. USA* **1997**, 94, 227–232.
 - 105 QUAN, N., STERN, E. L., WHITESIDE, M. B., HERKENHAM, M., Induction of pro-inflammatory cytokine mRNAs in the brain after peripheral injection of subseptic doses of lipopolysaccharide in the rat. *J. Neuroimmunol.* **1999**, 93, 72–80.
 - 106 SANTARELLI, L., SAXE, M., GROSS, C., et al., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **2003**, 301, 805–809.

- 107 BREDER, C. D., DINARELLO, C. A., SAPER, C. B., Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science* **1988**, *240*, 321–324.
- 108 LECHAN, R. M., TONI, R., CLARK, B. D., et al., Immunoreactive interleukin-1B localization in the rat forebrain. *Brain Res.* **1990**, *514*, 135–140.
- 109 MOLENAAR, G. J., BERKENBOSCH, F., VAN DAM, A.-M., LUGARD, C. M. J. E., Distribution of interleukin 1 β immunoreactivity within the porcine hypothalamus. *Brain Res.* **1993**, *608*, 169–174.
- 110 QUAN, N., SUNDAR, Q. N., WEISS, J. M., Induction of interleukin-1 in various brain regions after peripheral and central injections of lipopolysaccharide. *J. Neuroimmunol.* **1994**, *49*, 125–134.
- 111 WATKINS, L. R., MAIER, S. F., GOEHLER, L. E., Cytokine-to-brain communication: a review and analysis of alternative mechanisms. *Life Sci.* **1995**, *57*, 1011–1026.
- 112 QUAN, N., ZHANG, Z., EMERY, M., BONSALE, R., WEISS, J. M., Detection of interleukin-1 bioactivity in various brain regions of normal healthy rats. *Neuroimmunomodulation* **1996**, *3*, 47–55.
- 113 FARRAR, W. L., KILIAN, P. L., RUFF, M. R., HILL, J. M., PERT, C. B., Visualization and characterization of interleukin 1 receptor in brain. *J. Immunol.* **1987**, *139*, 459–463.
- 114 HAOUR, F., BAN, E., MARQUETTE, C., MILON, G., FILLION, G., Brain Interleukin-1 receptors: mapping, characterization and modulation. In ROTHWELL, N. J., DANTZER, R. D. (Eds.), *Interleukin-1 in the Brain*. Oxford: Pergamon Press, **1992**, 13–25.
- 115 TAKAO, T., CULP, S. G., NEWTON, R. C., DE SOUZA, E. B., Type I interleukin-1 receptors in the mouse brain-endocrine-immune axis labelled with [¹²⁵I]-recombinant human interleukin-1 receptor antagonist. *J. Neuroimmunol.* **1992**, *41*, 51–60.
- 116 YABUUCHI, K., MINAMI, M., KATSUMATA, S., SATOH, M., Localization of type 1 interleukin-1 receptor mRNA in the rat brain. *Mol. Brain Res.* **1994**, *27*, 27–36.
- 117 ERICSSON, A., LIU, C., HART, R. P., SAWCHENKO, P. E., Type 1 interleukin-1 receptor in the rat brain: distribution, regulation, and relationship to sites of IL-1-induced cellular activation. *J. Comp. Neurol.* **1995**, *361*, 681–698.
- 118 DANTZER, R., AUBERT, A., BLUTHÉ, R.-M., et al., Mechanisms of the behavioural effects of cytokines. *Adv. Exp. Med. Biol.* **1999**, *461*, 83–105.
- 119 PUGH, C. R., NGUYEN, K. T., GONYEA, J. L., et al., Role of interleukin-1 beta in impairment of contextual fear conditioning caused by social isolation. *Behav. Brain Res.* **1999**, *106*, 109–118.
- 120 BORSODY, M. K., WEISS, J. M., The effects of endogenous interleukin-1 bioactivity on locus coeruleus neurons in response to bacterial and viral substances. *Brain Res.* **2004**, *1007*, 39–56.
- 121 YIRMIYA, R., Endotoxin produces a depressive-like episode in rats. *Brain Res.* **1996**, *711*, 163–174.
- 122 SHEN, Y., CONNOR, T. J., NOLAN, Y., KELLY, J. P., LEONARD, B. E., Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat. *Life Sci.* **1999**, *65*, 1773–1786.
- 123 YIRMIYA, R., POLLAK, Y., BARAK, O., et al., Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacology* **2001**, *24*, 531–544.
- 124 CASTANON, N., BLUTHÉ, R.-M., DANTZER, R., Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1 β in the rat. *Psychopharmacology* **2001**, *154*, 50–60.
- 125 DUNN, A. J., SWIERGIEL, A. H., The reductions in sweetened milk intake induced by interleukin-1 and endotoxin are not prevented by chronic antidepressant treatment. *Neuroimmunomodulation* **2001**, *9*, 163–169.
- 126 CASTANON, N., LEONARD, B. E., NEVEU, P. J., YIRMIYA, R., Effects of antidepressants on cytokine production and actions. *Brain Behav. Immun.* **2002**, *16*, 569–574.
- 127 CAMPISI, J., HANSEN, M. K., O'CONNER, K. A., et al., Circulating cytokines and endotoxin are not necessary for the activation of the sickness or corticosterone response produced by peripheral *E. coli* challenge. *J. Appl. Physiol.* **2003**, *95*, 1873–1882.

- 128 SHERRILL, J. T., ANDERSON, B., FRANK, E., et al., Is life stress more likely to provoke depressive episodes in women than in men. *Depress. Anxiety* **1997**, *6*, 95–105.
- 129 CHARLTON, B. G., The malaise theory of depression: major depressive disorder is sickness behavior and antidepressants are analgesic. *Med. Hypotheses* **2000**, *54*, 126–130.
- 130 SILVERMAN, M. N., PEARCE, B. D., MILLER, A. H., Cytokines and HPA axis regulation. In KRONFOL, Z. (Ed.), *Cytokines and Mental Health*. Norwell, MA: Kluwer Academic Publishers, **2003**, 85–122.
- 131 DUNN, A. J., Cytokine activation of the hypothalamo-pituitary-adrenal axis. In STECKLER, T., KALIN, N. (Eds.), *Handbook on Stress, Immunology and Behaviour*. New York: Elsevier, **2004** (in press).
- 132 WANG, J. P., DUNN, A. J., The role of interleukin-6 in the activation of the hypothalamo-pituitary-adrenocortical axis induced by endotoxin and interleukin-1b. *Brain Res.* **1999**, *815*, 337–348.
- 133 SHIMIZU, H., OHTANI, K.-I., SATO, N., NAGAMINE, T., MORI, M., Increase in serum interleukin-6, plasma ACTH and serum cortisol levels after systemic interferon- α administration. *Endocrinol. J.* **1995**, *42*, 551–556.
- 134 CAPURON, L., RAISON, C. L., MUSSELMAN, D. L., LAWSON, D. H., NEMEROFF, C. B., MILLER, A. H., Association of exaggerated HPA axis response to the initial injection of interferon- α with development of depression during interferon- α therapy. *Am. J. Psychiatry* **2003**, *160*, 1342–1345.
- 135 HOLSBOER, F., STALLA, G. K., VON BARDELEBEN, U., HAMMANN, K., MÜLLER, H., MÜLLER, O. A., Acute adrenocortical stimulation by recombinant gamma interferon in human controls. *Life Sci.* **1988**, *42*, 1–5.
- 136 MENZIES, R. A., PHELPS, C. P., WIRANOWSKA, M., et al., The effect of interferon- α on the pituitary-adrenal axis. *J. Interferon Cytokine Res.* **1996**, *16*, 619–629.
- 137 SMAGIN, G. N., SWIERGIEL, A. H., DUNN, A. J., Peripheral administration of interleukin-1 increases extracellular concentrations of norepinephrine in rat hypothalamus: comparison with plasma corticosterone. *Psychoneuroendocrinology* **1996**, *21*, 83–93.
- 138 FLESHNER, M., GOEHLER, L. E., HERMANN, J., RELTON, J. K., MAIER, S. F., WATKINS, L. R., Interleukin-1 β induced corticosterone elevation and hypothalamic NE depletion is vagally mediated. *Brain Res. Bull.* **1995**, *37*, 605–610.
- 139 BELL, C., ABRAMS, J., NUTT, D., Tryptophan depletion and its implications for psychiatry. *Brit. J. Psychiat.* **2001**, *178*, 399–405.
- 140 CLEMENT, H. W., BUSCHMANN, J., REX, S., et al., Effects of interferon- γ , interleukin-1 β , and tumor necrosis factor- α on the serotonin metabolism in the nucleus raphe dorsalis of the rat. *J. Neural Transm.* **1997**, *104*, 981–991.
- 141 BROWN, R. R., OZAKI, Y., DATTA, S. P., BORDEN, E. C., SONDEL, P. M., MALONE, D. G., Implications of interferon-induced tryptophan catabolism in cancer, autoimmune diseases and AIDS. *Adv. Exptl. Med. Biol.* **1991**, *294*, 425–435.
- 142 RAMAMOORTHY, S., RAMAMOORTHY, J. D., PRASAD, P. D., et al., Regulation of the human serotonin transporter by interleukin-1 β . *Biochem. Biophys. Res. Commun.* **1995**, *216*, 560–567.
- 143 VAN DER MEER, M. J. M., SWEEP, C. G. J., RIJNKELS, C. E. M., et al., Acute stimulation of the hypothalamic-pituitary-adrenal axis by IL-1 β , TNF α and IL-6: a dose response study. *J. Endocrinol. Invest.* **1996**, *19*, 175–182.
- 144 VAN DER MEER, M. J., SWEEP, C. G., PESMAN, G. J., TILDERS, F. J., HERMUS, A. R. M. M., Chronic stimulation of the hypothalamus-pituitary-adrenal axis in rats by interleukin 1 β : central and peripheral mechanisms. *Cytokine* **1996**, *8*, 910–919.
- 145 MENDELSON, S. D., McEWEN, B. S., Quantitative autoradiographic analyses of time course and reversibility of corticosterone-induced decreases in binding at 5-HT1A receptors in rat forebrain. *Neuroendocrinology* **1992**, *56*, 881–888.
- 146 MONGEAU, R., BLIER, P., DE MONTIGNY, C., The serotonergic and noradrenergic systems of the hippocampus, their interactions and the effects of antidepressant treatments. *Brain Res. Rev.* **1997**, *23*, 145–195.

- 147 MERALI, Z., LACOSTA, S., ANISMAN, H.,
Effects of interleukin-1b and mild stress
on alterations of norepinephrine,
dopamine and serotonin neurotrans-
mission: a regional microdialysis study.
Brain Res. **1997**, 761, 225–235.
- 148 SONG, C., MERALI, Z., ANISMAN, H.,
Variations of nucleus accumbens
dopamine and serotonin following
systemic interleukin-1, interleukin-2 or
interleukin-6 treatment. *Neuroscience*
1999, 88, 823–836.
- 149 MILLER, G. W., GAINETDINOV, R. R.,
LEVEY, A. I., CARON, M. G., Dopamine
transporters and neuronal injury.
Trends Pharmacol. Sci. **1999**, 20, 424–429.
- 150 MILLER, A. H., PARIANTE, C. M., PEARCE,
B. D., Effects of cytokines on gluco-
corticoid receptor expression and
function. Glucocorticoid resistance and
relevance to depression. *Adv. Exptl. Med.
Biol.* **1999**, 461, 107–116.
- 151 ANTELMAN, S. M., LEVINE, J., GERSHON,
S., Time-dependent sensitization, the
odyssey of a scientific heresy from the
laboratory to the door of the clinic.
Mol. Psychiatry **2000**, 5, 350–356.
- 152 SCHMIDT, C. J., SORENSSEN, S. M.,
KEHNE, J. H., CARR, A. A., PALFREYMAN,
M. G., The role of 5-HT_{2A} receptors in
antipsychotic activity. *Life Sci.* **1995**, 56,
2209–2222.
- 153 ANISMAN, H., MERALI, Z., HAYLEY, S.,
Sensitization associated with stressors
and cytokine treatment. *Brain Behav.
Immun.* **2003**, 17, 86–93.

23

Borna Disease Virus: Impact on Mood and Cognition

Liv Bode, Detlef E. Dietrich and Hanns Ludwig

Abstract

This chapter introduces an unique RNA virus, Borna disease virus (BDV), into biological psychiatry, thereby summarizing current knowledge on the agent's unusual properties, diagnosis, therapy, and animal models, with respect to BDV's potential impact on psychiatric disorders. BDV preferentially infects the limbic system of the brain of animals as well as humans and, in case of animals, is unequivocally able to cause complex behavioral disorders. Regarding human infections the chapter provides correlative evidence for the concept that BDV contributes to periodicity and symptom spectrum at least of mood disorders. This concept integrates virus and host factors as close interdependent players which finally lead to overt clinical symptoms. Virus factors are the ability to transiently interfere with or to modulate neurotransmitter network functioning, most probably by virus proteins (major antigens). Likely host factors are acute and chronic stress causing altered neuro-endocrine and immune system functioning, thereby facilitating activation of persistent BDV infection. The chapter describes, how virus activation indicated by immune complexes and viral proteins can meanwhile be monitored in the blood through easy-to-use assays, and argues in favor of implementing the respective triple-EIA (enzyme immune assay) as a "gold standard" for infection diagnosis. Furthermore, the apparently beneficial option of an antiviral treatment of depression by the low-risk drug amantadine is considered referring to first clinical trials, as are *in vitro* studies demonstrating the compound's effectiveness to inhibit virus replication. Finally, experimental animal models are critically reviewed due to their limited if not misleading results for the understanding of natural infections. The chapter does not miss to address the fact that human BDV research has been and still is controversial since the first antibody findings in psychiatric patients. However, this is regarded as expected process in the course of establishing a novel field of research. In summary, the chapter aims to encouraging and guide psychiatrists and medical professionals to pay attention to new concepts by considering aspects that can not be disproved, and to support unusual and/or unconventional approaches in favor of their patients.

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23.1

Introduction

The aim of integrating behavioral neurology and biological psychiatry into a better understanding of brain–behavior relationships has been accompanied by an overwhelming number of studies in recent years. The suggestion that central nervous system infections lead to severe neurological diseases and secondary psychosis as a result of structural brain damage has been readily accepted. Neurotropic viruses like herpes viruses, rabies virus, influenza virus, and HIV can cause encephalitis. The measles virus may lead to sub-acute sclerosing pan-encephalitis, and Creutzfeldt–Jakob disease is known to be an infectious spongiform encephalopathy. In addition to viruses, numerous bacteria and parasites are also able to induce fatal destructive brain diseases [1].

Unlike many infectious agents, there is only one known virus, namely the Borna disease virus (BDV) that under natural and experimental conditions primarily afflicts limbic structures of the brain and causes a non-cytopathogenic (non-destructive) persistent infection in animals [2]. The limbic system consists of several evolutionary “old” brain structures, such as hippocampus and amygdala, which are connected to each other and cortical areas by a complex network of neurons. A deeper understanding of information processing pathways, from cortex to limbic system and reciprocally, is one of the most fascinating topics of modern neurobiology, of which biological psychiatry is one important area. Meanwhile, it is textbook knowledge [3] that disturbances of these pathways are mainly due to dysfunction or modulation of important monoamine neurotransmitter networks, such as glutamate, serotonin, dopamine, and GABA. As severe pathological changes may result in clinical symptoms affecting mood, cognition, and behavior, it is feasible that this infection may present as major depression (MDD), bipolar disorder (BP I and II), obsessive–compulsive disorder (OCD), anxiety disorders, or as part of the chronic fatigue syndrome (CFS).

BDV is a unique enveloped RNA virus, which has adapted to target a vulnerable part of the brain in warm-blooded animals (mammals, including man, and birds) [2]. This process has most probably occurred during millions of years of co-evolution, given its extremely conserved non-segmented, negative-stranded RNA genome [4]. The majority of infected subjects have sub-clinical symptoms and their hosts are asymptomatic carriers; therefore, only a minority of infected subjects will have life-long relapsing behavioral syndromes [5]. Experimental animal infections (mainly studied in rats) have already emphasized the effectiveness of BDV in disturbing cognitive functions, such as learning and memory [6, 7]. These CNS disturbances are likely to affect the neurotransmitters, in particular glutamate [8], which is the most important excitatory neurotransmitter. The existence in humans of a similar BDV infection of possible clinical relevance has been the subject of heated debate [5] since the discovery of the presence of antibodies against BDV in psychiatric patients [9]. Recently, however, the evidence linking BDV and depression has become more compelling due to significant improvements in methods of detection [10] and reports that an

antiviral therapeutic approach produces beneficial results in some patients [5, 11–13].

The possibility that an infectious agent may contribute to the etiology of major psychiatric disorders such as MDD is very provocative, as this would certainly lead to a major paradigmatic shift in biological psychiatry. This chapter will therefore provide a summary of the data pertaining to this fascinating virus. The intriguing ability of BDV to influence mood and cognition may provide novel insights into biological psychiatry and may have an important impact on the provision of alternative therapeutic approaches for the treatment of MDD. We believe that this topic is of broad relevance to clinical medicine and neuroscience research.

23.2

Milestones of Discovery in Human Infection

23.2.1

Antibodies

The history of BDV infections in humans can be traced back a quarter of a century to 1976, when sera from psychiatric patients (including the patient ISOLA with an epilepsy-like syndrome), kindly provided by Jay Amsterdam of the University of Pennsylvania, Philadelphia, were found to be antibody-positive in serologic assays (Ludwig, Rott, and Koprowski, unpublished observations). Ten years later, samples from a collection of hospitalized psychiatric patients in Germany and the US reacted positively in immune fluorescence (IF) antibody assays against BDV [9]. These observations were confirmed by studies describing the presence of BDV infection in control individuals and in immune-compromised patients with HIV infection [14, 15]. An overview of serologic data from 17 771 subjects collected worldwide, namely in Germany, Japan, Africa, and the USA, and investigated mainly by our and Rott's group, convincingly demonstrated significant serologic reactivity (2–23%) to BDV [16]. These individuals suffered from a variety of psychiatric syndromes, including affective disorders and schizophrenia, chronic fatigue syndrome or neurological diseases including multiple sclerosis (MS); they also suffered from infections with various other viruses (EBV, HIV) and blood parasites (malaria, schistosomiasis). A small percentage of healthy volunteers and blood donors (1–2%) were also found to be serologically reactive to BDV.

23.2.2

Nucleic Acid

The discovery of antigen- and BDV-specific RNA in peripheral white blood cells (PBMC) [17, 18] was a milestone for human BDV research. This discovery was followed by the recovery of the first BDV isolates [19] in humans. These findings initiated numerous investigations, including the report of the first Japanese isolate from the brain of a schizophrenic patient [20], and it supported a broader worldwide

acceptance of human BDV infection [5]. However, BDV diagnosis in blood has revealed inconsistent results because different groups used heterogeneous methods and markers (antibodies or RNA or both; for reviews see [5, 21]). These inconsistencies have initiated controversial debates in the field. The clinical significance of BDV in humans is still questionable, despite the proven disease association in animals (for review see [7]).

Even after BDV-specific RNA was found in post-mortem brain tissue from psychiatric patients [20, 22–24], criticisms still persist, given the sensitivity problems related to the low replication rate of BDV, and the low number of infected PBMC in blood [25], in addition to the low IF antibody titres. The specificity of human BDV IF antibodies has recently been in doubt [26] but was confirmed later, by the very same group [27]. Prior to the availability of human-specific antibodies, human BDV isolates were thought to be laboratory contaminants [28], which seemed reasonable due to the known low genetic divergence of animal and human BDV [29, 30]. However, those assumptions were wrong [31] with respect to three strains originating from two bipolar and one OCD patients (Section 23.5.1) [19, 30, 31], but recently the isolate described by another German group [32, 33] was found to be a contaminant.

23.2.3

Pathological Antigens and Immune Complexes

In 2001, the discovery of circulating immune complexes (CIC), a product of antigenemia (release of viral proteins into the blood plasma) and host antibodies, resolved the main discrepancies regarding BDV infections [10]. BDV-CIC formation explained the transient disappearance of antibodies and also clarified the crucial aspect of this condition, which was the realization that persistent BDV infection alternates between activated and dormant phases. Activation is characterized by an over-expression of two major structural proteins (N, p40 and P, p24), while replication to form new infectious particles is low, which is quite in contrast to most other viruses [2, 5].

We have suggested that BDV proteins have a relevant role in the disease, because infected rats who show sub-clinical symptoms but have abundant amounts of BDV protein present in structurally normal hippocampal neurons exhibit learning deficiencies [6]. Extensive investigations in the rat model have recently been summarized [8, 34]. They supported evidence that these proteins have the ability to interfere with the function of a non-NMDA glutamate receptor (activated by kainate1) [34]. The presence of BDV proteins in cerebrospinal fluid (CSF) of human patients with recurrent major depression (MDD) in a double-blind study [35] confirmed the presence of BDV replication in human brain. This last data suggest a likely association of BDV infection and symptoms because more than 90% of acutely depressed patients with MDD and bipolar disorder (BP I and II) were positive for BDV-CIC and the severity of depression correlated with high levels of plasma antigen (pAg) [10].

23.2.4

Infection and Disease

CIC have been confirmed to be the predominant markers of BDV infection (see Section 23.3.4). Their detection also disclosed an infection rate of around 30% for asymptomatic carriers; this incidence is about 10-fold higher than that estimated by IF antibody tests. Although the mode(s) of transmission is still elusive, the existence of healthy carriers that represent the majority of BDV infections in humans and animals is key to the basic understanding of both clinical presentations and BDV epidemiology. The prevalence of antigen markers (CIC and pAg) in healthy subjects is significantly different from that among sick patients; thus it is possible that differences in individual risks for virus activation can lead to antigenemia. In addition to a genetic predisposition for MDD and BP (refer to Chapters 29 to 31), psychosocial stress seems to be one of the major factors that could promote such events [36]. Differences in individual vulnerability may account for high or low morbidity risk for BDV infection and lead to approximately 5% of disease relapse among 30% of healthy carriers (Figure 23.1). These facts do not imply that BDV is the only cause of “limbic system disorders” such as MDD or BP, but they suggest that this viral infection represents a major factor that triggers the disease in vulnerable individuals within a multi-factorial scenario of disease-promoting events [37, 38] (Figure 23.2; see Section 23.4.3).

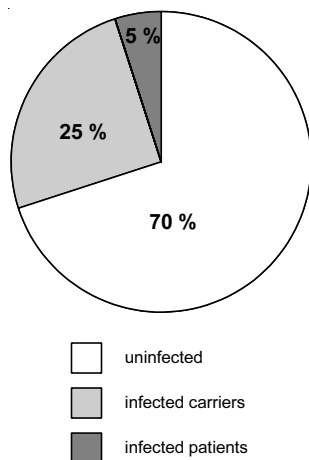


Figure 23.1 Assessment of the prevalence of silent and symptomatic human BDV infections. Data are based on the screening of randomized sets of blood samples for BDV-specific CICs (circulating immune complexes). Of infected subjects, the majority are healthy carriers (25%, gray segment) with low CIC levels, versus a vulnerable minority (5%, black segment), presenting with elevated CIC levels and clinical symptoms (e.g. depression). (For details see Sections 23.2.4, 23.3.2, 23.4.1 and 23.4.2.)

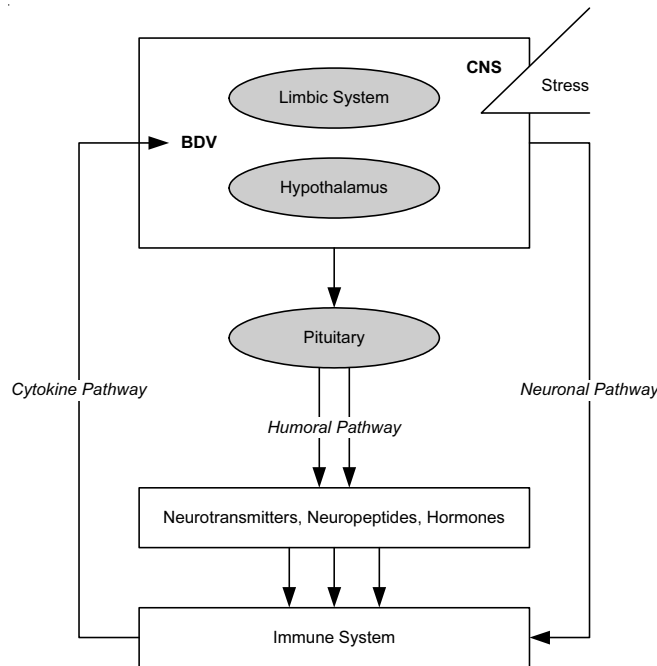


Figure 23.2 Model of viro-psycho-immunological interactions in symptomatic BDV infection. Illustration of how BDV may contribute to a subtype of affective disorder within interdependent reactions of host-determined factors. (For details see Section 23.4.3; figure modified from [37].)

23.2.5 Therapy

Our discovery that antiviral treatment can result in amelioration of depressive symptoms has provided important information that strongly supports a link between BDV and depression [11]. During the course of this line of investigation, amantadine sulfate was shown to be very effective in one case of therapy-resistant depression in bipolar disorder and in the prevention of infection with human BDV *in vitro*, as well as in the inhibition of replication in infected cell cultures [11]. Again, controversies emerged because the *in vitro* efficacy of amantadine against BDV was difficult to replicate in laboratory strains of BDV [39–41]. In contrast to wild-type BDV of human or equine origin, laboratory strains were found to be resistant to amantadine [5, 7, 42] (see Section 23.5.2).

The unexpected finding that amantadine is efficacious in the treatment of depressed patients infected by BDV was further substantiated by two open trials [12, 13]. The history of human BDV infections and their particular psychiatric manifestations can be compared with previous data which confirmed the pathogenicity of this virus in animals. Extensive reviews have summarized the broad

spectrum of BDV infections in animal species [7, 43–45] and have highlighted analogies with current knowledge regarding human infections [5, 16].

This enveloped virus has a non-segmented, single and negative-stranded RNA and replicates in the nucleus where it activates a complex splicing mechanism. With regard to the taxonomic classification of Bornavirus, it has recently been assigned to its own family, *Bornaviridae*, within the order *Mononegavirales*. This order includes several other neurotropic viruses, such as rabies, measles, and canine distemper virus [4]. The unique feature of the non-cytopathogenic Bornavirus is its ability to cause persistent CNS infection [2].

The study of natural BDV infections in animals (with and without the manifestation of disease) and their diagnosis provides valuable information which can be applied to humans. Extensive studies of experimental infections in animals as model systems will be discussed below (see Section 23.6) in relation to the human patient.

23.3

Properties of the Virus and Diagnosis

23.3.1

Virus Components

About a decade ago, electron microscopy studies of purified virus preparations from cell culture supernatants revealed BDV to exist as icosahedral particles of 90 and 50–60 nm in size [46]. The BDV virion is enveloped and therefore, its infectivity can be rapidly destroyed by disinfectants containing organic solvents, detergents, chlorine or formaldehyde. Viral RNA is also sensitive to ultraviolet irradiation and heat treatment (3 days at 56 °C) [2].

The viral genome consists of a linear non-segmented single-stranded RNA of 8.915 kilobases (kb) with negative polarity [47, 48], and its replication is similar to that of other members of the order *Mononegavirales*. However, two outstanding differences in the replication process, namely nuclear (instead of cytoplasmic) replication and multiple splicing, have led to the establishment of a new family, the *Bornaviridae* family, of which Bornavirus is the sole member at the present time. Genomic RNA strands with positive and negative polarities are present in the cell nucleus, where transcription and replication occur [4]. The BDV genome encodes at least six open reading frames (ORF = genes) which start from the 3' end: N (nucleoprotein), P (phosphoprotein), X (p10-protein), M (matrix protein), G (glycoprotein), and L (large polymerase). All of these genes are highly conserved (< 5% divergence at the nucleotide level) [47, 48], which suggests a long period of evolution.

In infected hosts, the proteins N, P, M, and G are the basis for the antigenicity of BDV, but N and P play the principal role. The N protein is expressed early during the infectious cycle, and exists in two isoforms (38/40 kDa) [49]. This protein covers and protects the RNA, probably in conjunction with the P protein (24 kDa) and the L polymerase. Ribonucleoproteins (RNPs) have been isolated from cell nuclei and

have been shown to be infectious [50]. Prior to the availability of genetic data, a protein complex known as the “s (soluble)-antigen”, formed by the N and P protein, was found to be abundant in supernatants obtained from brain cells of infected animals or tissue culture preparations [2]. As previously mentioned, these two proteins are the major antigenic components which play a key role in the diagnosis of an infection; they also contribute to the unique pathogenicity of the virus [5].

23.3.2

Virus Properties

BDV preferentially targets limbic system neurons, but it can also infect other cells inside (glial cells, astrocytes) [8] and outside the brain (at least PBMC in blood) [17, 18]. Furthermore, BDV has an unusually broad spectrum of hosts, which covers a wide variety of mammalian and avian species (Figure 23.3) [2, 7]. Viral persistence that most probably lasts throughout the life-span of the host, is achieved with the help of several effective immune-escape strategies: (a) non-cytopathogenicity (no structural cell loss), (b) restricted reactivation most likely controlled by variations in host vulnerability, (c) low replication rates (producing low numbers of infectious particles) and over-expression of core proteins N and P, which elicit no protective host immunity, and (d) production of very low amounts of functional glycoprotein G, thereby avoiding any relevant virus-neutralizing antibody capacity of the host

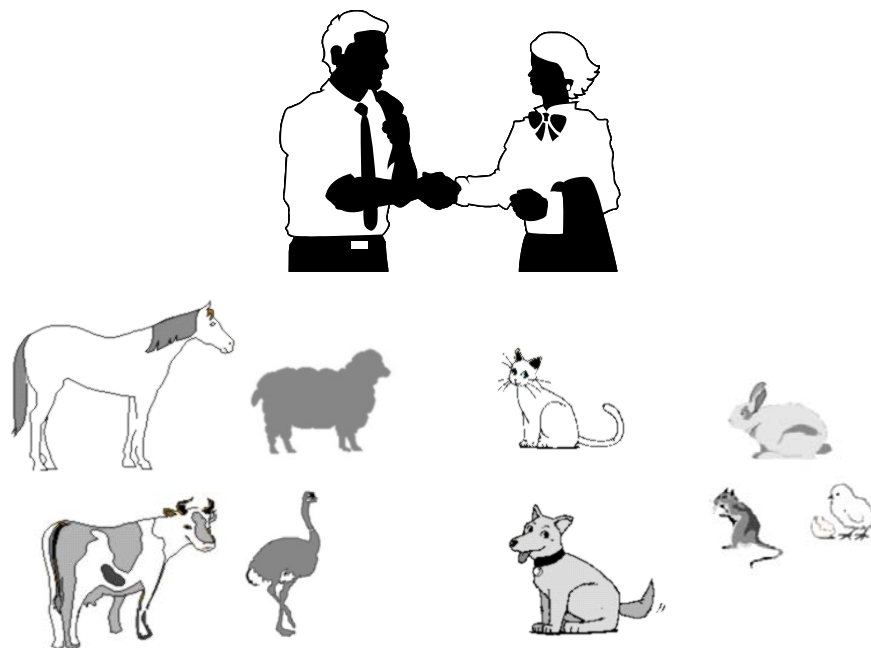


Figure 23.3 Host spectrum of BDV: relevant host species in natural and experimental infections. (For details see Sections 23.3, 23.4, 23.6.)

[5, 51]. Together, these strategies result in relatively low pathogenicity, which would promote a fairly high infection prevalence of 30% (recently estimated based on positive CIC test) in healthy humans [10]. The prevalence rates are even higher among randomly selected horses from different geographic areas in Germany [7]. Based on elevated antigen levels (antigen/CIC) in plasma that reflect a higher frequency and/or longer duration of virus activity phases (Figure 23.1), approximately 5% of the human population appear to have an elevated morbidity risk. Intriguingly, the percentage of high-risk individuals in the population (5%), matches the worldwide prevalence of MDD [3, 52].

23.3.3

Pathogenic Proteins

The presence of antibodies against the N and P protein complex (anti-s-antigen) in the blood of human psychiatric patients marked the first indication of human infection 20 years ago (for a review see [16]). Detection of these antibodies was first achieved using immune fluorescence (IF) and the technique is still widely used today. However, we have recently developed reliable sensitive assays that can detect disease-relevant infection markers such as BDV antigen (N/P proteins), in human (and animal) blood (for review see [5]). These assays have been successfully used in PBMCs (cAg) [17, 18], plasma (pAg) and immune complexes (CIC) [10].

The pathogenic significance of one of these antigens was independently and directly demonstrated in non-infected transgenic mice in 2003. These mice showed distinct behavioral and neurotransmitter alterations based solely on the expression of BDV P protein in glial cells in the absence of cell damage [53]. This experimental finding supported the concept that the primary pathological mechanism used by the virus is located in the brain, which is consistent with the non-cytopathogenic properties of the agent, periodicity, and type of symptoms (at least in mood disorders). Our concept considers functional (instead of structural) disturbances of brain neurotransmitter circuits either by direct or indirect interference of N/P proteins (or their components) with neurotransmitter receptor sites, thereby changing and/or modulating their sensitive balance [5, 8, 7, 19, 34, 37]. Experimental data obtained using persistently infected rats that displayed cognitive deficits, have suggested the involvement of a non-NMDA glutamate receptor (activated by kainate-1) [34] (see Section 23.4.3).

23.3.4

Virus Markers and Assays for Diagnosis

Detection of viral proteins is the main priority for the conclusive diagnosis of BDV infection. They are useful in the determination of antigen load in symptomatic patients, and they can also be used to monitor the therapeutic efficacy of treatments. We became pioneers in applying this approach and developing easy-to-use versatile assays in standardized format (enzyme immune assays [EIA]). These assays monitor the relevant proteins that appear during a period of virus activity. The assays target

N and P proteins, which are abundantly produced by PBMCs (cAg) and other cells/organs in the body; these proteins are finally released into the bloodstream (pAg), and circulate as N/P complexes supposedly bound to host transport proteins. Plasma antigens will induce antibodies (Ab) and form circulating immune complexes (CIC); the latter predominate as a result of this dynamic process [10]. Our “triple-EIA” system detects CIC, but also free pAg and antibodies, and thus provides a reliable method to determine the presence of infection even if antigenemia is absent or present only at a very low level (Figure 23.4).

In 2002, competitive groups in Germany evaluated this versatile and novel BDV triple-EIA. In a workshop held at the Robert Koch Institute in Berlin, this test was found to be reproducible, robust, and easy to handle. Meanwhile, investigators in other countries have successfully applied this system to the determination of infection prevalence and the study of patients (Australia, Italy, UK, Czech Republic) in collaborative projects. Our own laboratories have evaluated the sensitivity and specificity of these assays over the past 8 years (20,000 samples; 2/3 human, 1/3 horses and other animals) [5, 7]. The specificity of such tests is, of course, crucial and should be carefully controlled. Two monoclonal antibodies (W1 against N; Kfu2 against P) [54] have shown their extraordinarily high quality in terms of both specificity and sensitivity, because they have high binding capacities to the native conformation of N and P protein [10, 42]. These assays are described in full detail

BDV triple-EIA: flow diagram for diagnosis

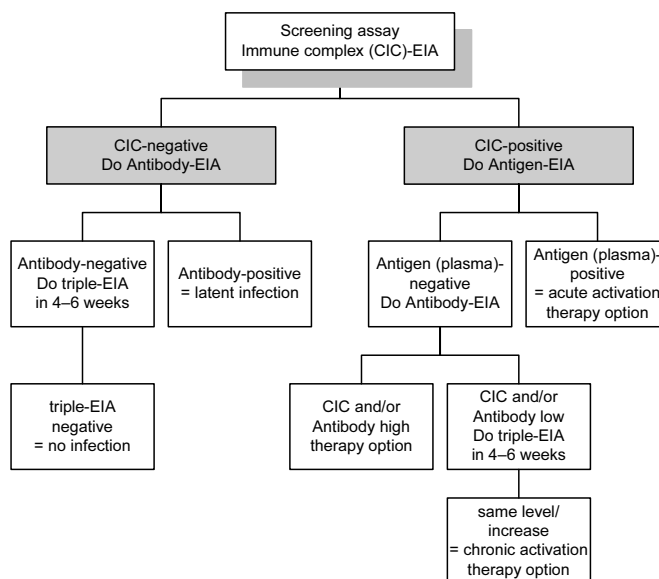


Figure 23.4 Diagnosis of BDV infection in blood with an enzyme immune assay (EIA) system. Flow diagram illustrating how monitoring of antibodies, immune complexes (CIC) and antigens facilitates the identification of positive individuals and disease- and therapy-relevant antigen/CIC load.

elsewhere [10]. In addition to what has already been published, the mapping of epitopes on the N and P proteins of natural antibodies has confirmed the specificity of the EIA and its superiority to the widely used IF technique [5].

Nevertheless, BDV infection studies in human subjects as well as in animals, still rely on several methods and infection markers which are too insensitive and/or do not relate to the disease. We were the first to amplify BDV nucleic acid from PBMC of patients [18] spearheading worldwide studies (for reviews see [7, 21]). However, we do not recommend RNA detection (by RT-PCR) in PBMC as the best diagnostic tool. RNA detection is less reliable than the detection of antigens due to the low replication of this virus [25]. However, as BDV genome sequences have been published and are easily and widely accessible, RNA detection assays can be easily implemented. Several studies showed a lack of correlation between IF-antibodies and RNA-positive cells (for a review see [5]). This issue can now be explained because CIC formation accounts for the decline of antibodies in plasma. But this discrepancy adds to the ongoing controversies in this field, thus investigators who have consistently doubted the existence of BDV infections in humans continue to avoid considering their potential clinical impact [26, 28, 55].

Current systems used for the detection of BDV infection have recently been summarized [7]; a comparative ranking of the value of these techniques was undertaken to provide a guide for psychiatrists, patients and those who are engaged in the study of this viral infection [5]. To date our assays offer a clear answer to the following questions: (1) is the patient infected? (2) Is the infection active? (3) How intense is the antigen/CIC load? As detailed below (Section 23.5), the possibility of an infection contributing to MDD pathophysiology could provide a new antiviral therapeutic option for patients who suffer from a relapsing mood disorder.

23.4

Relationship of the Virus to Major Mood Disorders

The etiologic relationship between BDV and human disease remains the key issue to be clarified in BDV research. An important, if not inevitable prerequisite, for any clinical approach is to consider that the majority of infected individuals are healthy carriers. However, the evidence which supports the discovery and validation of human infections has focused much more on patients than normal subjects. Initial reports focused on the detection of antibodies in large patient cohorts that included those with psychiatric disorders (for a review see [16]); subsequent reports have focused on the detection of antigen [17] and nucleic acid in PBMCs of patients with mood disorders [18] and schizophrenia (for reviews see [5, 21]). Viruses have been isolated from PBMCs [19] and post-mortem brain tissue [20]. BDV RNA has been detected in brain bank samples of psychiatric patients [22, 23] and BDV antigens have been found in the CSF of depressed patients [35]. Recent studies report the presence of CIC and antigenemia in the plasma of MDD and BP patients [10].

23.4.1

Healthy Carriers

Prior to the realization that CIC are the predominant markers of BDV infection in the blood, it was unfeasible to obtain an accurate prevalence rate of this infection in healthy people. A prevalence rate of 0 to 2–3% was reported in studies that used detection of IF antibodies as an indication of infection (for a review see [16]), and studies which used RNA detection in PBMCs, reported prevalence rates between 0 and 4–5%. However this data could not be substantiated in corresponding samples, using these two markers [7, 21]. Although in the majority of studies, the frequency of antibody- and/or RNA-positive samples obtained from psychiatric patients was higher than that from healthy subjects [16, 21, 55, 56], the lack of concordance in prevalence data promoted controversies about the clinical role of this virus. Thus, studies focusing solely on BDV antibodies and RNA have “muddied the waters”, because the absence of serum antibodies or of RNA in PBMCs cannot exclude infection, as antibodies may bind to plasma antigen forming CICs [10], and RNA may be present in only one per 10^5 PBMCs [25]. Unlike viral antigens and CIC, free antibodies and (PBMC) RNA have no meaning in terms of identifying a currently active infection state. Antibodies, if found alone, may only indicate a dormant state or previous infection [5]. As mentioned earlier, the introduction of CICs revealed a substantially higher prevalence of infection (20–30%) in people with no clinical signs.

23.4.2

Patients with Affective Disorders

A high prevalence of healthy carriers would imply that the agent has relatively low pathogenicity, and this would suggest little or no morbidity risk for the majority of infections. This is in line with the finding of a prevalence rate of about 100% in patients with MDD or BP who presented with an acute episode of depression (Figure 23.5), thus supporting a link between infection and disease symptoms. According to WHO data [52], MDD has a worldwide lifetime prevalence of at least 5%. In summary, prevalence data based on the assessment of CIC levels indicated significant differences between healthy carriers and sick patients. The levels of antigenemia, as measured by pAg and CIC levels, during an acute depression episode correlate with the severity of symptoms (Figure 23.5).

In such patients, persistent BDV infection is characterized by a significant level of markers of viral activity (pAg and CIC), while in the majority of healthy infected subjects, only low levels of CIC, with or without free antibodies, have been documented. A small proportion (about 4–5%) of silent carriers, however, exhibited elevated CIC and/or pAg levels in independent cross-sectional studies [5]. Due to data protection (in the case of anonymized samples from blood donors) access to clinical records and follow-up investigations was not possible in some studies. Nevertheless, this 5% prevalence intriguingly mirrors the prevalence of MDD; therefore, these patients could be considered to have an elevated risk of morbidity.

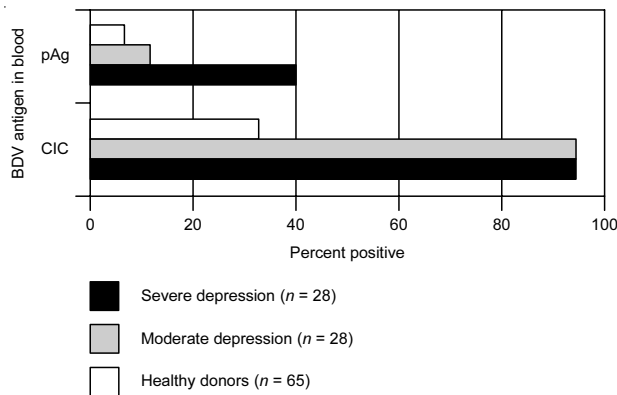


Figure 23.5 Prevalence of BDV antigenemia in acutely depressed patients vs. healthy carriers. Patients with Major Depressive Disorder (MDD) or Bipolar disorder (BP I and II) differed significantly from healthy infected subjects in terms of both infection prevalence (> 90 vs. 30%) and virus antigen load (CIC, immune complexes; pAg, plasma antigen), when their blood was tested during an acute episode. (For details see Section 23.4; figure modified from [5].)

The main significant difference between infected individuals who stay healthy, and infected individuals who become symptomatic, seems to be related to the level of antigen production by the virus, which results in a different prevalence of CIC. Evidence which supports an etiologic role for BDV in mood disorders is presently based on the following findings (for a review see [5]):

1. Temporal relationship of BDV infection markers and symptomatic episode [10, 18]
2. Frequent presence of antigenemia (CIC and/or pAg) in acute depression [5, 10]
3. Strength/duration of antigenemia correlating with severity of acute symptoms [10]
4. Isolation of virus from PBMCs of severely sick patients with high antigenemia [19]
5. Correlation of BDV activation and elevated stress hormone levels in acute depression [36]
6. Long-term benefit of antiviral treatment in infected depressed patients [11–13] (details in Section 23.5)
7. Analogies in clinical and virological parameters between infected animals and humans [7] (details in Section 23.6).

23.4.3

Concept of a Link between BDV and Affective Disorders

The possibility of a significant contribution of an infectious agent to the pathogenesis of affective and other neuropsychiatric disorders implies a change of paradigm,

and requires the consideration of other infection-associated factors, especially immune defense mechanisms because they are the first line of defense. Empirical evidence suggests that there are alterations in immune functions in subgroups of mentally-ill patients; these alterations may lead to activation or suppression of the immune system. The following interdependent possibilities should be considered in the etiology of mental disorders:

- Immune system alterations may occur as a result of stress
- Neuroendocrine and humoral functions may be altered in neuropsychiatric (e.g. depressive) patients due to genetic factors
- Different viruses, particularly BDV, may be activated by alterations in the immune system (as a result of stress)
- Viral infections may directly interfere with psychiatric diseases

In line with previous concepts [5, 10, 19, 37, 38] we hypothesize that BDV, due to its unique properties, is supposedly the only virus that satisfies the above profile, provided that the individual host is vulnerable to frequent viral attacks by reason of his inherent genetic make-up and levels of stress; this in turn, may directly contribute to the frequency, severity, and duration of affective episodes, or other neuropsychiatric disorders. This concept integrates host and virus factors as interdependent contributors in a spiral-event cascade which eventually, after reaching an individual threshold, leads to overt clinical symptoms. Once the cycle has started, the source of the initial signal, either the host or virus, becomes less relevant given their close interdependence.

A scheme of possible events for a subtype of affective disorder is detailed above [37] (Figure 23.2). We propose that the initial step in our model is the presence of acute and chronic stressors [57] which causes alterations in the immune system via neuronal and humoral pathways which then induce a new clinical episode (and involve neurotransmitters, neuropeptides, and hormones). Second, altered immune functions may be responsible for the reactivation of persistent BDV in limbic structures. Activation of a persistent virus, particularly as a consequence of immune deficiency is known to occur with several other neurotropic viruses, e.g. herpes viruses [58, 59], but unlike BDV infection, these viruses cause cell damage and encephalitis. Third, BDV activation in limbic structures which involves over-expression of structural core proteins N and P may disrupt neurotransmitter system circuits. They may be influenced directly, due to the affinity of BDV for glutamate and aspartate receptors [8, 34] or indirectly, via immune mediators, namely cytokines [60, 61]. A secondary reaction of the immune system following virus activation may occur and lead to immunological signs of an inflammatory reaction [62]. Furthermore, changes in limbic neurotransmitter systems may also influence information processing by serotonergic and dopaminergic pathways. Direct interference of BDV with these systems may also be possible. This cascade of events would finally culminate in a major imbalance of neurotransmitter systems, which may be responsible for the various neurobehavioral changes observed in psychiatric disorders. Once such a disorder has been established, it may indirectly influence

the immune system via neuronal and humoral pathways and could lead to further activation of BDV, thereby promoting relapsing episodes. Moreover, these mechanisms may initiate a cycle of disruption of psychosocial, immunological, virological, and neuroendocrine factors that would synergistically influence the complex disease process.

23.4.4

Impact on the Chronic Courses of Depression

After several acute episodes, many patients run into a chronic course of the disease that either does not respond or responds only partially to antidepressants. This phenomenon represents one of the most serious complications of recurrent MDD and BP and cannot be explained by popular theories. The introduction of BDV infection as a major contributor to these types of disorder provides two quite plausible reasons for the chronic course of the illness. One reason is that every relapse will be accompanied by an antigen production cycle and it may well be that despite recovery from the first episodes, antigen residues still remain in the central nervous system, and may therefore accumulate from one cycle to another. Indeed, biochemical analysis has revealed that BDV N and P proteins are quite resistant to cleavage. In addition, it is not known how these proteins are marked for apoptosis in surviving cells such as neurons. The other reason for the establishment of a chronic course of illness may relate to the parallel host adaptation processes. It is likely that the total absence of BDV proteins is not crucial for staying healthy, but the threshold level of antigen required for disease manifestation may vary between individuals. This threshold may change according to the number of relapses. Chronically depressed patients generally have low CIC and/or pAg levels (Figure 23.6) in contrast to those patients who still have an episodic course of disease (compare with Figure 23.5). An adaptation process occurring during multiple

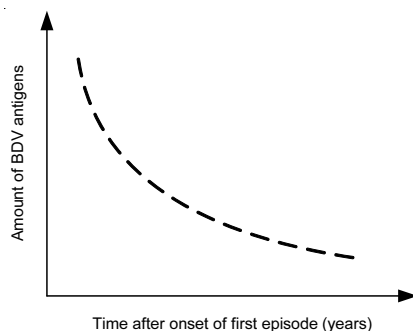


Figure 23.6 Decrease in BDV antigen load with number of episodes. In patients with chronic depression, it has frequently been observed that there is a reverse correlation of pathological proteins with previous episodes of depression and severity of symptoms, suggesting an increasing sensitivity to virus proteins with time. (For details see Section 23.4.4.)

activation cycles would explain this surprising finding, which may eventually lead to the disease becoming evident at a lower threshold level of antigen residue i.e. increased sensitivity to the antigen. As a plausible consequence, each clinical episode may be initiated by lower antigen levels than the previous episode, eventually resulting in a chronically low level of both maintaining CICs and symptoms.

23.4.5

Other “Limbic Disorders”

As mentioned earlier, clinical studies have focused mainly on major affective disorders and schizophrenia. In contrast with the body of evidence for recurrent depression, the lack of clinical sub-typing and methodological limitations has prevented the establishment of a relationship between schizophrenia and BDV [21, 56].

The above viral disease model (Figure 23.2), which suggests that the central process of the disease focuses on interference/modulation of the monoamine neurotransmitter system by BDV proteins, supports the hypothesis that several functional limbic system disorders may be associated with this infection. Thus, depending upon the respective structure that is affected by BDV (e.g. hippocampus and/or amygdala) and their multiple projections to associative cortical areas, a range of behavioral changes may be manifested, which include alterations in mood and interest, obsessive thoughts and compulsions, as well as attention deficit and anxiety. Although these emotional and cognitive changes are categorized into different clinical disorders, they seem to have in common disturbed inhibitory or excitatory neurotransmitter circuits between the limbic system and cortical areas (particularly

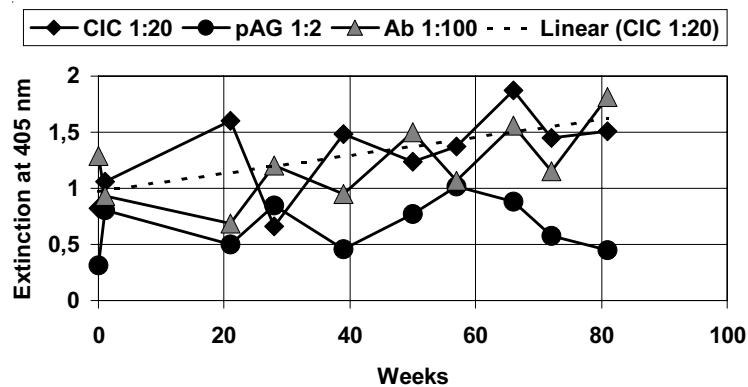


Figure 23.7 Chronic BDV antigenemia in a patient with severe obsessive-compulsive disorder (OCD). A 20-months follow-up blood monitoring in a chronically symptomatic OCD patient (male, age 26 years), indicated chronically activated infection and the maintenance of high values of immune complexes (CIC), plasma antigen (pAg), and antibodies (extinction at the indicated dilutions). (For details see Section 23.4.5.)

the ventro-medial part of the pre-frontal cortex). In this respect, it may not be so speculative to consider BDV as the unifying link between conditions that affect mainly cognitive functions that are emotionally controlled.

We have recently studied patients with obsessive-compulsive disorder (OCD), a proportion of whom presented with secondary depression [63]. We not only found a considerable prevalence of infection, but longitudinal investigations revealed enduring antigenemia (CIC and pAg) which paralleled the severe chronic course of OCD, indicating a chronically productive state of infection (Figure 23.7).

Interestingly, recent findings from event-related potentials (ERP) in BDV-infected OCD patients demonstrated a significant correlation between pathological changes in information processing and BDV antigen load (CICs) in the blood. This represents the first clinical finding suggesting that BDV infection can cause cognitive changes in human patients.

23.5

Antiviral Treatment

23.5.1

History and Controversies

The concept of an infectious etiology or an infectious contribution to mood disorders may provide new therapeutic approaches, namely the introduction of antiviral therapy. In the 1920s researchers in France used hexamethylenetetramine (hexamine) with some success for the treatment of horses with Borna disease [64]. Our group was the first to report an *in vitro* and *in vivo* antiviral effect of amantadine sulfate (a chemical relative of hexamine) against a human BDV isolate. A severely depressed bipolar patient infected with BDV improved dramatically under low-dose amantadine therapy, the course of improvement for that patient paralleled the disappearance of viral markers in the blood [11]. Amantadine is a well-known drug that has been used for 30 years; it was initially licensed to treat influenza-A virus infections [65], and it is now mainly prescribed for Parkinson's disease.

The novel finding that an antiviral treatment against BDV also had an antidepressant effect supports the hypothesis of a link between the virus and affective disorders, and has initiated debates both in psychiatry and virology. Psychiatrists have questioned whether the antidepressant efficacy of amantadine is associated with its antiviral properties, since this versatile compound is also known to have certain amphetamine-like, NMDA-receptor antagonistic, and other psycho-pharmacological effects (for a review see [66]). However, even if these properties do contribute to the improvement in symptoms, the decrease in BDV activity markers in patients who show a clinical response, as documented in several trials, cannot be ignored (see Section 23.5.3). Virologists in the field have hastily questioned our discovery, as there are *in vitro* studies that report a lack of antiviral efficacy with amantadine treatment [39–41]. However, it should be pointed out that these studies are not comparable to our study since they used BDV laboratory strains while we

used only wild-type human isolates [11] and laboratory strains are known to become highly adapted after multiple *in vivo* and *in vitro* cross-species passages [2, 51, 54].

23.5.2

Amantadine Studies In Vitro and Human Isolates

No genetically-defined wild-type virus existed until the mid-1990s; laboratory strains of BDV [2] were sequenced in 1994 [47, 48], and a few horse isolates had been previously identified [67]. A concerted effort was necessary to obtain the first four human isolates. The sources for these isolates were PBMCs from two bipolar (Hu-H1, Hu-H3), one obsessive-compulsive disorder (Hu-H2), and one (American) chronic fatigue syndrome (Hu-HUSA1) patient [19]. Virus could only be recovered from individuals during severe and lasting phases of major mood disorders, who exhibited a significant antigen load in the blood cells. Moreover, at least 10 blind passages in human oligodendria (OL) cells used for co-cultivation were required to allow adaptation to the tissue culture system. This may explain, why only six human isolates have been described so far, the sixth being recovered from the brain of a Japanese schizophrenic patient [20].

Unfortunately, the fifth isolate, which was obtained from granulocytes of a schizophrenic patient [32] has recently been withdrawn by the authors due to contamination problems [33]. Nevertheless, the contentious issue of contamination due to the divergence of laboratory strains [28] has been found to have no foundation in practice [31] (except for [32]). Human BDV strains are closely related to animal strains [29], and differ genetically from each other and animal strains only by unique point mutations in several genes [19, 30]. Biologically, however, they induce a different syndrome in rabbits [19], and also show a different sensitivity to amantadine

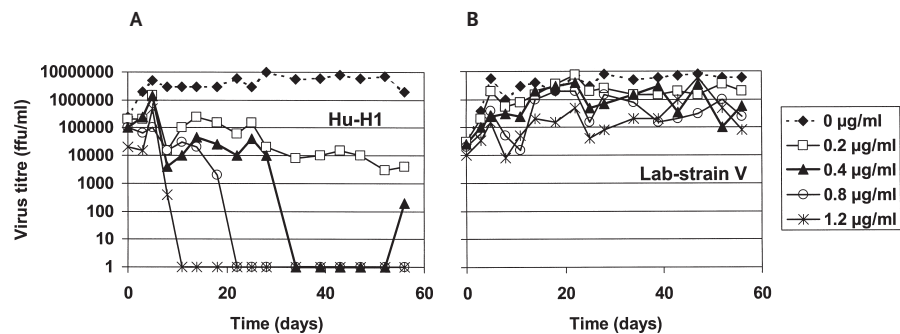


Figure 23.8 *In vitro* dose response studies using antiviral treatment (amantadine sulfate; AS) of different BDV strains. Human oligodendroglia cells persistently infected either with human isolate Hu-H1 (A) or laboratory strain V (B) were kept under different doses of 0 to 1.2 µg AS, and remaining virus titers were determined at indicated time-points. Note: dose- and time-dependent drop of infectious virus only in case of Hu-H1, but not in case of Lab-strain V. (For details see Section 23.5.2; for methods see refs. [11] and [5].)

[5, 42]. Their authenticity as human strains has undisputedly been proven by sequence identity of the original PBMC source and corresponding isolate [30].

There are numerous examples in other systems showing that one or a few mutations may cause significant phenotype variations that alter the characteristics of the virus [68]. This may also explain the remarkable difference in response to amantadine of wild-type and laboratory strains, not only with regard to the described inhibition-of-replication effects [5] (Figure 23.8), but also to the prevention-of-infection [11, 42]. The ID_{50} (50% infection-inhibitory dose) of the most sensitive human strain differs by 6 \log_{10} units from that of a resistant laboratory strain [42].

23.5.3

Amantadine in Clinical Trials

Although the molecular mechanisms of viral inhibition and its putative mutations are still unknown, the *in vitro* efficacy of amantadine against human BDV has encouraged further clinical trials. The earliest study addressing the effects of amantadine on depression [69] was carried out before it was hypothesized that infection with BDV may be involved; 40 outpatients with a “chronic depressive syndrome” (32 women; mean age 34 years) were treated for 4 weeks. The antidepressant efficacy of amantadine was reported to be superior to placebo, but inferior to amitriptyline. This observation was ignored for more than 25 years, until we reported that amantadine had both antidepressant and antiviral effects in a case report [11].

23.5.3.1 Open Studies

Consequently, the therapeutic benefit of this well-known drug in the treatment of BDV-infected depressive (MDD and BP) patients was further evaluated in two independently conducted open trials (OT). Patients in the OTs were treated daily with a mean oral dose of 200 mg amantadine sulfate (AS) twice a day for a mean of 12 weeks, according to a dosing regimen of 2–4 mg amantadine per kg body weight. An oral dose of 200 mg AS will result in a blood level of the drug of 0.4 $\mu\text{g/ml}$, which corresponds to the concentration found to give *in vitro* efficacy.

The majority of patients showed a significant and rapid clinical response after an average of 3 weeks of treatment [12, 13]. Of the 68% (17/25) responders in the Hanover study [13], 70.6% showed no depression at all, and 29.4% had a > 50% decrease in symptoms, according to the 21-item Hamilton rating scale for depression (HAM-D). Bipolar I (BP I) patients showed a more rapid improvement and did not show any subsequent hypomania. In addition, BP II and MDD patients suffering from a melancholic subtype of depression responded significantly better than patients with evidence of a neurotic or “reactive” type of depression [70].

In the Berlin study [12], 63.3% (19/30) of the patients showed a significant decrease in depressive symptoms, measured by at least a 40% reduction in points on the Montgomery–Asberg Depression Rating Scale (MADRS). Remarkably, this considerable favorable effect of amantadine therapy, comparable to that of the Hanover study, was achieved in patients, who were recruited due to poor or even complete lack of response (17/30 = 56.7%) to any antidepressant for more than 1 year [12].

In both open trials improvement of depressive symptoms tended to parallel the decrease in viral activity, indicating a virus-static effect. No significant adverse effects were observed. In conclusion, the antidepressant efficacy in both OTs was considered to be comparable to standard antidepressants, and likely to be the result of antiviral efficacy against BDV rather than of short-term effects attributable to the psychopharmacological properties of the drug as mentioned above [66]. These results could be substantiated by a meanwhile completed placebo-controlled study [5] with long-term follow-up.

Further evidence of the beneficial use of amantadine may also be taken from studies and case reports of OCD patients infected with BDV [63]. In summary, the presently available data clearly support firstly, the view that infected patients significantly benefit from this drug, and secondly that the clinical response parallels the virus-static efficacy as indicated by a drop in antigen/CIC load in the blood.

At present there is no alternative antiviral compound against BDV which can compete with amantadine. We had earlier shown that a mannose-derivative targeting BDV matrix (M) protein (gp17) inhibited infection *in vitro* [71]. An almost universal antiviral compound, Ribavirin, was reported to interfere with BDV *in vitro*-replication [72, 73], and more recently, the inhibiting effects of Ara-C (1- β -D-arabinofuranosylcytosine) on both replication and virus spread were described [74]. However, even if *in vitro*-effective doses are analogously effective *in vivo*, clinical trials among psychiatric patients with either compound would not be advisable, given the known severe adverse effects of these drugs, in contrast to the well-tolerated drug amantadine.

23.6

Relevance and Role of Animal Models

In general, animal models are important in viral infections in the following cases:

- studies in which human virus had been transmitted to and was studied in animals (e.g. HSV or polio virus)
- etiologic studies in animals, using the human or a similar animal virus, allow insights into the disease processes in human patients by analogy (such as rotaviruses, corona viruses, or HIV), and
- studies in which the virus itself is used as a tool to manipulate and elucidate agent–cell, agent–organ, or agent–organism interactions without relevance to the natural host

BDV has been studied in relation to all three cases, although BDV isolates from human PBMCs have only been transmitted to rabbits by our group [19], and the Japanese brain isolate was only studied in gerbils [20]. Many studies in BDV research fall into the third category, such as those studying eye disease in rabbits [75, 76], brain alterations in monkeys [7], or neurodevelopmental and pharmacological effects in the rat [77–79]. To understand the impact of BDV infection on mood and cognition

one must clearly differentiate between natural and experimental infection. In the former case small amounts of virus enter the animal, and in the latter case an aliquot of brain- or cell culture-adapted virus is inoculated into the animal brain, which would be equivalent to the size and weight of a walnut as compared to the dimensions of the human brain. The significant difference between natural and artificial infection processes has often led to misinterpreted or over-interpreted conclusions.

The spectrum of BDV in nature is unusually broad (Figure 23.3). Host animals include preferentially the horse and ungulates, particularly sheep. Recently cats and dogs have been found to be virus carriers. Any data pertaining to possible viral transmission across the species barrier is based on pure speculation, and these possibilities are, at least in our experience, irrelevant. In addition to rabbits small rodents are also BDV susceptible, although infection can only occur after adaptation of the virus. Rats have served as the animal of choice [2, 7].

23.6.1

Experimental Infections

Many of the conclusions drawn from BDV rat experiments by major American and Japanese research groups, in addition to our own, especially those using variably adapted BDV strains, can be traced back to the pioneering studies of Nitzschke [80]. Basic information using the rat model was independently presented by Narayan's group [82] and our group [81] in 1983, followed by the first fundamental studies on behavioral changes and interference of BDV with learning and cognition [6].

However, it is becoming clear that these subtle emotional changes and learning deficiencies which appear in apparently healthy rats infected with BDV, are not associated with inflammatory reactions or obvious neural damage [6, 81], whereas in Narayan et al.'s study, immune-mediated processes were linked with behavioral abnormalities [82]. These discoveries paved the way for numerous studies in rats, the results of which changed mainstream thinking to include the concept that BDV may influence alterations in normal behavior.

Certainly the neonatal rat has evolved to present an optimal model for studying slight and subtle changes in normal instinctive behavior [2, 6, 78, 79, 83–86]. Similar data were obtained once BDV had been adapted to the mouse [87] with some heterogeneity among different mouse strains [88].

The main features of the vast literature on persistent, tolerant infections in rats, which can be compared to a certain degree with the impact of BDV on mood and cognition in man, are described below, together with the neuropharmacological alterations in the brain.

23.6.1.1 **Neonatal Rat**

Neonatal infection of rats resulted in locomotive hyperactivity, reduced anxiety, and significant deficits in spatial learning and memory [6, 89]. A review of the data reporting reduced resting behavior [6] and restlessness with hyperactivity which

was also observed in infected adult animals such as the tree shrew [90], rhesus monkey [7] and rat [82], revealed a pattern of disturbance to normal movement activity which appeared to be a prominent feature of infection. Quantification of this behavior together with exploration behavior in a novel environment by these rats amounted to a 5–10-fold increase in movement activity compared to normal animals [85]. Although the complex BDV antigen pattern which is visible at different times after infection and is characterized by localization of antigen residue in the limbic structures and accumulation of antigen in the Purkinje cells in the cerebellum, cannot completely explain these behavior changes, a reproducible periodical appearance of BDV antigens, first observed by our group, which seems to clear after 3 weeks along with the rostro-caudal progression of the infectious process [2, 8] may provide part of the explanation. These findings which have been replicated by many other groups [82, 85, 91] represent the neuropathological basis which helps to explain the complex modulation of functions controlled by the amygdala and cerebellar structures which result in altered behavior in rats. Vulnerability of the cerebellum in neonatal animals to viral infections has already been described as a characteristic feature [92].

A series of experiments by our group have offered explanations for some of these unusual behaviors in the rat, for example a significant accumulation of BDV antigen in neurons which belong to structures of the limbic system. This has also been observed in natural infections of the horse [67]. Increased amounts of antigen (N and P protein) with characteristic stratified patterns in their basal and apical dendrites were reported to predominate in the hippocampal pyramidal neurons. The antigen appears to have an affinity for excitatory neurotransmitters leaving the inhibitory synapses devoid of antigen [8, 93]. Glutamate and aspartate are the neurotransmitters associated with the synapses of the strata oriens and radiatum which carry the antigen; the other two strata however, have no such affinity. Furthermore, CA3 neurons (carrying antigen) and those of the CA1 region (free of antigen), are both glutamatergic, the major difference being that only the CA3 neurons harbor the non-NMDA (kainate-1; KA-1) receptor. Thus the hypothesis was put forward that KA-1 represents the BDV receptor in the brain [34]. This assumption is supported by the fact that the retina, a tissue that has a high expression of glutamate (KA-1) receptors, is severely affected in several experimentally-infected animal species [7, 75, 82].

23.6.1.2 Dentate Gyrus

The historically early observation in BDV neuropathology [2, 8, 34] of the destruction of granular cells in the dentate gyrus (DG) during the course of infection, may explain some of the characteristic features of learning and memory processes [94]. Several groups have replicated this phenomenon. The disappearance of neurons in this hippocampal structure relates to selective vulnerability and apoptosis [84, 85]. Our group, however, offers a more stringent explanation, which is based on the treatment of infected rats with N-acetyl-cysteine, a known anti-oxidant, which was able to inhibit DG degeneration. The vulnerability of these sensitive neurons to toxic mechanisms which result from the induction of oxidative stress (free oxygen

radicals) followed by destructive processes, was proposed as a plausible explanation for the involvement of DG and is still accepted today [34].

DG damage seems to be of general relevance in BDV infections, because transfer of infected cat brain material to rats induced the same pathological morphology, but lacked virus antigen expression [95].

23.6.1.3 Neurodevelopmental Disorders

Neonatal infection is also considered to be an appropriate model for studying neurodevelopmental disorders. Significant weight (growth) reduction was a prominent feature in sub-clinically but persistently infected mice; the lack of growth became apparent in the first week post infection and these animals were 30% smaller than their control littermates at 15 weeks [87]. Abnormal growth and physiology was also seen in the neonatal rat model, the reasons for which are as yet still unknown [77].

Other outstanding changes that accompany infection include disturbed play behavior [78] and impaired social communication between litters and mother [77], as described in the tree shrew [90]. It has been suggested that the neuropathological basis involves antigen accumulation in neurons or interactions of other infected brain cells located in the amygdala and hippocampus [94]. Neuropathological findings have been presented which led to the suggested explanation of an imbalance in the neurotransmitter equilibrium [8, 34, 93]. Although adult animals were used in the tree shrew model of BDV infection, the alterations in social behavior might fall into the same category as those in neonatal animals and may also be linked to dysfunction in limbic areas [90].

However, in general, animal infection models that display global inflammatory responses like those observed in the adult rat, rabbit, tree shrew, and rhesus monkey are regarded as experimental artifacts with no relevance to the understanding of human infections and their relationship to mood disorders [5, 7, 42]. This view on etiology is essentially shared by Hornig et al. [85].

23.6.1.4 Cytokines

Cytokine research is an important area to consider in the investigation of human infections. It is important to address the following questions: Are there similar changes in cytokine patterns after BDV infection? How can neuroimmunological profiles influence alterations in behavior?

Cytokine gene expression during CNS infection can be predicted by taking into account dysfunctions that occur during inflammatory processes in the body [62]. In BDV-infected neonatal rats the picture is still rather heterogeneous. Altered levels of IL-1 α , IL-1 β , IL-6, TNF- α , and an increase in TGF-1 β with higher levels of Tissue Factor have been reported. Since cytokine mRNAs co-localize with a pathological morphology that indicates a disturbance in the metabolism of astrocytes and glial cells, activation of these cell groups may well correlate with cytokine production [77, 88, 96, 97].

The neuroimmunological profile of BDV-infected neonates still remains obscure. In common with other virus models, changes in Th1- and Th2-type reactivity from

the acute to chronic stages of disease have been postulated [77]. Data concerning the immune reactions of neonates who are also receiving immune-suppressive treatment are questionable, as results relating to the immune reactions in different animal strains have been contradictory [98]. From our basic studies using Wistar rats [81] or different mouse strains [87], it became clear that no cellular immune reaction was observed in the CNS, but a definite humoral response producing antibodies against the major antigenic components (N- and P-protein) together with the considerable production of neutralizing antibodies, was demonstrated during the course of such silent infections. The presence of virus outside the brain, which has also recently been shown to occur in infected humans, might have triggered these immune reactions [5, 8, 81].

23.6.1.5 Neuropharmacology

The original hypothesis that some of the changes in behavior can be linked to the interaction of structural elements of BDV with neurotransmitter receptors [93] has been strengthened by further neuropharmacological investigations [8, 34]. The affinity of BDV for glutamate-neurotransmitter neurons was evidenced by specific antigen co-localization in the limbic structures and in the retina. Furthermore, recent experiments have focused our interest on the importance of the KA-1 (non-NMDA) receptor as a specific protein formation in certain CNS areas, where BDV proteins may contribute to or protect against a selective vulnerability [34].

Additionally, Lipkin's and Solbrig's groups have amassed considerable evidence showing that the dopaminergic and cholinergic system might also be involved in BDV brain pathology, although these systems were mainly studied in the more mature rat brain (see also Table 1 in [79]), and have also discussed in detail the similarities with human psychiatric disorders [79].

A recent review by Solbrig and Koob [86] elegantly summarizes the complexity of neuropharmacological changes and the wealth of new information gained in the field of neuroscience from the study of experimentally-induced infection in the rat. However, any conclusions extrapolated from this data to explain the expression of psychiatric disorders in humans should be regarded with caution [5]. Interpretations of neuropathological and *in situ* hybridization (based on mRNA detection) patterns support the basic view that BDV infection disturbs a neurotransmitter balance in the rat brain [8, 93, 99]. By analogy this may serve as a blueprint for what may be occurring in natural infections of animals and man, but should be used with caution.

23.6.2

Natural Infections

In relation to the topic covered in this chapter of a book which has endeavoured to assemble the biological factors contributing to depression, only BDV-infected horses and cats are of any relevance to the comparison of behavioral changes with the symptoms attributable to BDV infections in human patients (see Section 23.4).

The transmission and infection mechanisms in mammals are most probably similar. The virus can be transmitted horizontally or vertically. Both methods of

transmission can be demonstrated in the horse with a rostro-caudal progression of CNS manifestation. Once the agent has reached its preferred sites in the older areas of the brain and structures of the limbic system, a spectrum of symptoms is expressed, depending on the instinctive behavioral repertoire of the particular animal species (ungulate or carnivore), namely, unusual ear position, trembling of skin areas, lowered head with anxious look in the eyes, sudden drop of performance, lack of drive, apathy and somnolence, head shaking, loss of appetite, colic, and stumbling. Along with the progression of neurological symptoms, mydriasis, paralysis mainly of the hind limbs, circling movements, ataxia, and falling down is the known sequence of events in the course of Borna disease in the horse [2, 7, 43, 83]. In cats a similar repertoire of symptoms has been reported which is characterized by more frequent meowing than usual, anxious mydriatic eyes expressing a staring gaze, and depressive symptoms. Infected animals avoid familiar persons, become shy, stop eating, and often show hyperaesthesia to light and noise. Occasionally the inability to withdraw their claws accompanies the increase in neurological symptoms [7, 95]. It is of interest that experimentally-infected cats only showed mild symptoms and recovered with no significant overt residual symptoms [100].

Importantly, in both these mammals (horse, cat), Borna disease presents mainly with mild to moderate behavioral changes which may become more severe, and in rare cases, lead to severe neurological disease and death. This undoubtedly represents an etiopathogenetic sequence caused by the persistence of the virus in selected limbic areas. Moreover, recent studies in horses have considerably changed the previous opinion that the outcome of Borna disease is always fatal, because many clinical cases presented as transient episodes with spontaneous remission. As in human patients with affective disorders, symptomatic phases were paralleled by antigenemia (pAg, CIC) in the blood [5, 7, 10]. Interestingly, amantadine treatment using the same dose range as that for human patients (2–4 mg per kg body weight), was similarly effective and well tolerated. Silent carriers are also prevalent among the horse population, and their percentage in the population may even be twice that estimated for the prevalence of silent carriers in the human population, thus can be as high as 60%; this novel finding has been facilitated by the determination of CICs in blood, and is in contrast to previous textbook information [43–45]. Thus, naturally-infected animals are supposedly a better guide for the comparative study of BDV infection and disease in humans than are experimental studies conducted on small rodents, as there is already a large literature base relating to natural infections in animals.

23.6.3

Critical Review of Animal Models

As a result of investigations spanning several decades [2, 5, 10, 18, 19, 83, 90, 101], we have now learned that the vast majority of efforts to study BDV infection in experimental animals have failed with respect to the elucidation of the mechanism of infection in the human patient. Unfortunately, they have misled our group and

most other groups in this field. In our opinion, some of the data has been very misleading, particularly the immune pathology data which endeavored to clarify the causal link between BDV and psychiatric disease.

These facts are summarized below:

- Age, virus strain passages, and immunological competence of the experimental animals clearly determine disease mechanisms and outcome [7]. For example, in Wistar rats two to three more passages of the adapted virus in rat brain tissues changed the neonatal symptoms from a persistent, tolerant infection into a dramatic sub-acute disease (see Figure 12 in [83]). Neuropathological analyses of these animals showed no immune pathological signs, but distinct cytopathological alterations in the brain (see Figure 14 in [8]). Similar observations were recently reported in gerbils infected during the neonatal period [102]. The response of different strains of rat (Wistar, Lewis, Black Hooded, Fischer etc.) to varying numbers of passages of Borna virus has yet to be defined.
- Animal models showing inflammatory reactions are seemingly irrelevant in relation to an explanation of BDV-specific pathogenesis in humans. We have over-interpreted the tree shrew model for the human patient, because several tree shrews living for a number of years without overt symptoms, were found to have severe neuropathological inflammatory reactions [7, 90]. The same is true for the experimental cat model. In this case persistently infected animals recovered from the early slight behavioral alterations, but were found to have considerable infiltrations of lymphocytes in the brain [100]. Furthermore, it is known that horses dying from Borna disease may or may not have inflammatory reactions. We assume that the virus infection, for unknown reasons, may run an unrestricted course, thereby inducing an overflow of antigen production in the brain, which could finally lead to fatal brain dysfunction. This leaves immune pathology as a secondary event that is unlikely to be a driving force behind the behavioral changes, and which may play no part in the fatal outcome resulting from a severe course of natural Borna disease; these views however, are contradictory to the general assessment of immune pathological events published by other scientists [98].
- The use of the wrong BDV strain (laboratory instead of wild-type) in *in vitro* inhibition assays [39, 40, 41] was sufficient to lead to an unfortunate setback and confusion in the use of amantadine against BDV infection, despite encouraging clinical studies with antidepressive and virus-static effectiveness, the details of which are discussed in Section 23.5.

In conclusion, experimental animal models might be useful in addressing neuroscience problems, but have not helped clarify the complex events associated with BDV infection in humans. The use of intracerebrally-infected animals has given some insight into the etiologic mechanisms of animal infections, but unfortunately these studies are of limited value for elucidating the different infection states in humans, and they cannot explain the different morbidity risks. The theory of mild encephalitis in human patients due to BDV infection [103] has added even more confusion to understanding the pathological mechanisms [7].

23.7

Concepts for future studies and perspectives

Our survey on the broad body of data obtained from persistently sub-clinically infected animals has emphasized the manifold impact of BDV on behavior, mood regulation, and cognition, but has also referred to the often underestimated limitations of animal experiments. In natural animal infections, however, an impressive similarity of infection markers (antigenemia), symptom spectrum, and periodicity could be demonstrated, if horses with (transient) Borna disease and patients with mood disorders are compared [7, 10].

The study of natural infections in animals and humans provided evidence to support, first the concept of BDV as an unique virus that influences mood and cognition in vulnerable individuals of all host species; second, that periodical BDV antigenemia is the likely primary pathogenic factor, and third, that immune complexes and plasma antigen in the blood are suitable markers for monitoring the course of the disease and the efficacy of therapy.

Future studies should address:

- The implementation of a “gold standard” for the diagnosis of infection
- The identification of the spectrum of the pathogenicity of BDV in humans
- The benefit of antiviral treatment in different “limbic system” disorders
- The worldwide prevalence of human infection and morbidity risks of healthy carriers
- The identification of relevant modes of transmission and risk assessment of infected animals as source for human infection

23.7.1

Future Diagnosis

The varying suitability of host and virus components for the determination of BDV infection in blood has been outlined in Sections 23.2 and 23.3. To overcome the present lack of comparability between studies from different research groups, a unifying “gold” standard should be introduced. According to both the pathological significance and predominant prevalence of immune complexes, we consider these markers to be appropriate standards for improving clinical and epidemiological approaches. BDV-specific tools for use in respective triple-EIAs (for detection of CICs) [10] will be made available for research on a collaborative basis as has already been implemented in some cases. In this context, we support multicenter and bilateral studies to further evaluate the assays, as well as participating in regular quality-control monitoring of collaborating laboratories.

Until an internationally accepted “gold” standard can be implemented, we recommend regular screening (at least) of BDV-CICs in clinical samples [5], supplemented by in-house tests of the respective laboratory, namely for antibodies and/or RNA.

23.7.2

Future Clinical Studies

Priority should be given to further investigations into the effectiveness of amantadine among depressed patients, who are either BDV-positive or BDV-negative. A multi-center approach using a double-blind randomized design seems appropriate for enrolling a larger number of patients as compared to previous studies. Furthermore, the use of multivariate analyses for repeated measures of BDV markers and standard depression inventories would allow further evaluation of the influence of infection on the efficacy of amantadine.

In addition to major depression, obsessive-compulsive disorder (OCD) should be a priority for future investigations and therapeutic trials (see Section 23.4.4), as should anxiety disorders, and chronic fatigue syndrome (CFS). Since only a subgroup of OCD patients was found to be infected [63], screening for BDV-CIC facilitates the identification of potential clinical and/or immunological differences between the groups. Added risk factors for BDV infection should be identified and treated.

23.7.3

Epidemiology and Risk Assessment in Carriers

The introduction of CICs for screening healthy individuals revised previous assumptions and revealed that 20–30% of the normal population were carriers (see Sections 23.4.1 and 23.4.2). Future longitudinal studies should investigate randomized cohorts in different countries and continents to obtain representative worldwide prevalence data with regard to carriers. In addition, these studies should address the morbidity risk in different age groups and for those with elevated CIC levels, investigate the potential transmission modes between family members, and finally should assess the potential risk of animal infections; all of these studies should be complemented by standardized questionnaires.

23.7.4

Conclusions and Perspectives

This chapter introduces a unique RNA virus, Borna disease virus (BDV), into biological psychiatry. The presence of persistent BDV infection in the brain and blood of humans and animals is the only evidence which supports the possibility of an infectious etiology in mood disorders and of BDV being the only candidate agent. This view at first seems provocative, but is supported by an intriguing body of correlative evidence which has been amassed so far.

Clinical data obtained from humans and animals fit in the concept that BDV contributes to periodicity and symptoms by transiently disrupting the limbic system–cortical neurotransmitter circuits via its proteins (antigens), as part of a multifactorial cascade of events, which involves both host and virus in an interdependent manner. Virus activation, indicated by the presence of immune complexes and antigens,

can be monitored in blood samples with easy-to-use assays, and similarly, antiviral treatment with the low-risk drug amantadine is apparently effective. However, in contrast to this are controversies that have led to setbacks in human BDV research. This chapter aims to encourage biological psychiatrists who are interested in the fascinating impact of our concept, not to be deterred by these debates which detract attention from the scientific information associated with this complex research issue.

This chapter also aims to provide a guide for medical professionals who are interested in novel therapeutic options, and for patients who are suffering from often therapy-resistant mood disorders and are seeking help. A novel field of research will always provide more questions than answers, and will always have more opponents than advocates. At this point it is important to consider the aspects that cannot be disproved. Regarding the spectrum of properties of BDV and its preferential target cells in a crucial and sensitive area of the brain, both unusual efforts and unconventional approaches will be required to further confirm the impact of this agent on mood and cognition in mankind.

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References

- 1 CUMMINGS, J. L., MEGA, M. S., *Neuropsychiatry and behavioural neuroscience*. Oxford University Press, New York, 2003.
- 2 LUDWIG, H., BODE, L., GOSZTONYI, G., Borna disease: a persistent virus infection of the central nervous system. *Prog. Med. Virol.* 1988, 35, 107–151.
- 3 GOODWIN, F. K., JAMISON, K. R., *Manic-depressive Illness*. Oxford University Press, New York, 1990.
- 4 DE LA TORRE, J. C., BODE, L., CARBONE, K. M., DIETZSCHOLD, B., IKUTA, K., LIPKIN, W. I., LUDWIG, H., RICHT, J. A., STAEHEL, P., STITZ, L., Family *Borna-viridae*. In VAN REGENMORTEL, M. H. V., FAUQUET, C. M., BISHOP, D. H. L. (Eds.), *Virus Taxonomy*, Academic Press, London, 2000, 531–538.
- 5 BODE, L., LUDWIG, H., Borna disease virus infection, a human mental-health risk. *Clin. Microbiol. Rev.* 2003, 16, 534–545.
- 6 DITTRICH, W., BODE, L., LUDWIG, H., KAO, M., SCHNEIDER, K., Learning deficiencies in Borna disease virus-infected but clinically healthy rats. *Biol. Psychiatry* 1989, 26, 818–828.
- 7 LUDWIG, H., BODE, L., Borna disease virus: new aspects on infection, disease, diagnosis and epidemiology. *Rev. sci. tech. Off. int. Epiz.* 2000, 19, 259–288.

- 8 GOSZTONYI, G., LUDWIG, H., Borna disease – neuropathology and pathogenesis. *Curr. Top. Microbiol. Immunol.* **1995**, *190*, 39–73.
- 9 ROTT, R., HERZOG, S., FLEISCHER, B., WINOKUR, A., AMSTERDAM, J., DYSON, W., KOPROWSKI, H., Detection of serum antibodies to Borna disease virus in patients with psychiatric disorders. *Science* **1985**, *228*, 755–756.
- 10 BODE, L., RECKWALD, P., SEVERUS, W. E., STOYLOFF, R., FERSZT, R., DIETRICH, D. E., LUDWIG, H., Borna disease virus-specific circulating immune complexes, antigenemia, and free antibodies – the key marker triplet determining infection and prevailing in severe mood disorders. *Mol. Psychiatry* **2001**, *6*, 481–491.
- 11 BODE, L., DIETRICH, D. E., STOYLOFF, R., EMRICH, H. M., LUDWIG, H., Amantadine and human Borna disease virus *in vitro* and *in vivo* in an infected patient with bipolar depression. *Lancet* **1997**, *349*, 178–179.
- 12 FERZST, R., KÜHL, K.-P., BODE, L., SEVERUS, E. W., WINZER, B., BERGHÖFER, A., BEELITZ, G., BRODHUN, B., MÜLLER-OERLINGHAUSEN, B., LUDWIG, H., Amantadine revisited: An open trial of Amantadine sulfate treatment in chronically depressed patients with Borna disease virus infection. *Pharmacopsychiatry* **1999**, *32*, 142–147.
- 13 DIETRICH, D. E., BODE, L., SPANNHUTH, C. W., LAU, T., HUBER, T. J., BRODHUN, B., LUDWIG, H., EMRICH, H. E., Amantadine in depressive patients with Borna disease virus (BDV) infection: an open trial. *Bipolar Disord.* **2000**, *2*, 65–70.
- 14 BODE, L., RIEGEL, S., LUDWIG, H., AMSTERDAM, J. D., LANGE, W., KOPROWSKI, H., Borna disease virus-specific antibodies in patients with HIV infection and with mental disorders. *Lancet* **1988**, *2*, 689.
- 15 BODE, L., RIEGEL, S., LANGE, W., LUDWIG, H., Human infections with Borna disease virus: seroprevalence in patients with chronic diseases and healthy individuals. *J. Med. Virol.* **1992**, *36*, 309–315.
- 16 BODE, L., Human infections with Borna disease virus and potential pathogenic implications. *Curr. Top. Microbiol. Immunol.* **1995**, *190*, 103–130.
- 17 BODE, L., STEINBACH, F., LUDWIG, H., A novel marker for Borna disease virus infection. *Lancet* **1994**, *343*, 297–298.
- 18 BODE, L., ZIMMERMANN, W., FERSZT, R., STEINBACH, F., LUDWIG, H., Borna disease virus genome transcribed and expressed in psychiatric patients. *Nature Med.* **1995**, *1*, 232–236.
- 19 BODE, L., DÜRRWALD, R., RANTAM, F. A., FERSZT, R., LUDWIG, H., First isolates of infectious human Borna disease virus from patients with mood disorders. *Mol. Psychiatry* **1996**, *1*, 200–212.
- 20 NAKAMURA, Y., TAKAHASHI, H., SHOYA, Y., NAKAYA, T., WATANABE, M., TOMONAGA, K., IWAHASHI, K., AMENO, K., MOMIYAMA, N., TANIYAMA, H., SATA, T., KURATA, T., DE LA TORRE, J. C., IKUTA, K., Isolation of Borna disease virus from human brain tissue. *J. Virol.* **2000**, *74*, 4601–4611.
- 21 IKUTA, K., IBRAHIM, M. S., KOBAYASHI, T., TOMONAGA, K., Borna disease virus and infection in humans. *Front. Biosci.* **2002**, *7d*, 470–495.
- 22 DE LA TORRE, J. C., GONZALEZ-DUNIA, D., CUBITT, B., MALLORY, M., MUELLER-LANTZSCH, N., GRÄSSER, F. A., HANSEN, L. A., MASLIAH, E., Detection of Borna disease virus antigen and RNA in human autopsy brain samples from neuropsychiatric patients. *Virology* **1996**, *223*, 272–282.
- 23 SALVATORE, M., MORZUNOV, S., SCHWEMMLE, M., LIPKIN, W. I., Borna disease virus in brains of North American and European people with schizophrenia and bipolar disorders. Bornavirus Study Group. *Lancet* **1997**, *349*, 1813–1814.
- 24 CZYGAN, M., HALLENSLEBEN, W., HOFER, M., POLLAK, S., SAUDER, C., BILZER, T., BLUMCKE, I., RIEDERER, P., BOGERTS, B., FALKAI, P., SCHWARZ, M. J., MASLIAH, E., STAEHEL, P., HUFERT, F. T., LIEB, K., Borna disease virus in human brains with a rare form of hippocampal degeneration but not in brains of patients with common neuropsychiatric disorders. *J. Infect. Dis.* **1999**, *180*, 1695–1699.
- 25 SAUDER, C., DE LA TORRE, J. C., Sensitivity and reproducibility of RT-PCR to detect Borna disease virus (BDV) RNA in blood: implications for BDV epidemiology. *J. Virol. Meth.* **1998**, *71*, 229–245.

- 26 ALLMANG, U., HOFER, M., HERZOG, S., BECHTER, K., STAEHEL, P., Low avidity of human serum antibodies for Borna disease virus antigens questions their diagnostic value. *Mol. Psychiatry* **2001**, *6*, 329–333.
- 27 BILICH, C., SAUDER, C., FRANK, R., HERZOG, S., BECHTER, K., TAKAHASHI, K., PETERS, H., STAEHEL, P., SCHWEMMLE, M., High-avidity human serum antibodies recognizing linear epitopes of Borna disease virus. *Biol. Psychiatry* **2002**, *51*, 979–987.
- 28 SCHWEMMLE, M., JEHLE, C., FORMELLA, S., STAEHEL, P., Sequence similarities between human bornavirus isolates and laboratory strains question human origin. *Lancet* **1999**, *354*, 1973–1974.
- 29 SCHNEIDER, P. A., BRIESE, T., ZIMMERMANN, W., LUDWIG, H., LIPKIN, W. I., Sequence conservation in field and experimental isolates of Borna disease virus. *J. Virol.* **1994**, *68*, 63–68.
- 30 DE LA TORRE, J. C., BODE, L., DÜRRWALD, R., CUBITT, B., LUDWIG, H., Sequence characterization of human Borna disease virus. *Virus Res.* **1996**, *44*, 33–44.
- 31 BODE, L., STOYLOFF, R., LUDWIG, H., Human bornaviruses and laboratory strains. *Lancet* **2000**, *355*, 1462.
- 32 PLANZ, O., RENTZSCH, C., BATRA, A., WINKLER, T., BÜTTNER, M., RZIHA, H.-J., STITZ, L., Pathogenesis of Borna disease virus: granulocyte fractions of psychiatric patients harbor infectious virus in the absence of antiviral antibodies. *J. Virol.* **1999**, *73*, 6251–6256.
- 33 PLANZ, O., RZIHA, H.-J., STITZ, L., Genetic relationship of Borna disease virus isolates. *Virus Genes* **2002**, *26*, 25–30.
- 34 GOSZTONYI, G., LUDWIG, H., Interactions of viral proteins with neurotransmitter receptors may protect or destroy neurons. *Curr. Top. Microbiol. Immunol.* **2001**, *253*, 121–144.
- 35 DEUSCHLE, M., BODE, L., HEUSER, I., SCHMIDT, J., LUDWIG, H., Borna disease virus proteins in cerebrospinal fluid of patients with recurrent depression and multiple sclerosis. *Lancet* **1998**, *352*, 1828–1829.
- 36 DEUSCHLE, M., BODE, L., SCHNITZLER, P., MEYDING-LAMADÉ, U., PLESCH, A., LUDWIG, H., HAMANN, B., HEUSER, I., Hypothalamic–pituitary–adrenal (HPA) system activity in depression and infection with Borna disease virus and *Chlamydia pneumoniae*. *Mol. Psychiatry* **2003**, *8*, 469–470.
- 37 DIETRICH, D. E., SCHEDLOWSKI, M., BODE, L., LUDWIG, H., EMRICH, H. M., A viro-psycho-immunological disease-model of a subtype affective disorder. *Pharmacopsychiatry* **1998**, *31*, 77–82.
- 38 LUDWIG, H., BODE, L., SCHEDLOWSKI, M., EMRICH, H. M., DIETRICH, D. E., Stress and human Borna virus infection. In BOLIS, C. L., LICINIO, J. (Eds.), *Stress and the Nervous System*. WHO/RPS/98.2. World Health Organization, Geneva, **1998**, 119–128.
- 39 CUBITT, B., DE LA TORRE, J. C., Amantadine does not have antiviral activity against Borna disease virus. *Arch. Virol.* **1997**, *142*, 2035–2042.
- 40 HALLENSLEBEN, W., ZOCHER, M., STAEHEL, P., Borna disease virus is not sensitive to amantadine. *Arch. Virol.* **1997**, *142*, 2043–2048.
- 41 STITZ, L., PLANZ, O., BILZER, T., Lack of antiviral effect of amantadine in Borna disease virus infection. *Med. Microbiol. Immunol.* **1998**, *186*, 195–200.
- 42 BODE, L., LUDWIG, H., Borna disease virus – a threat for human mental health? In SMITH, G. L., IRVING, W. L., McCAULEY, J. W., ROWLANDS, D. J. (Eds.), *New Challenges to Health: The Threat of Virus Infection*. Society for General Microbiology 60, Cambridge University Press, **2001**, 269–310.
- 43 ZWICK, W., Bornasche Krankheit und Enzephalomyelitis der Tiere. In GILDENMEISTER, E., HAAGEN, E., WALDMANN, O. (Eds.), *Handbuch der Viruskrankheiten*, Vol. 2. Fischer-Verlag, Jena, **1939**, 254–354.
- 44 NICOLAU, S., GALLOWAY, I. A., Borna disease and enzootic encephalomyelitis of sheep and cattle. *Medical Research Council Special Reports Series*, Vol. 121. His Majesty's Stationery Office, London, **1928**.
- 45 DÜRRWALD, R., LUDWIG, H., Borna disease virus (BDV), a (zoonotic?) worldwide pathogen. A review of the history of the disease and the virus

- infection with comprehensive bibliography. *J. Vet. Med. B* **1997**, *44*, 147–184.
- 46 ZIMMERMANN, W., BRETER, H., RUDOLPH, M., LUDWIG, H., Borna disease virus: immunoelectron microscopic characterization of cell-free virus and further information about the genome. *J. Virol.* **1994**, *68*, 6755–6758.
 - 47 BRIESE, T., SCHNEEMANN, A., LEWIS, A. J., PARK, Y.-S., KIM, S., LUDWIG, H., LIPKIN, W. I., Genomic organization of Borna disease virus. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4362–4366.
 - 48 CUBITT, B., OLDSTONE, C., DE LA TORRE, J. C., Sequence and genome organization of Borna disease virus. *J. Virol.* **1994**, *68*, 1382–1396.
 - 49 PYPER, J. M., GARTNER, A. E., Molecular basis for the differential subcellular localization of the 38- and 39-kilodalton structural proteins of Borna disease virus. *J. Virol.* **1997**, *71*, 5133–5139.
 - 50 CUBITT, B., DE LA TORRE, J. C., Borna disease virus (BDV), a nonsegmented RNA virus, replicates in the nuclei of infected cells where infectious BDV ribonucleoproteins are present. *J. Virol.* **1994**, *68*, 1371–1381.
 - 51 LUDWIG, H., BODE, L., The neuro-pathogenesis of Borna disease virus infections. *Intervirology*, **1997**, *40*, 185–197.
 - 52 BRUNDTLAND, G. H., Message from the Director General. In *The World Health Report 2001. Mental Health: New Understanding*. New Hope. WHO, Geneva, **2001**.
 - 53 KAMITANI, W., ONO, E., YOSHINO, S., KOBAYASHI, T., TAHARAGUCHI, S., LEE, B.-J., YAMASHITA, M., KOBAYASHI, T., OKAMOTO, M., TANIYAMA, H., TOMONAGA, K., IKUTA, K., Glial expression of Borna disease virus phosphoprotein induces behavioral and neurological abnormalities in transgenic mice. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 8969–8974.
 - 54 LUDWIG, H., FURUYA, K., BODE, L., KLEIN, N., DÜRRWALD, R., LEE, D. S., Biology and neurobiology of Borna disease viruses (BDV), defined by antibodies, neutralizability and their pathogenic potential. *Arch. Virol.* **1993**, *Suppl. 7*, 111–133.
 - 55 CARBONE, K. M., Borna disease virus and human disease. *Clin. Microbiol. Rev.* **2001**, *14*, 513–527.
 - 56 LIPKIN, W., HORNIG, M., BRIESE, T., Borna disease virus and neuropsychiatric disease – a reappraisal. *Trends Microbiol.* **2001**, *9*, 295–298.
 - 57 LAUDENSLAGER, M. L., Psychosocial stress and susceptibility to infectious disease. In KURSTAK, E., LIPOWSKI, Z. J., MORZOV, P. V. (Eds.), *Viruses, Immunity, and Mental Disorders*. Plenum Press, New York, **1987**.
 - 58 KIECOLT-GLASER, J. K., GLASER, R., Psychosocial influences on herpes virus latency. In KURSTAK, E., LIPOWSKI, Z. J., MORZOV, P. V. (Eds.), *Viruses, Immunity, and Mental Disorders*. Plenum Press, New York, **1987**.
 - 59 GLASER, R., PEARSON, G. R., JONES, J. F., HILLHOUSE, J., KENNEDY, S., MAO, H., KIECOLT-GLASER, J. K., Stress-related activation of Epstein-Barr virus. *Brain Behav. Immun.* **1991**, *5*, 219–232.
 - 60 TURNBULL, A. V., RIVIER, C. L., Regulation of the hypothalamic–pituitary–adrenal axis by cytokines: actions and mechanisms of action. *Physiol. Rev.* **1999**, *79*, 1–71.
 - 61 WATKINS, L. R., MAIER, S. F., GOEHLER, L. E., Cytokine-to-brain communication: a review and analysis of alternative mechanisms. *Life Sci.* **1995**, *57*, 1011–1026.
 - 62 WONG, M. L., BONGIORNO, B. P., RETTORI, V., MCCANN, S. M., LICINIO, J., Interleukin (IL) 1 β , IL-1 receptor antagonist, IL-10, and IL-13 gene expression in the central nervous system and anterior pituitary during systemic inflammation: pathophysiological implications. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 227–232.
 - 63 DIETRICH, D. E., BODE, L., VON RIMON, G., LUDWIG, H., EMRICH, H. M., Effective treatment of amantadine in patients with obsessive-compulsive disorder and Borna disease virus-infection. *World J. Biol. Psychiatry*, **2001**, *2*, 154S.
 - 64 MOUSSU, R., MARCHAND, L., L'encéphalite enzootique du cheval (maladie de Borna). *Rec. Méd. vét.* **1924**, *100*, 5–44, 65–90.
 - 65 DAVIES, W. L., GRUNERT, R. R., HAFF, R. F., MC GAHEN, J. W., NEUMAYER, E. M., PAULSHOCK, M., WATTS, J. C., WOOD, T. R., HERMANN, E. C., HOFFMANN, C. E., Antiviral activity of 1-adamantanamine (amantadine). *Science* **1964**, *144*, 862–863.

- 66 HUBER, T. J., DIETRICH, D. E., EMRICH, H. M., Possible use of amantadine in depression. *Pharmacopsychiatry* **1999**, 32, 47–55.
- 67 GOSZTONYI, G., LUDWIG, H., Borna disease of horses. An immunohistological and virological study of naturally infected animals. *Acta Neuropathol. (Berl.)* **1984**, 64, 213–221.
- 68 DOMINGO, E., HOLLAND, J., BIEBRICHER, C., EIGEN, M., Quasi-species: the concept and the word. In GIBBS, A., CALISHER, C. H., GARCIA-ARENAL, F. (Eds.), *Molecular Basis of Virus Evolution*. Cambridge University Press, Cambridge, 181–191, **1995**.
- 69 VALE, S., ESPEJEL, M. A., DOMINGUEZ, J. C., Amantadine in Depression. *Lancet* **1971**, 21, 437.
- 70 SPANNHUTH, C. W., DIETRICH, D. E., BODE, L., LAU, T., HUBER, T. J., LUDWIG, H., EMRICH, H. M., Psychopathology and treatment prognosis in BDV-infected patients. *Infection* **2000**, 28, Suppl. 1, 254S–255S.
- 71 STOYLOFF, R., BODE, L., WENDT, H., MULZER, J., LUDWIG, H., The hydrophobic mannose derivative 1B6TM efficiently inhibits Borna disease virus *in vitro*. *Antiviral Chem. Chemother.* **1996**, 7, 197–202.
- 72 MIZUTANI, T., INAGAKI, H., ARAKI, K., KARIWA, H., ARIKAWA, J., TAKASHIMA, I., Inhibition of Borna disease virus replication by ribavirin in persistently infected cells. *Arch. Virol.* **1998**, 143, 2039–2044.
- 73 JORDAN, I., BRIESE, T., AVERETT, D. R., LIPKIN, W. I., Inhibition of Borna disease virus replication by ribavirin. *J. Virol.* **1999**, 73, 7903–7906.
- 74 BAJRAMOVIC, J. J., SYAN, S., BRAHIC, M., DE LA TORRE, J. C., GONZALEZ-DUNIA, D., 1- β D-Arabinofuranosylcytosine inhibits Borna disease virus replication and spread. *J. Virol.* **2002**, 76, 6268–6276.
- 75 KREY, H. F., LUDWIG, H., BOSCHEK, C. B., Multifocal retinopathy in Borna disease virus infected rabbits. *Am. J. Ophthalmol.* **1979**, 87, 157–164.
- 76 KREY, H. F., LUDWIG, H., ROTT, R., Spread of infectious virus along the optic nerve into the retina in Borna disease virus-infected rabbits. *Arch. Virol.* **1979**, 61, 283–288.
- 77 HORNIG, M., WEISSENBOCK, H., HORSCHROFT, N., LIPKIN, W. I., An infection-based model of neuro-developmental damage. *Proc. Natl. Acad. Sci. USA* **1999**, 96, 12102–12107.
- 78 PLETNIKOV, M. V., RUBIN, S. A., VASUDEVAN, K. K., MORAN, T. H., CARBONE, K. M., Developmental brain injury associated with abnormal play behaviour in neonatally Borna disease virus-infected Lewis rats: a model of autism. *Behav. Brain Res.* **1999**, 100, 43–50.
- 79 SOLBRIG, M. V., FALLON, J. H., LIPKIN, W. I., Behavioral disturbances and pharmacology of Borna disease. *Curr. Top. Microbiol. Immunol.* **1995**, 190, 93–99.
- 80 NITZSCHKE, E., Untersuchungen über die experimentelle Bornavirus-Infektion bei der Ratte. *Zentralbl. Veterinärmed., B* **1963**, 10, 470–527.
- 81 HIRANO, N., KAO, M., LUDWIG, H., Persistent, tolerant or subacute infection in Borna disease virus-infected rats. *J. Gen. Virol.* **1983**, 64, 1521–1530.
- 82 NARAYAN, O., HERZOG, S., FRESE, K., SCHEEFERS, H., ROTT, R., Pathogenesis of Borna disease in rats: immune-mediated viral ophthalmoencephalopathy causing blindness and behavioral abnormalities. *J. infect. Dis.* **1983**, 148, 305–315.
- 83 LUDWIG, H., KRAFT, W., KAO, M., GOSZTONYI, G., DAHME, E., KREY, H., Borna-Virus Infektion (Borna-Krankheit) bei natürlich und experimentell infizierten Tieren: Ihre Bedeutung für Forschung und Praxis. *Tierärztl. Praxis* **1985**, 13, 421–453.
- 84 RUBIN, S. A., SYLVES, P., VOGEL, M., PLETNIKOV, M. V., MORAN, T. H., SCHWARTZ, G. J., CARBONE, K. M., Borna disease virus-induced hippocampal dentate gyrus damage is associated with spatial learning and memory deficits. *Brain Res. Bull.* **1999**, 48, 23–30.
- 85 HORNIG, M., SOLBRIG, M. V., HORSCHROFT, N., WEISSENBOCK, H., LIPKIN, W. I., Borna disease virus infection of adult and neonatal rats: models for neuro-psychiatric disease. *Curr. Top. Microbiol. Immunol.* **2001**, 253, 157–177.
- 86 SOLBRIG, M. V., KOOB, G. F., Neuro-pharmacological sequelae of persistent CNS viral infections: lessons from Borna disease virus. *Pharmacol. Biochem. Behav.* **2003**, 74, 777–787.

- 87 KAO, M., LUDWIG, H., GOSZTONYI, G., Adaptation of Borna disease virus to the mouse. *J. Gen. Virol.* **1984**, 65, 1845–1849.
- 88 SAUDER, C., WOLFER, D. P., LIPP, H. P., STAEHEL, P., HAUSMANN, J., Learning deficits in mice with persistent Borna disease virus infection of the CNS associated with elevated chemokine expression. *Behav. Brain Res.* **2001**, 120, 189–201.
- 89 PLETNIKOV, M. V., RUBIN, S. A., SCHWARTZ, G. J., MORAN, T. H., SOBOTKA, T. J., CARBONE, K. M., Persistent neonatal Borna disease virus (BDV) infection of the brain causes chronic emotional abnormalities in adult rats. *Physiol. Behav.* **1999**, 65, 823–831.
- 90 SPRANKEL, H., RICHARZ, K., LUDWIG, H., ROTT, R., Behavior alterations in tree shrews (*Tupaia glis*, Diard 1820) induced by Borna disease virus. *Med. Microbiol. Immunol.* **1978**, 165, 1–18.
- 91 PLETNIKOV, M. V., RUBIN, S. A., CARBONE, K. M., MORAN, T. H., SCHWARTZ, G. J., Neonatal Borna disease virus infection (BDV) – induced damage to the cerebellum is associated with sensorimotor deficits in developing Lewis rats. *Dev. Brain Res.* **2001**, 126, 1–12.
- 92 MONJAN, A. A., GILDEN, D. H., COLE, G. A., NATHANSON, N., Cerebellar hypoplasia in neonatal rats caused by lymphocytic choriomeningitis virus. *Science* **1971**, 171, 194–196.
- 93 GOSZTONYI, G., LUDWIG, H., Neurotransmitter receptors and viral neurotropism. *Neuropsychiat. Clin.* **1984**, 3, 107–114.
- 94 KANDEL, E. R., SCHWARTZ, J. H., JESSEL, T. M. (Eds.), *Essentials of Neuroscience and Behavior*. Appleton and Lange, Oxford, **1995**.
- 95 LUNDGREN, A.-L., ZIMMERMANN, W., BODE, L., CZECH, G., GOSZTONYI, G., LINDBERG, R., LUDWIG, H., Staggering disease in cats: isolation and characterization of the feline Borna disease virus. *J. Gen. Virol.* **1995**, 76, 2215–2222.
- 96 PIATA-SALAMAN, C. R., ILYSIN, S. E., GAYLE, D., ROMANOVITCH, A., CARBONE, K. M., Persistent Borna disease virus infection of neonatal rats causes brain regional changes of mRNAs for cytokines, cytokine receptor components and neuropeptides. *Brain Res. Bull.* **1999**, 49, 441–451.
- 97 GONZALEZ-DUNIA, D., EDDLESTON, M., MACKMAN, N., CARBONE, K. M., DE LA TORRE, J. C., Expression of tissue factor is increased in astrocytes within the central nervous system during persistent infection with Borna disease virus. *J. Virol.* **1996**, 70, 5812–5820.
- 98 STITZ, L., DIETZSCHOLD, B., CARBONE, K. M., Immunopathogenesis of Borna disease. *Curr. Top. Microbiol. Immunol.* **1995**, 190, 75–92.
- 99 LIPKIN, W. I., CARBONE, K. M., WILSON, M. C., DUCHALA, C. S., NARAYAN, O., OLDSTONE, M. B. A., Neurotransmitter abnormalities in Borna disease. *Brain Res.* **1988**, 475, 366–370.
- 100 LUNDGREN, A.-L., JOHANNISSON, A., ZIMMERMANN, W., BODE, L., ROZELL, B., MULUNEH, A., LINDBERG, R., LUDWIG, H., Neurological disease and encephalitis in cats experimentally infected with Borna disease virus. *Acta Neuropathol. (Berl.)* **1997**, 93, 391–401.
- 101 LUDWIG, H., BECHT, H., Borna disease – a summary of our present knowledge, p. 75–83. In TER MEULEN, V., KATZ, M. (Eds.), *Slow Virus Infections of the Central Nervous System. Investigational Approaches to Etiology and Pathogenesis of these Diseases*. Springer, New York, **1977**.
- 102 WATANABE, M., LEE, B.-J., YAMASHITA, M., KAMITANI, W., KOBAYASHI, T., TOMONAGA, K., IKUTA, K., Borna disease virus induces acute fatal neurological disorders in neonatal gerbils without virus- and immune-mediated cell destructions. *Virology* **2003**, 310, 245–253.
- 103 BECHTER, K., *Borna Disease Virus, mögliche Ursache neurologischer Störungen des Menschen*. Monographien aus dem Gesamtgebiet der Psychiatrie, Steinkopff, Darmstadt, **1998**, 177.

24

Depression and Heart Disease

Robert M. Carney and Kenneth E. Freedland

*Oh mother, oh mother, go dig my grave
Make it long and narrow,
Sweet William died of love for me
And I will die of sorrow.*

(From *Barbara Allan*, a traditional English ballad)

24.1

Background

The belief that depression, mourning, or prolonged grief can cause death has been part of Western culture for a very long time, finding its way into stories, poems, and songs such as the English ballad, *Barbara Allan*. Over 350 years ago, Sir William Harvey, the great pioneer of research on the cardiovascular system, wrote that negative emotions adversely affect the heart [1]. In more recent times, however, the scientific community has been reluctant to entertain this possibility. In the 1930s, psychiatric researchers observed a higher incidence of deaths due to coronary heart disease (CHD) in depressed psychiatric patients than in various comparison groups [2, 3]. These studies were largely ignored for decades, perhaps because the results were unexpected, or because there was no obvious explanation for the findings. Little research was conducted on this subject until the 1980s when larger, better controlled studies confirmed the relationship between depression and cardiovascular mortality in depressed psychiatric patients [4–6]. Although better designed than those of the 1930s, most of these studies still suffered from methodological limitations including inadequate documentation of cardiac endpoints and causes of death. Nevertheless, they yielded reasonably consistent findings. Like the earlier studies, however, they attracted little interest, and their implications were appreciated only by a small group of researchers. The findings were virtually unknown outside of psychiatry, despite the fact that cardiologists and epidemiologists were busily identifying other risk factors for cardiovascular disease. Only recently have

depression and other psychosocial problems been acknowledged as cardiovascular risk factors in treatment guidelines and standards of care.

A new wave of studies began to appear in the mid-1980s. Unlike the earlier studies, these new investigations did not focus on depressed psychiatric patients. Some of them followed cohorts of community residents who were free of clinically apparent heart disease at enrollment. Others focused on patients with established heart disease, and sought to determine whether depression affected the course and outcome of the disease.

This chapter reviews both of these types of study. In addition, the current evidence for a variety of possible mechanisms that may explain the relationship between depression and cardiac mortality and morbidity is evaluated and finally, recent research on the cardiovascular effects of pharmacological and psychotherapeutic treatments for depression is discussed.

24.2

Depression and Coronary Heart Disease

Heart disease and depression are two of the most common disorders in the Western world. Coronary heart disease currently affects approximately 12 million people in the United States, and its incidence is expected to rise as the population ages. It is the most common cause of death in the United States and in most of the industrialized nations of the world. More than 500 000 people die from CHD-related causes in the United States every year, and over 1 million Americans suffer serious but non-fatal cardiac events [7]. The lifetime prevalence of major depression in the US is estimated to be about 16% [8], and in any given year, about 7% of the adult population has a major depressive episode. The World Health Organization (WHO) lists depression and heart disease as two of the most disabling and costly of illnesses worldwide. In the United States alone, approximately \$330 billion is spent on heart disease every year [7]. In a study of the effects of chronic medical illness in a community sample, heart disease and depression were the two illnesses with the worst impact on quality of life [9]. Individuals with comorbid depression reported worse psychosocial adjustment than non-depressed respondents across all chronic medical illnesses, including heart disease [10].

24.3

Depression and Incident CHD

During the 1990s, a series of studies found that a history of major depression [11, 12], depression symptoms [13–20], clinical depression [11, 21–24], and an increase in depression symptoms over time [24, 25], predict the incidence of heart disease and death from cardiac causes. These studies were of cohorts with no evidence of CHD at enrollment. The subjects were chosen from specified geographic areas or institutions [11, 26, 27], and some were participants in studies designed to identify

other CHD risk factors [13, 16, 25]. The ages of the participants ranged from early 20s [23] to over 65 years [24]. Although the majority of these studies found depression to be a predictor of incident heart disease or death from cardiac causes, a few [e.g. 28] did not confirm this.

Two meta-analyses of these studies were published recently. Using careful inclusion criteria, Rugulies [29] identified 11 studies of depression or depressed mood in initially healthy subjects with myocardial infarction or cardiac-related death as the outcome variables. He found that the overall relative risk for developing CHD in depressed individuals was 1.64 (95% CI: 1.29–2.08). Moreover, clinical depression (RR = 2.69; CI: 1.63–4.3) was associated with a higher relative risk than was depressed mood (RR = 1.49; CI: 1.16–1.92). With slightly different criteria, but with some overlapping studies, Wulsin and Singal [30] identified 10 studies for their meta-analysis, after reviewing 500 citations. They also found depression to have a relative risk of 1.64 (CI: 1.41–1.90) for incident CHD.

These results suggest that even self-report depression questionnaires can predict heart disease deaths and other cardiac events that may occur many years later. However, a clinical diagnosis of depression is associated with a greater risk of cardiac events compared to having just a few symptoms of depression. One study [22] found a relative risk of 3.4 for incident CHD in individuals with major depression. In another study, Pratt et al. [11] found a relative risk of 4.2 for incident CHD in community residents with major depression. On the other hand, studies that have relied on questionnaires to assess symptoms of depression have generally reported relative risks of 2.0 or lower [e.g. 27]. Moreover, all of the studies which have failed to find a relationship between depression and cardiac endpoints have relied on self-report depression questionnaires rather than structured interviews and clinical diagnoses.

24.4

Patients with Established CHD

Depression is common in patients with CHD. Approximately 20% of patients undergoing diagnostic angiography suffer from major depression [31–33], and about the same proportion suffer minor depression [32]. About 20% of patients with a recent cardiac event, such as an acute myocardial infarction (MI) or unstable angina (UA), also suffer from major depression [34–37], and approximately 20% experience minor depression [35]. During the 12 months following an acute coronary event, as many as 30% of patients develop major depression [38]. The 12-month prevalence of minor depression has not been reported, but it is also estimated to be about 30%. Thus, up to 60% of patients with a recent acute coronary event can be expected to have significant depressive symptoms within the following 12 months. Major depression tends to follow a chronic course in the months after an acute MI [35, 39], as well as in patients with stable coronary artery disease [32].

Depression predicts cardiac events in patients with known CHD, beginning from the time of initial diagnosis of coronary artery disease following cardiac catheteri-

zation and angiography [40, 41] or exercise stress testing [42]. It is also a significant predictor of mortality and cardiac events in patients undergoing coronary artery bypass graft (CABG) surgery [43–45]. Blumethal et al. [44], for example, assessed depression in 817 patients undergoing CABG surgery and followed the patients for an average of 5 years. Moderate to severe depression at baseline, as defined by a CES-D score ≥ 27 , had an adjusted hazard ratio of 2.4 for mortality. Even mild to moderate depression (CES-D, 16–26), if it persisted from baseline to 6 months following surgery, was associated with an increased risk for mortality, with an adjusted hazard ratio of 2.2.

Lespérance et al. [46] administered the Beck Depression Inventory (BDI) to 430 patients hospitalized with unstable angina. They found that patients who scored ≥ 10 on the BDI at index were at higher risk than non-depressed patients for sudden cardiac death and non-fatal myocardial infarction during a 12-month follow-up. The adjusted odds ratio for non-fatal MI or death was 6.7 (CI: 2.8–18.6; $p < 0.001$). The prognostic significance of depression in patients with unstable angina deserves further investigation.

Several studies have investigated whether depression increases the risk for mortality in patients with congestive heart failure (CHF). Prevalence estimates of depression in hospitalized patients with CHF differ considerably across studies, possibly due to the variety of assessment instruments used to assess depression, including self-report inventories. In a recent study of 682 patients using a standardized structured psychiatric interview (the DIS) and the DSM-IV criteria for depression diagnosis, Freedland et al. [47] reported point prevalence of 20% for major depression and 16% for minor depression. Moreover, 51% of the patients scored above the BDI ≥ 10 cut-off for depression. However, the prevalence of major depression differed significantly by age and the functional severity of heart failure, as well as by gender, employment status, dependence in activities of daily living, and past history of major depression. For example, the prevalence of major depression ranged from as low as 8% among patients in NYHA Class I failure to 40% among patients in Class IV. It thus appears that the prevalence of depression in hospitalized patients with CHF is similar to that found in post-MI patients, but the rate is highly dependent upon the functional severity of the heart failure.

Depression has also been associated with an increased risk for mortality in patients with CHF [48–54], although the results have been somewhat inconsistent. Most of the positive findings are based on univariate analyses of relatively small samples, and depression has not consistently emerged as an independent risk factor for mortality in multivariate models.

However, in the largest study to date, using a recognized standardized diagnostic interview and employing the DSM criteria, Freedland et al. [55], followed 551 hospitalized patients with congestive heart failure to determine the effect of depression on 1-year survival. A total of 110 patients suffered from major depression at enrollment; 102 patients died within 1 year. The risk of death was higher in patients with major depression (adjusted hazard ratio, 1.69; 95% CI: 1.05–2.71). Among patients with severe left ventricular dysfunction, the adjusted hazard ratio was 3.72 (95% CI: 1.46–9.49.) The authors concluded that major depression is an

independent risk factor for mortality in patients with heart failure, especially in patients with severe left ventricular dysfunction.

Depression is an important risk factor for medical morbidity and mortality following acute MI [37, 56–62]. One of the first studies of this relationship found that after adjusting for the severity of the MI, the risk of death was more than four times higher in the following 6 months among depressed than non-depressed patients [37]. Most published studies have found that depression predicts mortality even after adjusting for other risk factors [37, 56, 60–62]. A few, relatively small studies found only non-significant trends after risk factor adjustment [58, 59], probably due to inadequate power.

However, at least two studies have failed to find even univariate relationships between depression and mortality [63, 64]. Mayou et al. [63] reported a non-significant 1.6 relative risk of mortality. This study had a small sample size and relied on the Hospital Anxiety and Depression Scale (HADS) rather than on measures such as the BDI that have demonstrated prognostic value in other studies. Lane et al. [64] also failed to find any relationship between depression and mortality, despite using the BDI as a measure of depression. These studies are among the most recent to examine the relationship of depression to mortality in post-MI patients.

One of the possible explanations for these negative findings is that in recent years, there have been many major advances in the treatment of myocardial infarction. Perhaps depression has ceased to be a risk factor for mortality in the modern era of thrombolytic therapy, early revascularization, statins, and platelet inhibitors. In order to determine whether depression is still a risk factor for mortality despite these advances, Carney et al. [65] followed 358 patients who met the DSM-IV criteria for major or minor depression within 28 days of an acute MI, and a comparison group of 408 non-depressed patients, for up to 30 months. After adjusting for major risk factors, including ventricular dysfunction and prior history of MI, the depressed patients were at higher risk for all-cause mortality (HR = 2.4; 95% CI: 1.2–4.7; $p < 0.009$) but not for non-fatal recurrent infarction (HR = 1.2; 95% CI: 0.7–2.0; $p < 0.26$), compared to the non-depressed patients. However, the effect of depression on mortality was not apparent until 6 to 8 months after the index MI. Thus, depression remains an independent risk factor for death following acute MI, but modern, aggressive cardiological care may nevertheless diminish the adverse effects of depression during the first few months of recovery. This suggests that some of the more recent studies may have not included sufficiently long follow-ups to detect the current effects of depression on post-MI mortality. Also, consistent with the findings of Lespérance et al. [66], depression did not predict non-fatal recurrent infarction in our study.

Although the majority of studies have found at least a univariate relationship between depression and cardiac events, the mechanism through which depression confers this risk remains unclear, and we do not yet know whether particular subgroups are at especially high risk due to depression. A recent study by Frasure-Smith and Lespérance [67] reported that a number of individual depressive symptoms independently predict mortality in post-MI patients. These data suggest

that no single symptom or class of symptoms is unimportant. However, more work is needed to differentiate between depressed patients who are at increased risk for mortality and patients who are not at increased risk despite being depressed.

Based on the prevalence of depression and the increased risk for cardiac-related mortality associated with depression, it is possible to estimate the number deaths which can be attributed at least in part to depression among the cardiac patients who die each year following a myocardial infarction. As reviewed earlier, we know that about 20% of patients suffer major depression following an acute MI [34–37], and another 20% experience minor depression [35]. An estimated 1.5 million MIs occur each year in the United States, and just less than 7% of patients discharged alive will die within 1 year of an initial MI [7]. Conservatively assuming that the adjusted relative risk of post-MI mortality associated with depression is 2.5 for patients with major depression and 1.5 for those with minor depression, more than 80 000 deaths per year may be at least partially attributable to post-MI depression. It is important to note, however, that this estimate omits deaths attributable to depression that occur at other points in the course of heart disease. Moreover, the costs of the increased medical morbidity and health care utilization, diminished quality of life, and loss of productivity associated with depression in these patients, are much more difficult to estimate.

Few studies have directly compared the prognostic value of alternative methods of measuring depression. Of all of the measures that have been used, standardized diagnostic interviews and the BDI have shown the most consistent relationship to medical morbidity and mortality. Even patients who endorse just a few depression symptoms on the BDI are at increased risk for mortality [61, 66]. However, the relative risks tend to be higher for clinically significant depression than for sub-syndromal depressive symptoms. Thus, there may be a dose–response relationship that extends from sub-syndromal depressive symptoms to severe major depressive disorder [66].

Structured clinical interviews should be used to ensure that patients who screen positive for depression actually meet the DSM-IV criteria for depressive disorders. The BDI is not highly specific for depressive disorders; BDI scores tend to be high not only among depressed patients, but also among non-depressed patients with other psychiatric disorders, as well as psychiatrically well individuals with transient adjustment reactions.

This distinction is important because clinical depression tends to follow a chronic course after an acute MI [35, 39], as well as in stable coronary disease [32]. On the other hand, many patients have transient depressive reactions to acute MI and other life-threatening events [68]. Although it is possible that a single, brief period of mild depression somehow places individuals at risk for CHD-related death months or even years later, it is more likely that the long-term risk is elevated only in patients with chronic or recurrent depression. This may pertain not only to patients with major depression, but also to those with only a few symptoms of depression that persist for months or years.

24.5

Mechanisms

One of the important questions in this area is *how* depression increases a patient's risk for cardiac events. Many studies have attempted to identify the biological or behavioral pathways that link depression to medical outcomes. Identifying these mechanisms should help us develop more effective risk-reduction strategies and treatments for depressive disorders in cardiac patients. It could also enhance the credibility of the epidemiological relationships between depression and heart disease, and persuade more cardiologists that depression is a clinically significant risk factor for cardiac events.

It is possible that depression merely *seems* to increase the risk for cardiac morbidity and mortality, i.e. that it does not have a causal role. This would be the case if the cardiac patients who become depressed are the ones with the worst heart disease, and if their depression is caused by their heart disease. However, as reviewed earlier, most studies have found that depression is a significant predictor of cardiac events even after adjusting for indicators of disease severity, such as the size of the myocardial infarction or the severity of left ventricular dysfunction. Also, most studies of depression as a predictor of incident heart disease have controlled for other cardiac risk factors such as smoking. Although it cannot be entirely ruled out, the possibility that depression is related to the severity of the medical disease, and is not an independent risk factor for cardiac mortality and morbidity, has received little empirical support.

Another possibility is that the increased risk for morbidity and mortality may be due to the *treatments* patients receive for depression, rather than the depression itself. Tricyclic antidepressants and monoamine oxidase inhibitors have potentially lethal cardiotoxic side-effects, especially in patients with conduction disorders [69–71]. However, the selective serotonin reuptake inhibitors (SSRIs) have few cardiotoxic side-effects, and they are the most frequently prescribed antidepressants for patients with CHD [72]. Furthermore, despite the availability of SSRIs, most depressed cardiac patients are still not treated for depression, and associations between depression and adverse cardiac outcomes were reported before any antidepressants were routinely available [3]. Thus, although antidepressants must be carefully chosen for patients with heart disease, there is little evidence that they are responsible for the increased risk of medical morbidity and mortality in depressed patients.

Depression is associated with several major cardiac risk factors, including hypertension, diabetes, physical inactivity, and smoking [73]. These risk factors might be responsible for at least some of the excess cardiac morbidity and mortality seen in depressed patients, but depression has remained an independent predictor of cardiac morbidity and mortality even after adjusting for these risk factors [15, 21, 74]. Thus, it is unlikely that the association of depression with major cardiovascular risk factors explains all of the increased risk for mortality and morbidity.

However, the relationships among depression, hypertension, diabetes, abdominal obesity, and smoking require further investigation. There is recent evidence that

depression may be part of the so-called “metabolic syndrome” [75], which includes some of the risk factors discussed above, such as hypertension, diabetes, and pre-diabetic insulin resistance. This interesting possibility deserves further study. However, if depression is found to be part of the metabolic syndrome, like many of the factors currently known to be part of this syndrome, it could still make an independent contribution to coronary heart disease prognosis.

Depression is associated with poor adherence to prescribed treatments in many chronic medical illnesses [76]. Depressed CHD patients are less adherent to cardiac medication regimens [77], lifestyle risk factor interventions [78], and cardiac rehabilitation programs [79] than are non-depressed patients. This observation is potentially very important because medications such as beta blockers and ACE inhibitors have been shown to reduce cardiac morbidity and mortality. Whether poor adherence to cardiac treatment explains any or all of the risks associated with depression is unknown, but this certainly deserves further investigation.

Dysregulation of the autonomic nervous system and of the hypothalamic–pituitary–adrenal (HPA) axis has been found in medically-well patients with major depressive disorder. Evidence for this includes elevated plasma and urinary catecholamines, cortisol [80–83], and resting heart rate [81, 84–86]. Neurohormonal dysfunction and autonomic nervous system dysregulation may promote procoagulant and proinflammatory processes, increase platelet aggregation, lower the threshold for myocardial ischemia, increase the risk of coronary thrombosis, and even trigger cardiac events by promoting arrhythmias [73].

There is strong evidence that depression affects cardiac autonomic regulation. Heart rate variability (HRV) analysis is a widely used method for studying cardiac autonomic modulation [87]. Low HRV reflects excessive sympathetic and/or inadequate parasympathetic tone [87], and is a strong predictor of mortality in patients with CHD [88–90]. Depressed cardiac patients have higher resting heart rates and lower heart rate variability than non-depressed patients [91–95].

In the largest study of this phenomenon to date, we compared 24-h HRV levels in 380 patients with a recent MI who suffered from either major or minor depression to those in 425 post-MI patients who were free of depression [93]. In univariate analyses, four indices of HRV that were included in the study were significantly lower in the depressed than in the non-depressed patients. After adjustment for possible confounders, all but one HRV index (high frequency power) remained significantly lower in depressed than non-depressed patients.

It is important to consider the clinical significance of the differences in mechanistic variables that have been found between depressed patients and non-depressed controls. Unless the differences are large enough to affect clinical outcomes, they are unlikely to explain the increased risk for mortality in depressed patients. In the Multicenter Post Infarction Project (MPIP) study [89], VLF power $< 180 \text{ ms}^2$ was associated with relative risk of 4.7 for cardiac mortality over the 2.5 years following the acute MI. In our study, 7% of the non-depressed patients and 16% of the depressed patients had VLF power below this value, a difference which was significant even after adjusting for covariates ($p = 0.006$). This result suggests that a greater than two-fold increased risk of mortality in depressed patients is attributable

to low HRV. This estimated risk is within the range of the relative risk for mortality that has been reported for depression in post-MI patients (e.g. [65]).

Low HRV has consistently been found in depressed CHD patients, but only about half of the studies of medically-well depressed patients have reported lower HRV in depressed patients compared to controls. Furthermore, although low HRV is highly predictive of cardiac mortality, there is a great deal of uncertainty as to the physiological processes underlying specific HRV indices. Thus, although HRV clearly has the potential to explain the mortality/depression relationship, more work is needed to clarify the basis for low HRV, and to determine whether HRV can be improved by treating depression [96].

Neurohormonal dysfunction and autonomic nervous system dysregulation, as well as other biological and behavioral factors, may also promote procoagulant processes. Platelet aggregation plays a critical role in myocardial infarction, unstable angina, and atherogenesis [97–99], and it may be increased in medically-well depressed patients. For example, Musselman et al. [100] found that depressed patients exhibited 41% greater platelet activation and responsiveness than did healthy, non-depressed subjects. There is at least limited evidence for this effect in depressed CHD patients. Laghrissi-Thode et al. [101] found higher plasma concentrations of platelet factor 4 (PF4) and β thromboglobulin (BTG), two proteins that are secreted from alpha granules when the platelet is activated, in depressed patients with CHD than in healthy, non-depressed individuals, and in non-depressed patients with CHD. They also found that these differences could be reduced by paroxetine, but not by nortriptyline [102]. This is very similar to the finding of Musselman et al. [103] of normalization of platelet activation in depressed patients following administration of paroxetine. Thus, increased platelet activation may contribute to the process of atherogenesis as well as to the increased risk of cardiac events in depressed patients, especially in untreated cases. This problem may be responsive to certain antidepressants, particularly selective serotonin reuptake inhibitors such as sertraline [73, 100–102]. It is of interest that changes in platelet activation do not seem to correlate with change in depression [102]. This suggests that the SSRI antidepressants may have a direct effect on platelet function, independent of their antidepressant effects, possibly by blocking platelet serotonin uptake.

In a recent review of the literature on platelet function and depression, von Känel [104] concluded that there is very little evidence that depression is associated with increased platelet aggregation. Moreover, he noted that there were only three positive versus 16 negative studies demonstrating increased platelet activation in depressed patients that were published before 1996, but nine positive versus two negative studies since 1996.

One difference between earlier and more recent studies is the number of activation markers that are measured, largely as a result of using flow cytometry techniques. In addition to facilitating measurement of multiple indices of platelet function, the newer technologies are more sensitive to differences in these markers. On the other hand, flow cytometry is subject to possible contamination resulting from the trauma of venipuncture.

Another concern is that the proportion of these markers that are found to be significant in the more recent studies has not been strongly supportive of the activation hypothesis. For example, in the Musselman et al. [100], study, nine markers were measured at rest and repeated after an orthostatic challenge. Out of 18 comparisons, four were significant but 14 did not differ between depressed patients and controls. Furthermore, most of these studies compared very small samples of patients and did not control for all possible confounders [104]. Thus, although the results of these studies are intriguing and worthy of careful consideration, more work clearly is needed to determine whether the relationship between depression and platelet function can account for the observed risk of cardiac events in depressed patients.

Coronary artery disease is currently believed to be a chronic inflammatory process involving immune responses to injuries of the vascular endothelium [105, 106]. A number of studies of medically-healthy depressed psychiatric patients have shown that depression is accompanied by higher circulating levels of the inflammatory risk markers interleukin-6, C-reactive protein, and tumor necrosis factor- α [107–110]. Although these findings suggest that depression may promote inflammatory processes which could contribute to the development of atherosclerosis or thrombosis [111–113], the studies have methodological problems which make interpretation difficult. For example, many of them failed to control for potential confounders such as medication use, cigarette smoking, and acute infectious illness [114].

In a recent study, Miller et al. [115] compared 50 healthy adults who met the DSM-IV criteria for major depression, with 50 age- and gender-matched controls without a history of psychiatric illness. None of the subjects had a recent acute infectious disease, chronic medical illness, or daily medication regimen aside from oral contraceptives. The depressed subjects had significantly higher levels of the inflammatory markers C-reactive protein (3.5 ± 0.5 vs. 2.5 ± 0.5 mg/l; $p = 0.04$) and interleukin-6 (3.0 ± 0.3 vs. 1.9 ± 0.2 pg/ml; $p = 0.007$) compared to the control subjects. Neither cigarette smoking nor subclinical infection with cytomegalovirus or *Chlamydia pneumoniae* explained the differences. Depressed subjects had greater body mass than control subjects, however, and larger body mass partially mediated the effects of depression on the inflammatory markers. Thus, in otherwise healthy adults, depression is associated with higher levels of inflammatory markers that have been implicated in the pathogenesis of CHD.

Unfortunately, there have been very few studies of depression and inflammatory processes in patients with existing CHD. Appels et al. [116] found elevations in circulating levels of interleukin- 1α and tumor necrosis factor- α among CHD patients reporting symptoms of depression or of “vital exhaustion”. It remains unclear whether the level of inflammation associated with depression would be sufficient to affect atherosclerotic or thrombotic processes to the degree necessary to affect coronary morbidity and/or mortality [117]. However, the relationship between depression, inflammatory processes, and CHD clearly represents another important area for further study.

24.6

Does Treating Depression in CHD Patients Reduce Risk of Cardiac Events?

Although there have been very few randomized clinical trials of antidepressants in patients with CHD, the existing studies have found that certain antidepressants are safe and effective for these patients [71, 72]. There is also recent evidence that sertraline is safe for use by patients who are depressed after an acute coronary event.

The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) [118] was designed to determine the safety and efficacy of sertraline (an SSRI) in depressed patients hospitalized for an acute MI or for unstable angina. SADHART provides the first real evidence that at least one of the SSRIs is safe for use shortly after an acute cardiac event. Moreover, it was found to be modestly efficacious, at least for relatively severe, recurrent depression. As we indicated in an editorial accompanying the primary SADHART report, this trial represents an important step toward improving the care of depressed cardiac patients [68]. Cardiologists, psychiatrists, and primary care physicians now have an acceptable alternative to ignoring depression, a comorbid psychiatric disorder that often has devastating consequences for cardiac patients.

Although there is evidence for the safety and efficacy of antidepressants for the treatment of depression in patients with CHD, little is known about the effects of treating depression on subsequent cardiac events. A case-control study by Avery and Winokur [119] is one of the few relevant studies published to date. They found that over a 3-year follow-up, non-suicidal deaths, especially cardiac-related deaths, occurred more frequently among depressed patients who had received inadequate treatment for depression than among those whose treatment was considered adequate. Although this is an intriguing finding, alternative interpretations are possible. For example, it is possible that the patients who received inadequate treatment for their depression also received inadequate care for other medical conditions. Additionally, the study was based on a small number of endpoints.

The SADHART study did not have a large enough sample to reliably address the question of whether sertraline reduces cardiac events in depressed post-MI patients. However, there was a nonsignificant trend toward fewer cardiac events among patients in the sertraline than in the placebo arm. This encouraging trend suggests the need for a future study with a larger sample of depressed patients.

Another recently completed prospective study was designed to determine whether treating depression reduces the risks of the combined endpoint of mortality and recurrent MI after an acute myocardial infarction. The Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial compared a group of depressed and/or socially-isolated post-MI patients who received the usual care to those who received cognitive behavior therapy, and in some cases sertraline, in addition to the usual medical care [120]. Unfortunately, the intervention failed to reduce the rate of recurrent infarction or all-cause mortality. The ENRICHD results are still being studied, and it is not yet clear why the trial failed, or whether any form of depression treatment can improve survival. The depressed participants who were treated with

antidepressants, regardless of whether they received cognitive behavior therapy, tended to survive longer than did patients who were not on an antidepressant. However, antidepressant therapy was not allocated by random assignment, so these results must be interpreted cautiously.

Although we do not yet know whether treating depression can reduce the risks of cardiac mortality and morbidity in depressed post-MI patients, we do know that depression is associated with significant psychological, social, and functional impairment [10, 73]. We also have evidence that treating depression improves quality of life and daily functioning in psychiatric and medical patients [121]. We therefore strongly recommend that depression be assessed and treated in patients with heart disease in order to improve quality of life and psychosocial adjustment. In addition, there is a need for more studies to address the question of whether treating depression improves survival in CHD patients. Less potent risk factors than depression have spawned numerous efforts to identify treatments to reduce the associated morbidity and/or mortality, even after initial attempts were unsuccessful. This remains an important, if somewhat neglected problem for cardiology and psychiatry.

24.7

Summary and Conclusions

There is substantial evidence that depression is a risk factor for cardiac morbidity and mortality in cohorts without clinical evidence of coronary heart disease at enrollment, and in patients with established coronary disease. The relationship between depression and cardiac mortality is especially significant in patients who have recently had an acute myocardial infarction. This finding has been replicated in several studies, despite differences in the methods used to assess depression and in the demographic and medical characteristics of the populations that have been studied. Whether treating depression can reduce the associated risks of morbidity and mortality remains unclear. Nevertheless, we believe that the goal of improving patients' quality of life is sufficient to justify treating depression in these patients.

References

- 1 WILLIS, R., *The works of William Harvey, MD: Translated from the Latin*. Johnson Reprint Corp., New York, 1965 (Originally published in London by Sydenham Society, 1847).
- 2 MALZBERG, B., *Am. J. Psychiatry* 1937, 93, 1231–1238.
- 3 FULLER, R. G., *Psychiatr. Quart.* 1935, 9, 95–104.
- 4 RABINS, P. V., HARVIS, K., DOVEN, S., *J. Affect. Disord.* 1985, 9, 165–167.
- 5 WEEK, A., JUEL, K., VAETH, M., *J. Affective Disord.* 1987, 13, 287–292.
- 6 TSUANG, M. T., WOOLSON, R. F., FLEMING, J. A., *Arch. Gen. Psychiatry* 1982, 37, 979–983.
- 7 American Heart Association, *Heart and Stroke Facts: 2002 Statistical supplement*.

- American Heart Association, Dallas, TX, 2002.
- 8 KESSLER, R. C., BERGLUND, P., DEMLER, O., et al., *JAMA* **2003**, 289, 3095–3105.
 - 9 STEWART, A. L., GREENFIELD, S., HAYS, R. D., et al., *JAMA* **1989**, 262, 907–913.
 - 10 WELLS, K. B., STEWART, A., HAYS, R., et al., *JAMA* **1989**, 262, 914–919.
 - 11 PRATT, L. A., FORD, D. E., CRUM, R. M., et al., *Circulation* **1996**, 94, 3123–3129.
 - 12 COHEN, H. W., MADHAVAN, S., ALDERMAN, M. H., *Psychosom. Med.* **2001**, 63, 203–209.
 - 13 FERKETICH, A. K., SCHWARTZBAUM, J. A., FRID, D. J., et al., *Arch. Intern. Med.* **2000**, 160, 1261–1268.
 - 14 SIMONSICK, E. M., WALLACE, R. B., BLAZER, D. G., BERKMAN, L. F., *Psychosom. Med.* **1995**, 57, 427–435.
 - 15 ANDA, R. F., WILLIAMSON, D., JONES, D., *Epidemiology* **1993**, 4, 285–294.
 - 16 ARIYO, A. A., HAAN, M., TANGEN, C. M., et al., *Circulation* **2000**, 102, 1773–1779.
 - 17 BAREFOOT, J. C., HELMS, M. J., MARK, D. B., et al., *Am. J. Cardiol.* **1996**, 78, 613–617.
 - 18 SESSO, H. D., KAWCHI, I., VOKONAS, P. S., et al., *Am. J. Cardiol.* **1998**, 82, 851–856.
 - 19 WHOOLEY, M. A., BROWNER, W. S., *Arch. Intern. Med.* **1998**, 158, 2129–2135.
 - 20 MENDES DE LEON, C. F., KRUMHOLZ, H. M., SEEMAN, T. S., et al., *Arch. Intern. Med.* **1998**, 158, 2341–2348.
 - 21 HIPPISELEY-COX, J., FIELDING, K., PRINGLE, M., *BMJ* **1998**, 316, 1714–1719.
 - 22 AROMAA, A., RAITASALO, R., REUNANEN, A., et al., *Acta Psychiatr. Scand.* **1994**, 377 (S), 77–82.
 - 23 FORD, D. E., MEAD, L. A., CHANG, P. P., et al., *Arch. Intern. Med.* **1998**, 158, 1422–1426.
 - 24 PENNINX, B., GURALNIK, J. M., MENDES DE LEON, C. F., et al., *Am. J. Cardiol.* **1998**, 81, 988–994.
 - 25 WASSERTHEIL-SMOLLER, S., APPLEGATE, W. B., BERGE, K., et al., *Arch. Intern. Med.* **1996**, 156, 553–561.
 - 26 PENNINX, B. W. J. H., BEEKMAN, A. T. F., HONIG, A., et al., *Arch. Gen. Psychiatry* **2001**, 58, 221–227.
 - 27 BAREFOOT, J. C., SCHROLL, M., *Circulation* **1996**, 93, 1976–1980.
 - 28 THOMAS, C., KELMAN, H. R., KENNEDY, G. J., et al., *J. Gerontology Soc. Sci.* **1992**, 476, S80–S87.
 - 29 RUGULIES, R., *Am. J. Prev. Med.* **2003**, 23, 51–61.
 - 30 WULSIN, L. R., SINGAL, B. M., *Psychosom. Med.* **2003**, 65, 201–210.
 - 31 CARNEY, R. M., RICH, M. W., TEVELDE, A. J., et al., *Am. J. Cardiol.* **1987**, 60, 1273–1275.
 - 32 HANCE, M., CARNEY, R. M., FREEDLAND, K. E., et al., *Gen. Hosp. Psychiatry* **1995**, 18, 61–65.
 - 33 GONZALEZ, M. B., SNYDERMAN, T. B., COLKET, J. T., et al., *Depression* **1996**, 4, 57–62.
 - 34 FORRESTER, A. W., LIPSEY, J. R., TEITELBAUM, M. L., et al., *Int. J. Psychiatry Med.* **1992**, 22, 33–46.
 - 35 SCHLEIFER, S. J., MACARI-HINSON, M. M., COYLE, D. A., et al., *Arch. Int. Med.* **1989**, 149, 1785–1789.
 - 36 CARNEY, R. M., FREEDLAND, K. E., JAFFE, A. S., *Psychosom. Med.* **1990**, 52, 603–609.
 - 37 FRASURE-SMITH, N., LESPÉRANCE, F., TALAJIC, M., *JAMA* **1993**, 270, 1819–1825.
 - 38 LESPÉRANCE, F., FRASURE-SMITH, N., TALJIC, M., *Psychosom. Med.* **1996**, 58, 99–110.
 - 39 TRAVELLA, J. I., FORRESTER, A. W., SCHULTZ, S. K., et al., *Int. J. Psychiatry Med.* **1994**, 24, 357–369.
 - 40 CARNEY, R. M., RICH, M. W., FREEDLAND, K. E., et al., *Psychosom. Med.* **1988**, 50, 627–633.
 - 41 BAREFOOT, J. C., HELMS, M. J., MARK, D. B., et al., *Am. J. Cardiol.* **1996**, 78, 613–617.
 - 42 HERRMANN, C., BRAND-DRIEHORST, S., BUSS, U., et al., *J. Psychosom. Res.* **2000**, 48, 455–462.
 - 43 CONNERNEY, I., SHAPIRO, P., McLAUGHLIN, J. S., et al., *Psychosom. Med.* **2000**, 62, 106.
 - 44 BLUMENTHAL, J. A., LETT, H. S., BABYAK, M. A., et al., *Lancet* **2003**, 362, 604–609.
 - 45 BURG, M. M., BENEDETTO, C. M., ROSENBERG, R., et al., *Psychosom. Med.* **2001**, 63, 103.
 - 46 LESPÉRANCE, F., FRASURE-SMITH, N., JUNEAU, M., et al., *Arch. Intern. Med.* **2000**, 160, 1354–1360.
 - 47 FREEDLAND, K. E., RICH, M. W., SKALA, J. A., et al., *Psychosom. Med.* **2003**, 65, 119–128.
 - 48 ABRAMSON, J., BERGER, A., KRUMHOLZ, H. M., et al., *Arch. Intern. Med.* **1993**, 161, 1725–1730.

- 49 JIANG, W., J. ALEXANDER, CHRISTOPHER, E., et al., *Arch. Intern. Med.* **2001**, 161, 1849–1856.
- 50 KOENIG, H. G., *Gen. Hosp. Psychiatry* **1998**, 20, 29–43.
- 51 KONSTAM, V., SALEM, D., POULEUR, H., et al., *Am. J. Cardiol.* **1996**, 78, 890–895.
- 52 MURBERG, T. A., BRU, E., SVEBAK, S., et al., *Int. J. Psychiatry Med.* **1999**, 29, 311–326.
- 53 ROZZINI, R., SABATINI, T., FRISONI, G. B., et al., *Arch. Intern. Med.* **2002**, 162, 362–364.
- 54 VACCARINO, V., KASL, S. V., ABRAMSON, J., et al., *J. Am. Coll. Cardiol.* **2001**, 38, 199–205.
- 55 FREEDLAND, K. E., RICH, M. W., CARNEY, R. M., et al. (manuscript submitted for publication).
- 56 FRASURE-SMITH, N., LESPÉRANCE, F., TALAJIC, M., *Circulation* **1995**, 91, 999–1005.
- 57 AHERN, D. K., GORKIN, L., ANDERSON, J. L., et al., *Am. J. Cardiol.* **1990**, 66, 59–62.
- 58 LADWIG, K. H., KIESER, M., KONIG, J., et al., *Eur. Heart J.* **1991**, 12, 959–964.
- 59 KAUFMANN, M. W., FITZGIBBONS, J. P., SUSSMAN, E. J., et al., *Am. Heart J.* **1999**, 138, 549–554.
- 60 DENOLLET, J., SYS, S. U., BRUTSAERT, D. L., *Psychosom. Med.* **1995**, 57, 582–591.
- 61 BUSH, D. E., ZIEGELSTEIN, R. C., TAYBACK, M., et al., *Am. J. Cardiol.* **2001**, 88, 337–341.
- 62 IRVINE, J., BASINSKI, A., BAKER, B., et al., *Psychosom. Med.* **1999**, 61, 729–737.
- 63 MAYOU, R. A., GILL, D., THOMPSON, D. R., et al., *Psychosom. Med.* **2000**, 62, 212–219.
- 64 LANE, D., CARROLL, D., RING, C., et al., *Psychosom. Med.* **2001**, 63, 221–230.
- 65 CARNEY, R. M., BLUMENTHAL, J. A., CATELLIER, D., et al., *Am. J. Cardiol.* **2003**, 92, 1271–1281.
- 66 LESPÉRANCE, F., FRASURE-SMITH, N., TALAJIC, M., et al., *Circulation* **2002**, 105, 1049–1053.
- 67 FRASURE-SMITH, N., LESPÉRANCE, F., *Arch. Gen. Psychiatry* **2003**, 60, 627–636.
- 68 CARNEY, R. M., JAFFE, A. S., *JAMA* **2002**, 288, 750–751.
- 69 GLASSMAN, A. H., ROOSE, S. P., BIGGER JR., J. T., *JAMA* **1993**, 269, 2673–2675.
- 70 COHEN, H. W., GIBSON, G., ALDERMAN, M. H., *Am. J. Med.* **2000**, 108, 2–8.
- 71 ROOSE, S. P., *Bio. Psychiatry* **2003**, 54, 262–268.
- 72 SHELIN, Y., FREEDLAND, K. E., CARNEY, R. M., *Am. J. Med.* **1997**, 102, 54–59.
- 73 CARNEY, R. M., FREEDLAND, K. E., MILLER, G. E., et al., *J. Psychosom. Res.* **2002**, 53, 897–902.
- 74 BRUMMET, B. H., BABYAK, M. A., SIEGLER, I. C., et al., *Am. J. Cardiol.* **2003**, 92, 529–532.
- 75 MCCAFFERY, J. M., NIAURA, R., TODARO, J. F., et al., *Psychosom. Med.* **2003**, 65, 490–497.
- 76 DIMATTEO, M. R., LEPPER, H. S., CROGHAN, T. W., *Arch. Intern. Med.* **2000**, 160, 2101–2107.
- 77 CARNEY, R. M., FREEDLAND, K. E., EISEN, S., et al., *Health Psychol.* **1995**, 14, 88–90.
- 78 ZIEGELSTEIN, R. C., FAUERBACH, J. A., STEVENS, S. S., et al., *Arch. Intern. Med.* **2000**, 160, 1818–1823.
- 79 BLUMENTHAL, J. A., WILLIAMS, R. S., WALLACE, A. G., et al., *Psychosom. Med.* **1982**, 44, 519–527.
- 80 ESLER, M., J. TURBOTT, SCHWARZ, R., et al., *Arch. Gen. Psychiatry* **1982**, 39, 285–300.
- 81 LAKE, C. R., PICKAR, D., ZIEGLER, M. G., et al., *Am. J. Psychiatry* **1982**, 139, 1315–1318.
- 82 ROY, A., PICKAR, D., DE JONG, J., et al., *Arch. Gen. Psychiatry* **1988**, 45, 849–857.
- 83 SIEVER, L., DAVIS, K., *Am. J. Psychiatry* **1985**, 142, 1017–1031.
- 84 WYATT, R. J., PORTNOY, B., KUPFER, D. J., et al., *Arch. Gen. Psychiatry* **1971**, 24, 65–70.
- 85 DAWSON, M. E., SCHELL, A. M., CATANIA, J. J., *Psychophysiology* **1977**, 14, 569–578.
- 86 LAHMEYER, H. W., BELLIER, S. N., *Psychiatr. Res.* **1987**, 21, 1–6.
- 87 Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology, *Circulation* **1996**, 93, 1043–1065.
- 88 KLEIGER, R. E., MILLER, J. P., BIGGER, J. T., et al., *Am. J. Cardiol.* **1987**, 113, 256–262.
- 89 BIGGER, J. T., FLEISS, J. L., STEINMAN, R. C., et al., *Circulation* **1992**, 85, 164–171.
- 90 SUDHAIR, V., STEVENSON, R., MARCHANT, A., et al., *Am. J. Cardiol.* **1994**, 73, 653–657.
- 91 CARNEY, R. M., SAUNDERS, R. D., FREEDLAND, K. E., et al., *Am. J. Cardiol.* **1995**, 76, 562–564.
- 92 CARNEY, R. M., FREEDLAND, K. E., VEITH, R. C., et al., *Biol. Psychiatry* **1999**, 45, 458–463.

- 93 CARNEY, R. M., BLUMENTHAL, J. A., STEIN, P. K., et al., *Circulation* **2001**, 104, 2024–2028.
- 94 STEIN, P. K., CARNEY, R. M., FREEDLAND, K. E., et al., *J. Psychosom. Res.* **2000**, 48, 493–500.
- 95 KRITTAYAPHONG, R., CASCIO, W. E., LIGHT, K. C., et al., *Psychosom. Med.* **1997**, 59, 231–235.
- 96 CARNEY, R. M., FREEDLAND, K. E., STEIN, P. K., et al., *Psychosom. Med.* **2000**, 62, 639–647.
- 97 MARKOVITZ, J. H., MATTHEWS, K. A., *Psychosom. Med.* **1991**, 53, 643–668.
- 98 FITZGERALD, D. J., ROY, L., CATELLA, F., et al., *N. Engl. J. Med.* **1986**, 315, 983–989.
- 99 TRIP, M. D., CATS, V. M., VAN CAPELLE, F. J. L., et al., *N. Engl. J. Med.* **1990**, 322, 1549–1554.
- 100 MUSSELMAN, D. L., TOMER, A., MANATUNGA, A. K., et al., *Am. J. Psychiatry* **1996**, 153, 1212–1217.
- 101 LAGHRISSE-THODE, F., WAGNER, W. R., POLLOCK, B. G., et al., *Biol. Psychiatry* **1997**, 42, 290–295.
- 102 POLLOCK, B. G., LAGHRISSE-THODE, F., WAGNER, W. R., *J. Clin. Psychopharmacol.* **2000**, 20, 137–140.
- 103 MUSSELMAN, D. L., MARZEC, U. M., MANATUNGA, A., et al., *Arch. Gen. Psychiatry* **2000**, 57, 875–882.
- 104 VON KÄNEL, R., *Acta Psychiatrica. Scand.* (under review).
- 105 BERLINER, A., NAVAB, M., FOGELMAN, A. M., et al., *Circulation* **1995**, 91, 2488–2496.
- 106 ROSS, R., *N. Engl. J. Med.* **1999**, 340, 115–126.
- 107 MAES, M., MELTZER, H. Y., BOSMANS, E., et al., *J. Affect. Disord.* **1995**, 34, 301–309.
- 108 MAES, M., BOSMANS, E., DE JONGH, R., et al., *Cytokine* **1997**, 9, 853–858.
- 109 DENTINO, A. N., PIEPER, C. F., RAO, K. M. K., et al., *Am. Geriatr. Soc.* **1999**, 47, 6–11.
- 110 MAES, M., *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1995**, 19, 11–38.
- 111 DANESH, J., COLLINS, R., APPLEBY, P., et al., *JAMA* **2000**, 279, 1477–1482.
- 112 RIDKER, P. M., RIFAI, N., STAMPFER, M. J., et al., *Circulation* **2000**, 101, 1767–1772.
- 113 RIDKER, P. M., RIFAI, N., PFEFFER, M., et al., *Circulation* **2000**, 101, 2149–2153.
- 114 MILLER, G. E., COHEN, S., HERBERT, T. B., *Psychosom. Med.* **1999**, 61, 850–860.
- 115 MILLER, G. E., STETLER, C. A., CARNEY, R. M., et al., *Am. J. Card.* **2003**, 90, 1279–1283.
- 116 APPELS, A., BAR, F. W., BAR, J., et al., *Psychosom. Med.* **2000**, 62, 601–605.
- 117 KOP, W. J., COHEN, N., *Psychoneuro-immunology*, Academic Press, New York, **2001**.
- 118 GLASSMAN, A. H., O'CONNOR, C. M., CALIFF, R. M., et al., *JAMA* **2002**, 288, 701–709.
- 119 AVERY, D., WINOKUR, G., *Arch. Gen. Psychiatry* **1976**, 33, 1029–1037.
- 120 WRITING GROUP, *JAMA* **2003**, 289, 3106–3116.
- 121 ORMEL, J., VON KORFF, M., *Arch. Gen. Psychiatry* **2000**, 57, 381–382.

25

Genetic Substrates Shared by Depression and Cardiovascular Disease

Brigitta Bondy

Abstract

There is an increasing accumulation of data concerning the co-morbidity of depression and cardiovascular disease, both of which are among the most common disorders in developed countries. Previously, the impact of depression was mostly related to pre-morbid cardiac disease status, but it is now well established that depression increases the morbidity and mortality risk independent of the baseline cardiac status. Further, the associated vulnerability to these conditions is not unidirectional, as the presence of cardiovascular disease can also influence mood states. Although this may be the result of psychological factors, it is now being speculated that common pathophysiological mechanisms including genetic mechanisms, may be responsible for this interaction, thus questioning whether variations in genes could be the predisposing factors for both conditions.

With respect to the multiple interactions in the pathophysiological mechanisms of depression and cardiovascular system disorders, as e.g. dysfunctions in the hypothalamic–pituitary–adrenocortical and sympathoadrenal axis, the renin–angiotensin system, or within the serotonergic and immune systems, several candidate genes are being investigated. Most available studies so far have dealt with the impact of polymorphisms in relation to either depression or cardiovascular disease, but recent studies have also covered the effects of gene–gene or gene–environment interactions. The significance of these various polymorphisms remains to be determined, as to whether they indicate common pathophysiological mechanisms or identify a subgroup of patients with somatic disorders who have closely related psychiatric symptoms.

25.1

Introduction

*“Give sorrow words: the grief that does not speak
whispers the o’erfraught heart and bids it break.”*
(William Shakespeare, Macbeth)

This citation formulates superbly what people have been aware of since ancient times: sadness is often portrayed as a feeling of heaviness in the chest or as “broken heart”. Thus the relationship between cardiovascular disease and depression is not only the subject of scientific research but also of popular interest.

In clinical studies a large body of evidence has emerged to suggest an extensive co-morbidity between depression and cardiovascular disease (CVD). Cross-sectional and prospective analyses have shown that depression may increase mortality and morbidity in patients with heart failure, regardless of its etiology and independent of traditional risk factors for cardiovascular disease such as hypertension, high cholesterol levels or obesity [1]. In patients who have already suffered an adverse cardiac event such as a myocardial infarction, depression increases the risk of further serious cardiac complications and worsens prognosis, causing a four-fold increment in mortality rate when compared to non-depressed patients [2]. Thus the predictive value of the presence of depression to subsequent cardiovascular events is equivalent to that of left ventricular dysfunction or previous myocardial infarction. This association is still evident after controlling for potential confounders such as family history, blood pressure, smoking, obesity and low levels of physical activity [3, 4].

Although the impact of depression has been mostly related to pre-morbid cardiac disease status, it is now well established that depression also increases the risk for cardiac morbidity and mortality independent of baseline cardiac status [3, 5]. The effects of major and minor depression have been investigated in recent studies among large community-dwellings samples of older subjects with or without cardiac disease. There has been a consensus that depression increases the risk for cardiac mortality independently of the baseline cardiac status of the subjects and furthermore, the excess mortality risk was more than two-fold higher for major depression than for minor depression [2, 6].

The associated vulnerability to these two conditions is not unidirectional, as the presence of cardiovascular disease can also influence mood states. An increase of up to 45% in the incidence of depression among post-myocardial infarction patients has been noted, as compared to about a 9% incidence in the general population [6]. Although this may be the result of psychological factors such as contemplation of one’s mortality, changes in lifestyle and social relationships, the influence of physiological, humoral factors released during cardiovascular pathology, might also be responsible for the development of depression [7]. This hypothesis is supported by the observation that depressed mood is also increased in other medical conditions such as cancer, but without the bi-directional relationship that exists between depression and CVD [8]. In summarizing all available clinical and epidemiological data, convincing evidence has accumulated which suggests that depression is a

major contributing factor to elevated morbidity and mortality after an index cardiac event and a risk factor for the development of atherosclerotic heart disease [9].

25.2

Interacting Pathophysiological Pathways

Although the interacting mechanisms have not as yet been fully elucidated, a variety of indirect and direct mechanisms have been proposed as possible substrates. These include hyperactivity of noradrenergic and hypothalamic–pituitary–adrenal (HPA) systems [10], reduced heart rate variability, myocardial ischemia and ventricular instability in response to psychological stress, exaggerated platelet activity as well as enhanced inflammatory-mediated atherogenesis [10, 11]. The relationship between the immune, autonomic, neuroendocrine and neurotransmitter processes is multidirectional; psychological factors act on the neuroendocrine, neurotransmitter and immune system and vice versa, thereby influencing vulnerability to affective and cardiovascular disorders (Figure 25.1).

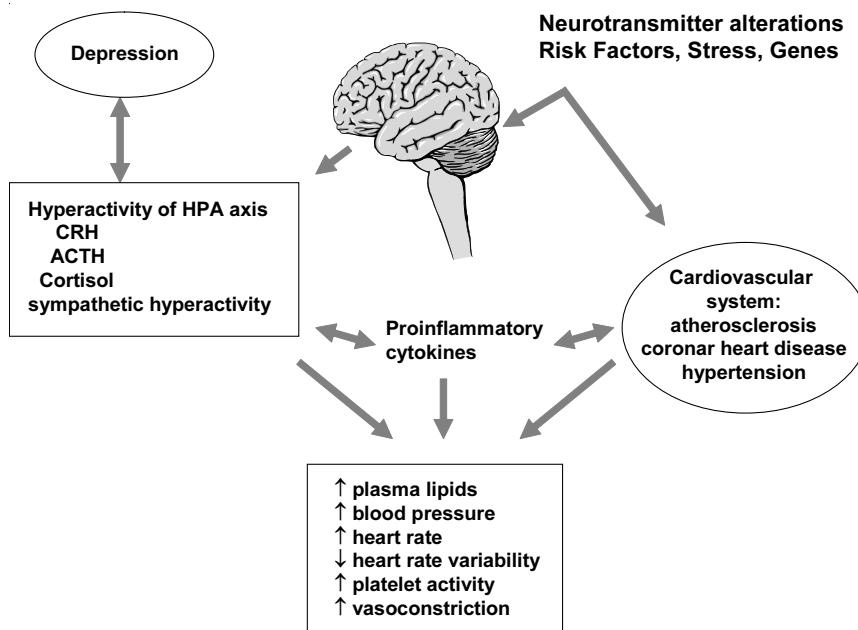


Figure 25.1 Common pathophysiological substrates for depression and cardiovascular disorders

25.2.1

Hypothalamic–Pituitary–Adrenocortical Axis and Sympathoactivity

There is extensive literature to demonstrate the importance of the HPA axis in response to stress and its hyperactivity in patients with major depression. Altered regulation of adrenocorticotropin (ACTH) and cortisol secretory activity [12], impaired feedback mechanisms and corticosteroid receptor (CR) signaling with increased production of corticotropin-releasing-hormone (CRH) [13] are well documented. It was further shown that the administration of cortisol can induce hypercholesterolemia, hypertriglyceridemia and hypertension and that elevated morning cortisol concentrations may induce atherosclerosis via injury of the vascular endothelial cells [14].

Dysfunction in the HPA axis during depression is mirrored by dysfunctions in the sympathetic nervous system with decreased noradrenergic activity within the central nervous system (CNS) but increased activity in the periphery [15]. This elevated sympathetic tone may in turn lead to cardiovascular dysregulation due to its effect on blood vessels, platelets and cardiac β -receptors, thus increasing heart rate and contractility. On the other hand, alterations in the tone of the sympathetic nervous system result in decreased heart rate variability which is also a risk for cardiac mortality [9]. Both increased heart rate and decreased heart rate variability were observed in depressed patients [10].

25.2.2

Serotonin Function and Cardiovascular Response to Stress and Depression

Serotonin (5-HT) is a neurotransmitter essential for a large number of physiological and psychological processes including the regulation of the contraction of vascular and non-vascular smooth muscle, modulation of platelet aggregation and the regulation of appetite, mood, anxiety, wakefulness and perception [16]. In depression research a number of alterations have been reported in the brain and periphery concerning 5-HT uptake, transporter and receptor binding sites [17–20] and altered platelet activation [21]. Moreover, reduced serotonergic function within the central nervous system (CNS) has been associated with smoking and alcohol abuse, and alterations in the HPA response to stress and reduced parasympathetic function, which all predict higher rates of coronary heart disease and increased mortality [22]. Due to the direct vasoconstrictive action of 5-HT, which is mediated via the 5-HT_{2A} receptors, this neurotransmitter has been implicated in the pathophysiology of essential and pulmonary hypertension, thrombosis and atheroma formation [23].

Markovitz and Matthews [24] were the first to propose that enhanced platelet response to psychological stress might trigger adverse coronary artery ischemic events. The activation of platelets is pivotal in the development of hemostasis and thrombosis and plays a role in the development of atherosclerosis via multiple interactions with endothelial vessel walls and plasma coagulation factors [25]. The formation and dissolution of small thrombi are part of a continuous process, and

any change in this balance may lead to a bleeding or clotting diathesis [21]. Following arterial injury, platelets readily adhere to subendothelial components, become activated and release a variety of chemical mediators from storage granules, including serotonin, platelet factor 4 (PF4), and β -thromboglobulin (β -TG) [11]. The 5-HT released induces both platelet aggregation and coronary vasoconstriction, mediated by 5-HT₂ receptors [21]. Essential hypertension, elevated plasma cholesterol levels, older age, and smoking, all known to be predisposing factors for CVD, contribute to the serotonin-mediated platelet activation.

25.2.3

Immune Activation in Depression and Cardiovascular Disease

In the last decade research in cytokine biology has expanded rapidly and the role of cytokines has been assessed in a variety of medical conditions that are not traditionally considered to have an infectious or inflammatory pathogenesis, such as heart failure and depression. A variety of immunological processes are altered during depression, including those of cellular components and soluble mediators, to produce acute phase proteins and cytokines (e.g. IL-1, IL-6 and TNF- α) [26, 27]. Cytokines induce neuroendocrine and central neurotransmitter alterations that are reminiscent of those implicated in depression and these effects are exacerbated by stressors [27].

Both IL-1 and IL-6 stimulate CRH secretion, resulting in increased ACTH and glucocorticoid release. On the other hand, CRH is a main regulatory hormone that is secreted in response to stress and has a wide range of immune functions, such as stimulation of pro-inflammatory cytokine secretion. On the other hand, pro-inflammatory cytokines have profound effects on peripheral and brain serotonergic systems, as they increase extracellular 5-HT concentration within different brain regions or modulate the activity of the 5-HT transporter [28]. Taking all these interactions into consideration, cytokines may well close the loop between the nervous and immune systems.

Although high plasma concentrations of cholesterol, particularly those of low density lipoprotein are considered to be one of the principal risk factors for atherosclerosis, it became evident that other factors should also be taken into consideration. Today there is no doubt that atherosclerosis is an inflammatory disease and does not simply result from the accumulation of lipids [29]. The long-term impact of pro-atherosclerotic factors on endothelium cells results in chronic inflammation with a consequent rise of C-reactive protein, adhesion molecules and the proinflammatory cytokines TNF- α and IL-6, which are now recognized to be powerful predictors of atherosclerosis and myocardial infarction [29]. On the other hand, it is known that a rise in blood pressure causes chronic inflammation of the endothelium which in turn may be responsible for further endothelial damage [30].

25.3

Candidate Genes for a Common Genetic Basis

The importance of biological vulnerability factors and environment has been heavily debated and it was proposed that a substantial proportion of morbidity may be attributed not only to a specific risk for one disorder, but also to several underlying liability factors that are applicable to both cardiovascular and depressive disorders [31]. Thus, even if both conditions did not affect each other, they might still co-segregate if they shared common underlying factors, including genetic factors. As both disorders are complex and multifactorial in origin involving multiple genes with interactive or additive effects together with environmental factors, depression and cardiovascular disease could be different manifestations of the same genetic substrate. Another possibility is that both are the result of a common pathological process, the most obvious candidate being atherosclerosis. This would support the notion that atherosclerotic disease of the brain predisposes to depression [32].

Despite convincing hypotheses and data on the pathophysiological interactions and despite interesting and promising genetic association studies for each disorder, only a few studies have considered a possible interaction between them on a genetic basis. The following section summarizes several important findings derived from association studies with candidate genes, which could indicate that a common pathology may initiate both conditions.

25.3.1

Genes of the Serotonergic Pathway

With respect to the key position of serotonin in physiological and psychological processes it is not surprising that genes coding for the serotonergic pathway have been repeatedly investigated for several years. The studies have investigated not only a possible association with psychiatric states such as anxiety, hostility, depression, or smoking behavior, but also several characteristics of platelet function or the effect of serotonin on the vessel wall and induction of atherosclerosis.

The serotonin transporter (5-HTT) in particular, has been the main subject of investigations. 5-HTT clears the synaptic cleft of neurotransmitters, thus limiting the duration of 5-HT function. As this transport protein is not only expressed by neuronal tissues but also by blood platelets where it is crucial in maintaining the homeostasis of the intracellular 5-HT level in blood [33], this gene is clearly of importance in both disorders.

The expression of the 5-HTT is predominantly under genetic control, but non-genetic factors including psychoactive drugs, stress, alcohol and the availability of the substrate also regulate its expression [34]. In particular, two polymorphic sites within the 5-HTT gene were the subject of a variety of investigations, one site being located in the promoter region with a deletion/insertion variation of 44 bp, creating short (S) and long (L) alleles, the serotonin-transporter-linked promoter region (HTTLPR), and the second, a variable number tandem repeat (VNTR) polymorphism site, located in the second intron of the gene [35]. The presence of

the S allele of the HTTLPR is associated with decreased transcriptional activity and decreased 5-HT uptake, which, in turn results in a longer duration of serotonergic activity [36].

Although the results with psychiatric patients are not conclusive, this polymorphism may be of some importance in anxiety-related personality traits [37], depression [38] and suicidality [39]. Even though the data are not consistent, a recent meta-analysis yielded encouraging, modest but positive evidence implicating 5-HTT gene polymorphisms in affective disorders [40]. However, there are ethnic differences concerning the 5-HTTLPR, as in Chinese and Japanese populations the frequency of the L allele is low, in contrast to Caucasian populations with an L-frequency of between 55 and 63% [34].

Although there is a plethora of data relating to 5-HTT, data relating to the serotonergic receptor gene polymorphisms is less abundant. The 5-HT_{2A} receptor T102C polymorphism, which has been the subject of many pharmacogenetic investigations, was not found to be a susceptibility locus for unipolar or bipolar depression [41, 42]. With respect to a structural variant of the 5-HT_{2C} receptor gene which gives rise to a cysteine to serine substitution in the N-terminal extracellular domain of the receptor protein (cys23ser), a significant excess of the 23ser allele carriers were found among a large European cohort of depressive patients, which supports the proposed role of a genetically-based structural variation in depression [43]. This finding is interesting with respect to the development of diabetes and obesity, as the 5-HT_{2C} receptor is assumed to be at least partially responsible for the body mass index, and weight gain during treatment with psychotropic drugs and two polymorphisms within the promoter region of the 5-HT_{2C} receptor gene were recently associated with obesity and/or type II diabetes [44].

25.3.1.1 The 5-HTTLPR and Cardiovascular Disease

The role of 5-HTT gene polymorphisms in susceptibility to cardiovascular disease has only recently been the subject of several studies (Table 25.1) In concordance with the increased transcriptional activity of the L-allele it was shown that subjects being homozygous for this allele have higher blood serotonin concentrations than those with the S allele, presumably due to increased 5-HT uptake and storage [45]. These findings are in agreement with observation in geriatric depressed patients, that the 5-HTTLPR polymorphism influences the degree of platelet activation, as homozygosity for the long allele (L/L) was associated with platelet activation, increased platelet factor 4 and thromboglobulin levels [46]. On the basis of these findings it may be proposed that platelets of persons with the L/L genotype are more efficient in uptake and storage of 5-HT in their dense granules, followed by increased 5-HT release upon activation, which may consequently lead to a greater thrombus formation and finally to myocardial infarction. This hypothesis was supported by a study of > 600 patients with coronary artery disease, which showed that carriers of the LL genotype had a higher risk for myocardial infarction [47].

A recent combined analysis of the 5-HTTLPR and the silent T102C SNP in the 5-HT_{2A} receptor gene revealed no influence of the 5-HT_{2A} polymorphism on the

Table 25.1 The serotonin transporter polymorphism (5-HTTLPR) with S/L variants in relation to psychiatric states, cardiovascular function and stress response

<i>Allele/genotype</i>	<i>Association</i>	<i>Reference</i>
SL and SS	Anxiety	37
	Depression	38
	Suicidality	39
	Depressive symptoms in relation to stressful life events	59
LL	5-HT uptake and storage in platelets	45
	Platelet activation in depressives	46
LL and LS	Risk for myocardial infarction,	47
	pulmonary hypertension	50
	Risk for cardiovascular disease	54
	Increased CSF 5-HIAA levels and blood pressure and heart rate in response to stress	22
LS	Serum cholesterol and triglycerides	57

incidence of myocardial infarction in a Spanish population. Similarly, no relation was found between the 5-HTTLPR alleles and myocardial infarction, although the SS genotype was significantly more frequent among older patients. The authors concluded that the SS genotype would seem to have a protective effect against myocardial infarction [48]. This hypothesis was upheld by a recent study, which showed that selective serotonin reuptake inhibitors (SSRIs) attenuate platelet activation by depleting serotonin storage and may thus decrease the risk for myocardial infarction [49].

Serotonin not only has an effect on platelets but also a direct proliferative action on smooth muscle cells. The possibility of increased uptake and storage of 5-HT as a pathophysiological mechanism of pulmonary hypertension has been frequently debated, and indeed, an increased incidence of LL homozygotes among patients with pulmonary hypertension has been observed; an increase in 5-HT uptake and increased proliferation in response to 5-HT by the pulmonary artery smooth muscle cells was also demonstrated in these patients [50]. This provides evidence of a clinical relationship between a genetic abnormality and a cellular process critical in the development of pulmonary vascular disease.

25.3.1.2 The 5-HTTLPR and Risk Factors for Cardiovascular Disease

Smoking is one of the unquestioned risk factors for CVD, and dependence on tobacco, like many other drug dependencies, is a complex behavior with both genetic and environmental factors contributing to its variance [51]. As there is increasing evidence that chronic nicotine abuse decreases serotonin levels in the brain [52] and SSRIs in combination with a 5-HT₁ receptor antagonist may reverse the reward deficits during nicotine withdrawal in rats [53], the 5-HTT gene has attracted attention. Further it is well known, that smoking behavior is common among depressed patients. However, so far only a few relevant studies have been carried out, the results of which have been contradictory.

Studies in a Japanese population indicated a relationship between the L allele, myocardial infarction and smoking, as the LL and LS genotypes were more frequently observed among male CVD patients and smoking was found to have a synergistic effect [54]. In contrast, in an American population Lerman found no significant difference in the distribution of 5-HTT genotypes among smokers and non-smokers, but more recent analyses have revealed an interaction between the SS genotype and neuroticism in nicotine addiction [55]. This suggests that nicotine addiction may be influenced by a combination of the 5-HTT gene and anxiety-related personality traits rather than by each factor alone [51]. Furthermore, alcoholism, a known risk factor for hypertension and cerebral hemorrhagic infarction and a common co-morbid condition with depression, has been associated with the SS genotype in an American population [56].

These discrepancies are hard to explain, but may suggest that both S and L variants may increase the risk of vascular events via different mechanisms. Low transcription activity of the S allele results in low serotonergic activity and the compensatory up-regulation of 5-HT_{2A} receptors in platelets. Increased activation and thrombogenesis might be the consequences of these up-regulated 5-HT_{2A} receptors. On the other hand, subjects with the L allele or LL genotype may have a higher 5-HT concentration and thus higher vasoconstriction in the presence of an atherosclerotic lesion [34].

With regard to other cardiovascular risk factors, such as serum cholesterol and triglyceride levels, further support for the 5-HTT genetic hypothesis may be derived from a study of elderly athletes [57]. Furthermore, a significant association was found between the LS genotype and heart disease, angina pectoris and myocardial infarction among elderly subjects of > 70 years of age. The authors of this report have suggested that the effects of age and molecular heterosis may account for this association. Molecular heterosis refers to the more dominant phenotypic effects seen among heterozygotes as compared to homozygotes [58].

25.3.1.3 The 5-HTTLPR and Response to Stress

The possible impact of the 5-HTTLPR polymorphism on the effects of central serotonin on cardiovascular reactivity to mental stress was investigated in healthy volunteers. Persons with one or two L alleles had higher cerebrospinal fluid levels of the 5-HT metabolite 5-hydroxyindole-acetic-acid (5-HIAA) than those with the S/S genotype and exhibited increased blood pressure and heart rate in response to a mental stress protocol. This demonstrates that the 5-HTTLPR affects not only central 5-HT function, but also seems to be involved in the regulation of bio-behavioral characteristics as a consequence [22].

The link between depression and CVD is strengthened by recent evidence of a gene–environment interaction. Investigating a large representative cohort in a prospective–longitudinal study, Caspi and colleagues [59] were able to show that individuals with one or two copies of the S allele exhibited more depressive symptoms, more diagnosable depression and more suicidal ideation in relation to stressful life events than individuals homozygous for the L allele. This finding suggests that genetic variants may act to promote an individual's resistance to

environmental pathogens. Thus it may be suggested that the S allele moderates the depressiogenic influence of stressful life events and that these results support previous findings of an association between the S allele and depression [38].

25.3.2

Genes Coding for Proinflammatory Cytokines

Both, depression and myocardial infarction are stress-related disorders and stress may induce activation of the inflammatory response system with increased secretion of proinflammatory cytokines, such as interleukin-1 β (IL-1 β), IL-2, IL-6 and tumor necrosis factor- α (TNF- α) [28]. Thus cytokines may be the common mediator of this co-morbidity, although it still remains to be clarified whether depression could be a marker of inflammation or may foster inflammation, whether cytokines themselves amplify existing depression and whether sub-clinical heart failure leads to depression through cytokine involvement [27].

With respect to the fact that the expression and function of cytokines is highly influenced by genetic make-up, many studies have been undertaken to investigate their influence on cardiovascular disorders and conventional risk factors, such as diabetes and obesity (Table 25.2). However, up to now, and despite the findings of increased plasma levels of IL-6 and TNF- α among depressed patients [26], immunogenetic studies are so far negligible in depression research. In a recent study a bi-allelic polymorphism in the promoter region (–C511T) of the IL-1 β gene was investigated in a Japanese population who suffered from depression and who showed no association between any genotype or allele and the disorder, however, the response to treatment was better among those patients who were homozygous for the –511T allele [60].

The genes coding for IL-6 and TNF- α have functional variants that regulate their expression. The most extensively studied polymorphism of the IL-6 gene is a G/C conversion in the promoter region (–174G/C) which alters the cAMP binding site and affects the transcription and plasma level of IL-6 [61]. Although negative results

Table 25.2 Candidate genes of the immune system for cardiovascular disease and depression

Gene	SNP	Location	Function	Clinical association
TNF- α	G \rightarrow A	–308	A-allele: \uparrow TNF- α	History of myocardial infarction [71] Obesity and insulin resistance [70] No association with blood pressure [71, 75]
IL-6	G \rightarrow C	–174	C-allele: \uparrow IL-6 level	\uparrow C-reactive protein and IL-6 [63, 64] \uparrow Systolic blood pressure [65] \uparrow Risk for coronary heart disease [66], obesity [69] \uparrow Alcohol consumption and \uparrow carotis intima-media-thickness [69]
IL-1 β	C \rightarrow T	–511	T-allele: \uparrow IL-1 level	No association with depression TT \rightarrow better treatment response [60]

TNF- α , tumor necrosis factor- α ; IL, interleukin.

were also reported among patients with coronary artery disease and previous myocardial infarction [62], there now seems to be consensus that at least in men the $-174C$ allele is associated with an increased plasma concentration of C-reactive protein and IL-6 [63, 64], higher systolic blood pressure [65], especially among individuals with a body mass index of > 25 and increased risk of coronary heart disease (OD 1.54) [66]. Smoking appeared to have an additive effect to these associations, as both an increase in blood pressure and a detrimental effect on endothelial function was observed in $-174CC$ carriers who smoked [66, 67]. Obesity which represents an expansion of the adipose tissue and is closely related to insulin resistance and cardiovascular disease was also shown to be related to the IL-6 $-174C$ allele as the GG genotype occurs more commonly among lean male subjects with low concentrations of either insulin or glucose [68].

A relationship was shown to exist between alcohol consumption, clinical cardiovascular events and carotid atherosclerosis, as in subjects with a daily alcohol consumption of ≥ 30 g, the CC genotype revealed significantly higher plasma IL-6 levels and carotid artery intima-media thickening [69].

The data concerning TNF- α gene polymorphisms are less abundant. TNF- α is involved in the inflammation process of atherosclerosis and lipid metabolism. A common polymorphism in the promoter region (-308 G/A) regulates TNF- α production and was shown to be a candidate gene for the development of both obesity and insulin resistance [70]. In an Australian population it was shown that subjects who were homozygous for the A allele had higher fasting insulin levels, higher systolic blood pressure and lower high density lipoprotein (HDL) levels than subjects who were homozygous for the G allele. Thus, this variant confers an increased risk for the development of insulin resistance in obese subjects and low HDL levels further increase the risks associated with insulin resistance in carriers of the A allele [71].

Although the TNF- α AA genotype was also associated with myocardial infarction [72] this relationship is less well established [71, 73–75].

25.3.3

The Angiotensin Converting Enzyme Gene

The angiotensin-converting-enzyme (ACE) is a membrane-bound Zn^{+} metalloendopeptidase that is involved in the metabolism of many small peptides, such as the conversion of angiotensin I to angiotensin II or the hydrolysis of bradykinin, both being important for the regulation of vascular tone and cardiac function. In addition, the renin–angiotensin system has modulatory activities in the atherogenetic process, as angiotensin II has proinflammatory actions in the vascular wall, including the production of IL-6 and adhesion molecules and thus augments vascular inflammation, inducing endothelial dysfunction as well as enhancing the atherogenetic process [76].

However, the effects of this enzyme are not restricted to the vasculature, as several studies have demonstrated that ACE might also be involved in HPA axis regulation and catecholamine production via the ATII generation [77] and is required for

sympathoadrenal activation during stress. Further evidence suggests the involvement of the brain renin–angiotensin system in the regulation of mood as colocalization of angiotensin with dopamine-synthesizing neurones [78] has been demonstrated. The fact that ACE is involved in the metabolism of the neuropeptide substance P, which in turn is assumed to play a role in depression [79], in addition to the clinical observation that the treatment of hypertensives with ACE inhibitors might induce euphoric or depressive states [80], underlines the importance of ACE in affective disorders. Further, an animal study using angiotensinogen-deficient mice demonstrated a reduction in depressive-like behavior [81].

The ACE gene has several allelic polymorphisms, one of them consisting of the presence (I) or absence (D) of a 287-bp *alu* repeat sequence within intron 16 of the ACE gene; the D allele is associated with increased levels of circulating ACE [82]. Since the discovery of this polymorphism there has been considerable interest in its potential clinical associations. Numerous studies have implicated the ACE DD genotype with cardiovascular disorders, including myocardial infarction, hypertension and left ventricular hypertrophy [83, 84], but the associations were not consistent in all studies. Taken together the results are conflicting, although a review of the literature revealed a moderate degree of increased risk for myocardial infarction associated with the ACE DD genotype in most populations, especially Japanese populations [85]. Further, the frequency of the ACE genotypes varied with age, gender and ethnicity [86]. Despite all these problems, the ACE genotypes appear to confer susceptibility to a large number of diseases, including affective disorders, for which an overrepresentation of the DD genotype was shown for a Japanese population [87]. Although this finding with regard to affective disorders could not be replicated in our study [88, 89] or in other studies involving depressed European patients [90], we have observed that patients with the I/I genotype respond more rapidly to antidepressant treatment [88]. Furthermore we were able to demonstrate an interaction with the HPA axis, as patients with the DD genotype had higher basal and stimulated cortisol levels in the combined dexamethasone–CRH suppression test [91].

Considering the multiple interactions of ACE in the brain and periphery, it was proposed that the ACE gene acts as a “master gene” being associated with a large number of common adult diseases including cardiovascular disease, cancer and psychiatric disorders. Individual diseases are then distinguished by additional genetic polymorphisms that confer organ specificity [86].

25.3.4

Genes of the Signal Transduction Cascade: G-Proteins

Heterotrimeric G-proteins composed of α , β and γ subunits are important components of intracellular signal transduction and are ultimately responsible for the transduction of the signal into complex physiological responses [92]. The heterotrimeric complex dissociates after receptor activation into the $G\alpha$ and $G\beta\gamma$ subunits. The free GTP binds to the α -subunit, but the $\beta\gamma$ -complex also contributes to the specificity of G-protein interactions by inhibiting or activating a variety of

intracellular effectors [93]. It is therefore intriguing to suppose that mutations which affect the function of either subunit have a strong impact on intracellular signal transduction thereby modulating disease.

Despite the obvious importance of the $G\alpha$ subunit and the increasing body of evidence for the involvement of abnormal function and/or expression of these proteins in the pathophysiology of affective disorders [94] and hypertension [95], only a few genetic association studies are available. The gene coding for the α -subunit of the G(s) protein (GNAS 1) has a common silent polymorphism (T393C) which was investigated in relation to hypertension. Although only a marginal association between hypertension and the T393C polymorphism was observed, the interaction with confounding factors such as smoking [95] and alcohol abuse [96] was highly significant. In depression this variant of the $G\alpha$ s gene is apparently of less importance, as we were not able to detect any difference between > 200 depressed patients and control subjects [97].

In contrast, the literature is extensive concerning the $G\beta 3$ -subunit and a C to T exchange at position 825 in exon 10, which leads to the occurrence of a splice variant ($G\beta 3$ -s) with a deletion of 41 amino acids. The T-allele of this polymorphism results in increased ion flux across the membrane and increased signal transduction and is thus a candidate for the expression of hypertension and obesity [98]. Soon after the identification of this polymorphism a considerable number of ethnic differences were found: an increased frequency of the 825T allele among Australians, black Africans and Black-Americans (50–60%), a lower frequency in the Asian population (50–60%), and the lowest frequencies of this allele among Caucasians (20–40%) [99]. These ethnic differences are interesting in view of the fact that the frequency of the 825T allele, which has repeatedly been associated with hypertension, obesity and cardiovascular disorders [100–103], is highest among populations who are at highest risk for obesity and cardiovascular disorders such as hypertension and stroke, when they give up their natural lifestyle [99].

This genetic variant however, seems to contribute not only to somatic disorders but also to psychiatric conditions, as we found an increased frequency of the T-allele in patients with affective psychosis [104]. This preliminary data was replicated in an extended sample using the DNA of 201 patients suffering from major depression, but among whom the proportion of those suffering from hypertension was not greater than that in a healthy population [89]. Also, in healthy controls who were not suffering from clinical depression, an association was found between the 825T allele and depressive mood, as assessed with the Beck Depression Inventory [105]. In addition to the association of the 825T allele with various disorders in which altered signal transduction or ion fluxes are believed to be important pathophysiological mechanisms, this variant is of further importance in the response to treatment, as the response to antidepressants [104, 106] and phosphodiesterase inhibitors [107] was both more rapid and more efficacious in patients carrying the T-allele or TT genotype. These results imply that the signal transduction cascade is an important key mechanism of action for many drugs.

25.3.5

Gene–Gene Interaction

Recently the impact of the ACE DD genotype on myocardial infarction was re-evaluated using the paradigm of gene–gene interaction between the ACE gene variants together with the C825T polymorphism in the G-protein $\beta 3$ subunit (G $\beta 3$) in patients with coronary artery disease with and without myocardial infarction [108]. This analysis revealed that among myocardial infarction patients, the highest odds ratio (OR = 7.5) was found for those individuals who were of the combined homozygous G $\beta 3$ 825TT and ACE DD genotypes [108], suggesting a significant interaction between the G $\beta 3$ 825T and the ACE D allele as a possible contributing factor for myocardial infarction.

Based on our own previous results concerning an association of the G $\beta 3$ 825T allele with affective disorders [104] and a possible influence of the ID polymorphism of the ACE gene polymorphism on therapeutic outcome in affective disorders [88], we studied the interaction of both genes in 201 patients with unipolar major depression and 161 ethnically-matched controls. Interestingly, we also observed a combined action of ACE and G $\beta 3$ genotypes in depressed patients, as ACE-ID and DD/G $\beta 3$ -TT carriers were more than 4 times more likely to suffer from depression than the controls with a crude OR = 5.83, 95% CI 1.99–17.08, $p = 0.0002$ (Figure 25.2) [89]. As our study was carried out with depressive patients without serious cardiovascular impairment, we are presently unable to predict whether this combined action of the ACE-ID/DD–G $\beta 3$ -TT genotype increases the risk for both disorders. Nevertheless our study reports for the first time that the same allelic combination of two genes that has been shown to increase the risk for myocardial infarction [108] also increases vulnerability to depressive disorders and this could be a missing link in the substantiation of the interaction.

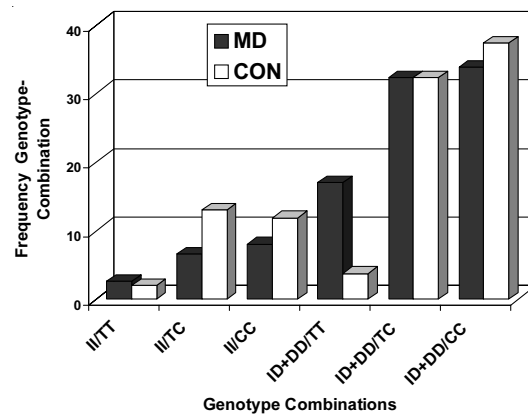


Figure 25.2 Combined ACE and G $\beta 3$ genotypes in patients with major depression ($n = 210$) and ethnically-matched healthy controls ($n = 161$). The ID + DD/TT genotype was at high risk of major depression with a significant increase in crude OR (OR = 5.83; 95% CI 1.99–17.08, $p = 0.0002$).

25.4

Summary and Conclusion

Despite the interesting and promising genetic findings regarding depression and cardiovascular disorders and despite the considerable overlap in pathophysiological mechanisms, up to now few studies have been carried out to investigate a possible combined genetic mechanism. Taking into account the fact that both disorders are complex traits resulting from multiple genotypes, gene–gene and gene–environment interactions, the identification of a gene responsible for either disorder is already made difficult. Some multifactorial disorders, instead of resulting from variations in many genes of small effect, may result from variations in fewer genes whose effects are conditional to exposure to environmental risks [59]. Within recent years many studies have investigated polymorphisms in candidate genes in relation to the functional characteristics of central or peripheral mechanisms that are involved in the development of cardiovascular disorders. The fact that it is possible that many of these genes also contribute to the presence of depression, raises the intriguing question of whether an interactive or synergistic effect is responsible for this bidirectional relationship.

Prospective studies of a large number of patients that include intensive clinical characterization, investigation of biological markers in both patient groups, and genotyping for relevant polymorphisms in genes which are assumed to be involved in both disorders, will need to be carried out in order to clarify the nature of the interaction between these disorders.

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References

- 1 JIANG, W., KRISHNAN, R. R., O’CONNOR, C. M., *CNS Drugs* **2002**, 16, 111–127.
- 2 PENNINX, B. W., BEEKMAN, A. T., HONIG, A., DEEG, D. J., SCHOEVERS, R. A., VAN EIJK, J. T., VAN TILBURG, W., *Arch. Gen. Psychiatry* **2001**, 58, 221–227.
- 3 FRASURE-SMITH, N., LESPERANCE, F., TALAJIC, M., *Circulation* **1995**, 91, 999–1005.
- 4 GLASSMAN, A. H., SHAPIRO, P. A., *Am. J. Psychiatry* **1998**, 155, 4–11.
- 5 FRASURE-SMITH, N., LESPERANCE, F., TALAJIC, M., *JAMA* **1993**, 270, 1819–1825.
- 6 GRIPPO, A. J., JOHNSON, A. K., *Neurosci. Biobehav. Rev.* **2002**, 26, 941–962.
- 7 SCHLEIFER, S. J., MACARI-HINSON, M. M., COYLE, D. A., SLATER, W. R., KAHN, M., GORLIN, R., ZUCKER, H. D., *Arch. Intern. Med.* **1989**, 149, 1785–1789.
- 8 ROOSE, S. P., GLASSMAN, A. H., SEIDMAN, S. N., *JAMA* **2001**, 286, 1687–1690.
- 9 MUSSELMAN, D. L., NEMEROFF, C. B., *Prog. Brain Res.* **2000**, 122, 43–59.
- 10 CARNEY, R. M., FREEDLAND, K. E., VEITH, R. C., CRYER, P. E., SKALA, J. A., LYNCH,

- T., JAFFE, A. S., *Biol. Psychiatry* **1999**, *45*, 458–463.
- 11 MUSSELMAN, D. L., EVANS, D. L., NEMEROFF, C. B., *Arch. Gen. Psychiatry* **1998**, *55*, 580–592.
- 12 NEMEROFF, C. B., MUSSELMAN, D. L., EVANS, D. L., *Depress. Anxiety* **1998**, *8* (Suppl. 1), 71–79.
- 13 HOLSBOER, F., *Neuropsychopharmacology* **2000**, *23*, 477–501.
- 14 TROXLER, R. G., SPRAGUE, E. A., ALBANESE, R. A., FUCHS, R., THOMPSON, A. J., *Atherosclerosis* **1977**, *26*, 151–162.
- 15 VEITH, R. C., LEWIS, N., LINARES, O. A., BARNES, R. F., RASKIND, M. A., VILLACRES, E. C., MURBURG, M. M., ASHLEIGH, E. A., CASTILLO, S., PESKIND, E. R., *Arch. Gen. Psychiatry* **1994**, *51*, 411–422.
- 16 KROEZE, W. K., KRISTIANSEN, K., ROTH, B. L., *Curr. Top. Med. Chem.* **2002**, *2*, 507–528.
- 17 STOCKMEIER, C. A., *J. Psychiatr. Res.* **2003**, *37*, 357–373.
- 18 HRDINA, P. D., BAKISH, D., CHUDZIK, J., RAVINDRAN, A., LAPIERRE, Y. D., *J. Psychiatry Neurosci.* **1995**, *20*, 11–19.
- 19 MENDELSON, S. D., *J. Affect. Disord.* **2000**, *57*, 13–24.
- 20 NEUGER, J., EL KHOURY, A., KJELLMAN, B. F., WAHLUND, B., ABERG-WISTEDT, A., STAIN-MALMGREN, R., *Psychiatry Res.* **1999**, *85*, 189–198.
- 21 NEMEROFF, C. B., MUSSELMAN, D. L., *Am. Heart J.* **2000**, *140*, 57–62.
- 22 WILLIAMS, R. B., MARCHUK, D. A., GADDE, K. M., BAREFOOT, J. C., GRICHNIK, K., HELMS, M. J., KUHN, C. M., LEWIS, J. G., SCHANBERG, S. M., STAFFORD-SMITH, M., SUAREZ, E. C., CLARY, G. L., SVENSON, I. K., SIEGLER, I. C., *Psychosom. Med.* **2001**, *63*, 2–5.
- 23 VANHOUTTE, P. M., *J. Cardiovasc. Pharmacol.* **1990**, *16* (Suppl. 3), S15–S19.
- 24 MARKOVITZ, J. H., MATTHEWS, K. A., *Psychosom. Med.* **1991**, *53*, 643–668.
- 25 LEFKOVITS, J., PLOW, E. F., TOPOL, E. J., *N. Engl. J. Med.* **1995**, *332*, 1553–1559.
- 26 MAES, M., *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1995**, *19*, 11–38.
- 27 PASIC, J., LEVY, W. C., SULLIVAN, M. D., *Psychosom. Med.* **2003**, *65*, 181–193.
- 28 HONIG, A., MAES, M., *Curr. Opin. Psychiatry* **2000**, *13*, 661–664.
- 29 ROSS, R., *Am. Heart J.* **1999**, *138*, S419–S420.
- 30 BARBIERI, M., FERRUCCI, L., CORSI, A. M., MACCHI, C., LAURETANI, F., BONAFE, M., OLIVIERI, F., GIOVAGNETTI, S., FRANCESCHI, C., PAOLISSO, G., *Am. J. Hypertens.* **2003**, *16*, 537–543.
- 31 NEELEMAN, J., ORMEL, J., BIJL, R. V., *Psychosom. Med.* **2001**, *63*, 2–47.
- 32 BALDWIN, R. C., O'BRIEN, J., *Br. J. Psychiatry* **2002**, *180*, 157–160.
- 33 OWENS, M. J., NEMEROFF, C. B., *Clin. Chem.* **1994**, *40*, 288–295.
- 34 RAMASUBBU, R., *Med. Hypotheses* **2003**, *61*, 36–44.
- 35 LESCH, K. P., BALLING, U., GROSS, J., STRAUSS, K., WOLOZIN, B. L., MURPHY, D. L., RIEDERER, P., *J. Neural Transm. Gen. Sect.* **1994**, *95*, 157–162.
- 36 HEILS, A., TEUFEL, A., PETRI, S., STOBBER, G., RIEDERER, P., BENDEL, D., LESCH, K. P., *J. Neurochem.* **1996**, *66*, 2621–2624.
- 37 LESCH, K. P., BENDEL, D., HEILS, A., SABOL, S. Z., GREENBERG, B. D., PETRI, S., BENJAMIN, J., MULLER, C. R., HAMER, D. H., MURPHY, D. L., *Science* **1996**, *274*, 1527–1531.
- 38 COLLIER, D. A., STOBBER, G., LI, T., HEILS, A., CATALANO, M., DI, B. D., ARRANZ, M. J., MURRAY, R. M., VALLADA, H. P., BENDEL, D., MULLER, C. R., ROBERTS, G. W., SMERALDI, E., KIROV, G., SHAM, P., LESCH, K. P., *Mol. Psychiatry* **1996**, *1*, 453–460.
- 39 BONDY, B., ERFURTH, A., DE JONGE, S., KRUGER, M., MEYER, H., *Mol. Psychiatry* **2000**, *5*, 193–195.
- 40 FURLONG, R. A., HO, L., WALSH, C., RUBINSZTEIN, J. S., JAIN, S., PAYKEL, E. S., EASTON, D. F., RUBINSZTEIN, D. C., *Am. J. Med. Genet.* **1998**, *81*, 58–63.
- 41 MASSAT, I., SOUERY, D., LIPP, O., BLAIRY, S., PAPADIMITRIOU, G., DIKEOS, D., ACKENHEIL, M., FUCHSHUBER, S., HILGER, C., KANEVA, R., MILANOVA, V., VERHEYEN, G., RAEYMAEKERS, P., STANER, L., ORUC, L., JAKOVljeVIC, M., SERRETTI, A., MACCIARDI, F., VAN BROECKHOVEN, C., MENDLEWICZ, J., *Am. J. Med. Genet.* **2000**, *96*, 136–140.
- 42 MINOV, C., BAGHAI, T. C., SCHULE, C., ZWANGGER, P., SCHWARZ, M. J., ZILL, P., RUPPRECHT, R., BONDY, B., *Neurosci. Lett.* **2001**, *303*, 119–122.

- 43 LERER, B., MACCIARDI, F., SEGMAN, R. H., ADOLFSSON, R., BLACKWOOD, D., BLAIRY, S., DEL FAVERO, J., DIKEOS, D. G., KANEVA, R., LILLI, R., MASSAT, I., MILANOVA, V., MUIR, W., NOETHEN, M., ORUC, L., PETROVA, T., PAPADIMITRIOU, G. N., RIETSCHER, M., SERRETTI, A., SOUERY, D., VAN GESTEL, S., VAN BROECKHOVEN, C., MENDLEWICZ, J., *Mol. Psychiatry* **2001**, 6, 579–585.
- 44 YUAN, X., YAMADA, K., ISHIYAMA-SHIGEMOTO, S., KOYAMA, W., NONAKA, K., *Diabetologia* **2000**, 43, 373–376.
- 45 HANNA, G. L., HIMLE, J. A., CURTIS, G. C., KORAM, D. Q., VEENSTRA-VANDERWEELE, J., LEVENTHAL, B. L., COOK, E.-H. J., *Neuropsychopharmacology* **1998**, 18, 102–111.
- 46 WHYTE, E. M., POLLOCK, B. G., WAGNER, W. R., MULSANT, B. H., FERRELL, R. E., MAZUMDAR, S., REYNOLDS, C. F., *Am. J. Psychiatry* **2001**, 158, 12–16.
- 47 FUMERON, F., BETOUILLE, D., NICAUD, V., EVANS, A., KEE, F., RUIDAVETS, J. B., ARVEILER, D., LUC, G., CAMBIEN, F., *Circulation* **2002**, 105, 2943–2945.
- 48 COTO, E., REGUERO, J. R., ALVAREZ, V., MORALES, B., BATALLA, A., GONZALEZ, P., MARTIN, M., GARCIA-CASTRO, M., IGLESIAS-CUBERO, G., CORTINA, A., *Clin. Sci. (Lond)* **2003**, 104, 241–245.
- 49 SAUER, W. H., BERLIN, J. A., KIMMEL, S. E., *Circulation* **2003**, 108, 32–36.
- 50 EDDAHIBI, S., MORRELL, N., D'ORTHO, M. P., NAEIJE, R., ADNOT, S., *Eur. Respir. J.* **2002**, 20, 1559–1572.
- 51 BATRA, V., PATKAR, A. A., BERRETTINI, W. H., WEINSTEIN, S. P., LEONE, F. T., *Chest* **2003**, 123, 1730–1739.
- 52 BENWELL, M. E., BALFOUR, D. J., ANDERSON, J. M., *Psychopharmacology (Berl.)* **1990**, 102, 68–72.
- 53 HARRISON, A. A., LIEM, Y. T., MARKOU, A., *Neuropsychopharmacology* **2001**, 25, 55–71.
- 54 ISHIKAWA, H., OHTSUKI, T., ISHIGURO, H., YAMAKAWA-KOBAYASHI, K., ENDO, K., LIN, Y. L., YANAGI, H., TSUCHIYA, S., KAWATA, K., HAMAGUCHI, H., ARINAMI, T., *Cancer Epidemiol. Biomarkers Prev.* **1999**, 8, 831–833.
- 55 LERMAN, C., SHIELDS, P. G., AUDRAIN, J., MAIN, D., COBB, B., BOYD, N. R., CAPORASO, N., *Cancer Epidemiol. Biomarkers Prev.* **1998**, 7, 253–255.
- 56 REICH, T., HINRICHS, A., CULVERHOUSE, R., BIERUT, L., *Am. J. Hum. Genet.* **1999**, 65, 599–605.
- 57 COMINGS, D. E., MACMURRAY, J. P., GONZALEZ, N., FERRY, L., PETERS, W. R., *Mol. Genet. Metab.* **1999**, 67, 248–253.
- 58 COMINGS, D. E., MACMURRAY, J. P., *Mol. Genet. Metab.* **2000**, 71, 19–31.
- 59 CASPI, A., SUGDEN, K., MOFFITT, T. E., TAYLOR, A., CRAIG, I. W., HARRINGTON, H., MCCLAY, J., MILL, J., MARTIN, J., BRAITHWAITE, A., POULTON, R., *Science* **2003**, 301, 386–389.
- 60 YU, Y. W., CHEN, T. J., HONG, C. J., CHEN, H. M., TSAI, S. J., *Neuropsychopharmacology* **2003**, 28, 1182–1185.
- 61 FISHMAN, D., FAULDS, G., JEFFERY, R., MOHAMED, A., YUDKIN, V., J. S., HUMPHRIES, S., WOO, P., *J. Clin. Invest* **2000**, 102, 1369–1376.
- 62 NAUCK, M., WINKELMANN, B. R., HOFFMANN, M. M., BOHM, B. O., WIELAND, H., MARZ, W., *J. Mol. Med.* **2002**, 80, 507–513.
- 63 JENNY, N. S., TRACY, R. P., OGG, M. S. L., LUONG, A., KULLER, L. H., ARNOLD, A. M., SHARRETT, A. R., HUMPHRIES, S. E., *Arterioscler. Thromb. Vasc. Biol.* **2002**, 22, 2066–2071.
- 64 VICKERS, M. A., GREEN, F. R., TERRY, C., MAYOSI, B. M., JULIER, C., LATHROP, M., RATCLIFFE, P. J., WATKINS, H. C., KEAVNEY, B., *Cardiovasc. Res.* **2002**, 53, 1029–1034.
- 65 LOSITO, A., KALIDAS, K., SANTONI, S., JEFFERY, S., *Kidney Int.* **2003**, 64, 616–622.
- 66 HUMPHRIES, S. E., LUONG, L. A., OGG, M. S., HAWES, E., MILLER, G. J., *Eur. Heart J.* **2001**, 22, 2243–2252.
- 67 BRULL, D. J., LEESON, C. P., MONTGOMERY, H. E., MULLEN, M., DEIVITIS, M., HUMPHRIES, S. E., DEANFIELD, J. E., LESSON, C. P., *Eur. J. Clin. Invest* **2002**, 32, 153–157.
- 68 BERTHIER, M. T., PARADIS, A. M., TCHERNOF, A., BERGERON, J., PRUD'HOMME, D., DESPRES, J. P., VOHL, M. C., *J. Hum. Genet.* **2003**, 48, 14–19.
- 69 JERRARD-DUNNE, P., SITZER, M., RISLEY, P., STECKEL, D. A., BUEHLER, A., VON KEGLER, S., MARKUS, H. S., *Stroke* **2003**, 34, 402–407.
- 70 PIHLAJAMAKI, J., YLINEN, M., KARHAPAA, P., VAUHKONEN, I., LAAKSO, M., *Obes. Res.* **2003**, 11, 912–917.

- 71 DALZIEL, B., GOSBY, A. K., RICHMAN, R. M., BRYSON, J. M., CATERSON, I. D., *Obes. Res.* **2002**, 10, 401–407.
- 72 WILSON, A. G., DI GIOVINE, F. S., BLAKEMORE, A. I., DUFF, G. W., *Hum. Mol. Genet.* **1992**, 1, 353.
- 73 HEIJMANS, B. T., WESTENDORP, R. G., DROOG, S., KLUFT, C., KNOOK, D. L., SLAGBOOM, P. E., *Genes Immun.* **2002**, 3, 225–228.
- 74 DENSEM, C. G., HUTCHINSON, I. V., YONAN, N., BROOKS, N. H., *J. Heart Lung Transplant.* **2001**, 20, 1265–1273.
- 75 KESO, T., PEROLA, M., LAIPPALA, P., ILVESKOSKI, E., KUNNAS, T. A., MIKKELSSON, J., PENTTILA, A., HURME, M., KARHUNEN, P. J., *Atherosclerosis* **2001**, 154, 691–697.
- 76 BRASIER, A. R., RECINOS, A., ELEDRI, M. S., *Arterioscler. Thromb. Vasc. Biol.* **2002**, 22, 1257–1266.
- 77 AGUILERA, G., KISS, A., LUO, X., *J. Neuroendocrinol.* **1995**, 7, 775–783.
- 78 JENKINS, T. A., MENDELSON-FREDERICK, A. O., CHAI, S. Y., *J. Neurochem.* **1997**, 68, 1304–1311.
- 79 KRAMER, M. S., CUTLER, N., FEIGHNER, J., SHRIVASTAVA, R., CARMAN, J., SRAMEK, J. J., REINES, S. A., LIU, G., SNAVELY, D., WYATT, K. E., HALE, J. J., MILLS, S. G., MACCROSS, M., SWAIN, C. J., HARRISON, T., HILL, R. G., HEFTI, F., SCOLNICK, E. M., CASCIERI, M. A., CHICCHI, G. G., SADOWSKI, S., WILLIAMS, A. R., HEWSON, L., SMITH, D., RUPNIAK, N. M., *Science* **1998**, 281, 1640–1645.
- 80 GUNDUZ, H., GEORGES, J. L., FLEISHMAN, S., *Am. J. Psychiatry* **1999**, 156, 1114–1115.
- 81 OKUYAMA, S., SAKAGAWA, T., SUGIYAMA, F., FUKAMIZU, A., MURAKAMI, K., *Neurosci. Lett.* **1999**, 261, 167–170.
- 82 RIGAT, B., HUBERT, C., ALHENC, G. F., CAMBIEN, F., CORVOL, P., SOUBRIER, F., *J. Clin. Invest.* **1990**, 86, 1343–1346.
- 83 CORVOL, P., SOUBRIER, F., JEUNEMAITRE, X., *Pathol. Biol. (Paris)* **1997**, 45, 229–239.
- 84 CAMBIEN, F., POIRIER, O., LECERF, L., EVANS, A., CAMBOU, J. P., ARVEILER, D., LUC, G., BARD, J. M., BARA, L., RICARD, S., TIRET, L., AMOUEL, P., ALHENC-GELAS, F., SOUBRIER, F., *Nature* **1992**, 359, 641–644.
- 85 O'MALLEY, J. P., MASLEN, C. L., ILLINGWORTH, D. R., *Circulation* **1998**, 97, 1780–1783.
- 86 MOSKOWITZ, D. W., *Diabetes Technol. Ther.* **2002**, 4, 683–711.
- 87 ARINAMI, T., LI, L., MITSUSHIO, H., ITOKAWA, M., HAMAGUCHI, H., TORU, M., *Biol. Psychiatry* **1996**, 40, 1122–1127.
- 88 BAGHAI, T., SCHÜLE, C., ZWANZGER, P., MINOV, C., SCHWARZ, J., DE JONGE, S., RUPPRECHT, R., BONDY, B., *Mol. Psychiatry* **2001**, 6, 258–259.
- 89 BONDY, B., BAGHAI, T. C., ZILL, P., BOTTLENDER, R., JAEGER, M., MINOV, C., SCHULE, C., RUPPRECHT, R., ENGEL, R. R., *Mol. Psychiatry* **2002**, 7, 1120–1126.
- 90 FURLONG, R. A., KERAMATPOUR, M., HO, L. W., RUBINSZTEIN, J. S., MICHAEL, A., WALSH, C., PAYKEL, E. S., RUBINSZTEIN, D. C., *Am. J. Med. Genet.* **2000**, 96, 733–735.
- 91 BAGHAI, T. C., SCHULE, C., ZWANZGER, P., MINOV, C., ZILL, P., ELLA, R., ESER, D., OEZER, S., BONDY, B., RUPPRECHT, R., *Neurosci. Lett.* **2002**, 328, 299–303.
- 92 DUMAN, R. S., HENINGER, G. R., NESTLER, E. J., *J. Nerv. Ment. Dis.* **1994**, 182, 692–700.
- 93 DUMAN, R. S., HENINGER, G. R., NESTLER, E. J., *Arch. Gen. Psychiatry* **1997**, 54, 597–606.
- 94 CHEN, G., HASANAT, K. A., BEBCHUK, J. M., MOORE, G. J., GLITZ, D., MANJI, H. K., *Psychosom. Med.* **1999**, 61, 599–617.
- 95 ABE, M., NAKURA, J., YAMAMOTO, M., JIN, J. J., WU, Z., TABARA, Y., YAMAMOTO, Y., IGASE, M., KOHARA, K., MIKI, T., *Hypertension* **2002**, 40, 3–5.
- 96 CHEN, Y., NAKURA, J., JIN, J. J., WU, Z., YAMAMOTO, M., ABE, M., TABARA, Y., YAMAMOTO, Y., IGASE, M., BO, X., KOHARA, K., MIKI, T., *Hypertens. Res.* **2003**, 26, 439–444.
- 97 ZILL, P., BAGHAI, T. C., ZWANZGER, P., SCHULE, C., MINOV, C., BEHRENS, S., RUPPRECHT, R., MOLLER, H. J., ENGEL, R., BONDY, B., *Am. J. Med. Genet.* **2002b** 114, 530–532.
- 98 SIFFERT, W., *Kidney Int.* **1998**, 53, 1466–1470.
- 99 SIFFERT, W., *Curr. Hypertens. Rep.* **2003**, 5, 47–53.
- 100 HENGSTENBERG, C., SCHUNKERT, H., MAYER, B., DORING, A., LOWEL, H., HENSE, H. W., FISCHER, M., RIEGGER, G. A., HOLMER, S. R., *Cardiovasc. Res.* **2001**, 49, 820–827.

- 101 MEIRHAEGHE, A., BAUTERS, C., HEL-BECQUE, N., HAMON, M., MCFADDEN, E., LABLANCHE, J. M., BERTRAND, M., AMOUYEL, P., *Eur. Heart J.* **2001**, *22*, 845–848.
- 102 HANON, O., LUONG, V., MOURAD, J. J., BORTOLOTO, L. A., SAFAR, M., GIRERD, X., *J. Vasc. Res.* **2002b**, *39*, 497–503.
- 103 SIFFERT, W., ROSSKOPF, D., SIFFERT, G., BUSCH, S., MORITZ, A., ERBEL, R., SHARMA, A. M., RITZ, E., WICHMANN, H. E., JAKOBS, K. H., HORSTHEMKE, B., *Nature Genet.* **1998**, *18*, 45–48.
- 104 ZILL, P., BAGHAI, T. C., ZWANZGER, P., SCHULE, C., MINOV, C., RIEDEL, M., NEUMEIER, K., RUPPRECHT, R., BONDY, B., *Neuroreport* **2000**, *11*, 1893–1897.
- 105 EXTON, M. S., ARTZ, M., SIFFERT, W., SCHEDLOWSKI, M., *Neuroreport* **2003**, *14*, 531–533.
- 106 SERRETTI, A., LORENZI, C., CUSIN, C., ZANARDI, R., LATTUADA, E., ROSSINI, D., LILLI, R., PIROVANO, A., CATALANO, M., SMERALDI, E., *Eur. Neuropsychopharmacol.* **2003**, *13*, 117–122.
- 107 SPERLING, H., EISENHARDT, A., VIRCHOW, S., HAUCK, E., LENK, S., PORST, H., STIEF, C., WETTERAUER, U., RUBBEN, H., MULLER, N., SIFFERT, W., *J. Urol.* **2003**, *169*, 1048–1051.
- 108 NABER, C. K., HUSING, J., WOLFHARD, U., ERBEL, R., SIFFERT, W., *Hypertension* **20**, *36*, 986–989.

26

History and Epidemiology of Depression

Ma-Li Wong

Abstract

Both history and epidemiology offer the opportunity to organize complex and multifaceted facts that enlighten our understanding of major depression, an ancient medical mystery that has been proven to be continually elusive in spite of advances in molecular biology, genomics and proteomics. Several interrelated questions await answers: When will we be able to fully address the controversies that surround this disorder? Are our difficulties associated with the fact that we consider this to be a disorder related to intrinsic human feelings? Will we be able to objectively evaluate our own liabilities and fears? We live in an era that has been called “the age of melancholy”. Is it sensible to assume that a reasonable proportion of people could be considered as suffering from a mental disease, for which we know of no cure and for which we prescribe long-term treatment? As we confront ourselves with these considerations, we hope that a deeper and fresh look into these problems will give us a better insight into this disorder.

26.1

Brief Historical Consideration of Major Depression

“Grief and fear, when lingering, provoke melancholia.”
(Hippocrates, 460–377 B.C.)

To a newcomer to the field, the fact that major depression was recognized before the birth of psychiatry could apparently defy logic. But, in reality psychiatry is a construct that was created at the end of the 18th century to encompass disorders of the mind [1]. Depression is a clinical syndrome(s) that was (were) described more than 2000 years ago. In 1986, Jackson published an invaluable volume that detailed the history of depression and which could be used as a reference for those interested in better understanding this disorder [2].

The term melancholia is the Latin transliteration of the Greek μελαγχολία, which referred to a mental disorder involving prolonged fear and depression [3]. That

Table 26.1 Four bodily humors were elements of health and disease

<i>Humor</i>	<i>Season</i>	<i>Qualities</i>	<i>Age of onset</i>
Blood	Spring	Warm and moist	Youth (~ 20 years)
Yellow bile	Summer	Warm and dry	Prime (~ 40 years)
Black bile	Autumn	Cold and dry	Decline (~ 60 years)
Phlegm	Winter	Cold and moist	Old age

term was in turn derived from black bile (μελαινα χηολε), one of the four humors in the humoral theory (Table 26.1). It could be argued that melancholia, a condition related to major depression as we define it today, was recognized as a distinct disease as early as the fifth or fourth centuries B.C. Essentially, accounts of its central cluster of symptoms and signs have been reasonably consistent and coherent over time. In fact, melancholia was one of the three fundamental forms of madness described since ancient times. The term “depression” is a relatively latecomer and derives from the Latin.

It also seem to defy logic that at present and at any particular time during previous centuries, “melancholia”, “depression” and related terms have been common expressions which refer to: (1) a disease (a condition of enough severity and duration), (2) a troublesome emotional state that is of short duration but not pathological, or (3) a temperament or type of character that is not pathological. Therefore, as we have all at some time experienced a wide range of emotions that could be described by terms such as feeling blue, down, low, or unhappy, being dejected, depressed, despairing, despondent, disappointed, discouraged, dispirited, dysphoric, melancholic, depressed or sad, we consider these feelings to be unusual and unhappy, but within the normal range. The concepts of normalcy and disease seem to be so intertwined that they pervade their distinction and make it extremely challenging to set convincing distinctive disease criteria based solely on subjective emotions. Only under circumstances in which these feelings are not only severe and prolonged, but also accompanied by a cluster of other symptoms (e.g. sleep, psychomotor and appetite disturbances, anhedonia, suicidal ideation, and social dysfunction), are they considered to be part of a pathological state.

In the history of medicine there has been an evolving definition of what it is considered a disease or syndrome, and what the disease “depression” encompasses. There have also been evolving conceptual etiological considerations, as well as treatment of this condition (see Figure 26.1, “Timeline”). It is interesting to consider that at different times, depression could be considered as a spiritual state brought to us by external forces, a disorder of imbalance of the four essential humors of health and disease, a disorder of the liver, spleen or thymus, or a disorder of the mind.

The notions from which we derive our current understanding of major depression have emerged from the work of Emil Kraepelin, who formulated theories about psychiatric disorders based on clinical and anatomical principles that classified it as a disease. These were important concepts in two important diagnostic and

collaborative projects, namely the United States–United Kingdom diagnostic project and the National Institute of Mental Health collaborative study of the psychobiology of depression [3], that have been reflected in the existing diagnostic criteria for this disorder (DSM IV and ICD-10; also refer to Chapter 1 of this book).

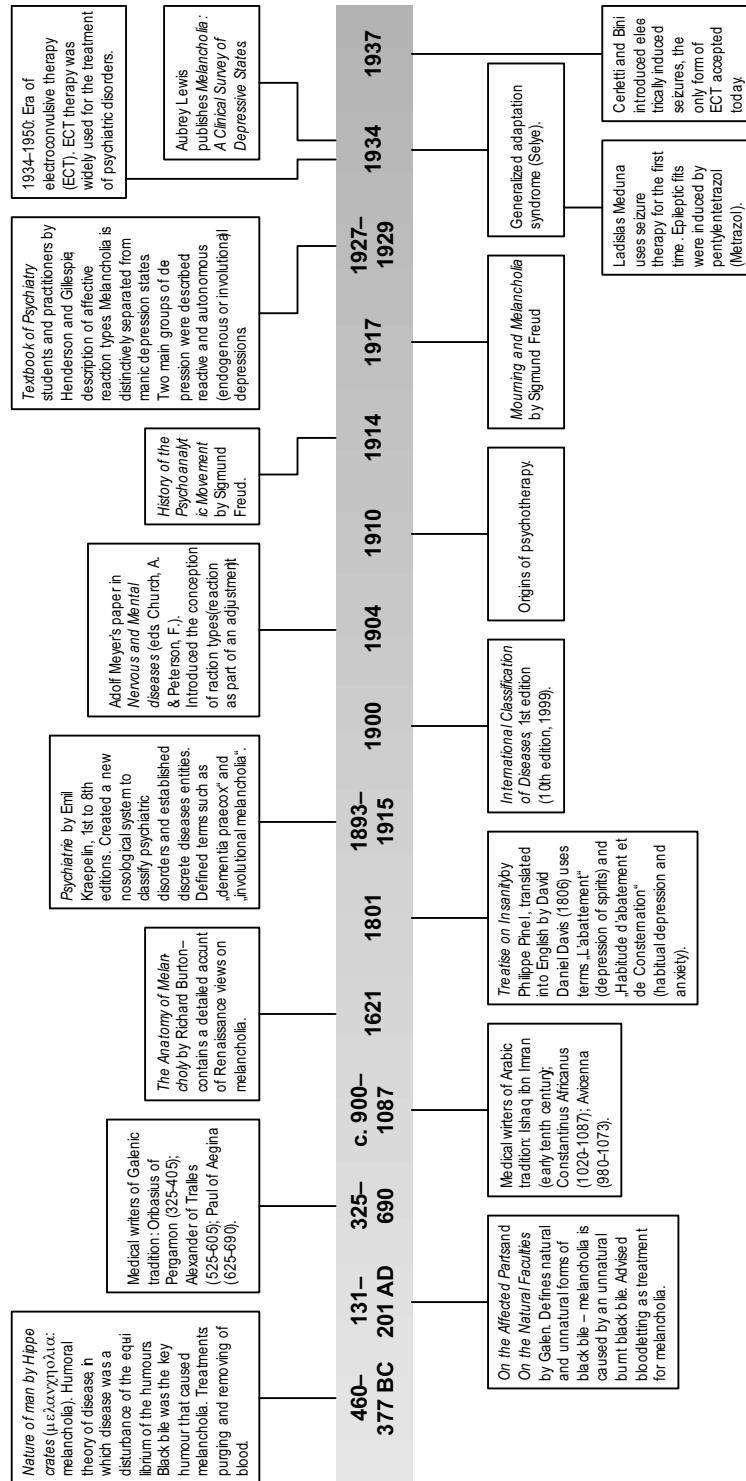
Controversies have arisen concerning biological and psychological theories for depression. It is noteworthy to consider that the current predominance of a biological basis for depression is not a new phenomenon. Indeed, before the dominance of Freudian psychoanalytic theories in psychopathology, a first biological era of psychiatry existed [1] and those principles subsequently gave way to the second (present) biological era in psychiatry. But this debate between biological and psychological psychopathologies does not seem entirely settled as yet. At least in the minds of the lay public, it seems that there is a perceived resistance to accepting the notion of disease, as a significant proportion of the public still choose to resort to prayer as a therapeutic/healing option (see Chapter 40).

It is also relevant to understand how modern antidepressant therapies have emerged. A detailed history of physical therapies (hydrotherapy, cold baths, insulin shock and electroconvulsive (ECT) therapies) was given by Shorter [1], while an interesting account of the history of pharmacological treatments can be found in the volume entitled *The Antidepressant Era* by David Healy [4]. Undoubtedly, the serendipitous discovery of antidepressants has propelled a flurry of scientific activity which has revolutionized our understanding of this disorder.

Naturalistic analyses of the course of major depression reveal that this disorder has a self-limiting but recurrent course [5, 6]. Typically, symptomatic periods are followed by periods of full clinical recovery. The disorder advances along a variable course, depressive periods can then occur more and more frequently leading to a severe unremitting symptomatic stage. Several treatment options may help mild to moderate cases, and they encompass orthodox and non-orthodox therapies, which vary from complementary and alternative medicine treatments (herbal and non-herbal), cognitive-behavioral or interpersonal psychotherapies, to antidepressant drugs. Severe major episodes often represent challenges to current therapeutic options. ECT continues to be a good therapeutic option that has been underutilized (see Chapter 7).

Currently the classical monoamine hypothesis continues to prevail among several emerging disease hypotheses and it continues to provide the main targets for drug development. Alternative hypotheses, which postulate the contribution of several other CNS systems and infectious agents, such as neuropeptides involved in the stress response, circadian dysregulation, neuroregeneration, Borna virus, and immune mediators have emerged to complement the main hypothesis [3]. These are covered in other chapters in this book. They have also provided the substrate for a prelude in paradigm shift of drug development in depression. Genetic factors that contribute to disease susceptibility or are involved in antidepressant drug response have been targeted by recent research initiatives. A current conceptual approach to depression is illustrated in Figure 26.2.

Timeline: Cornerstones in the history of major depression



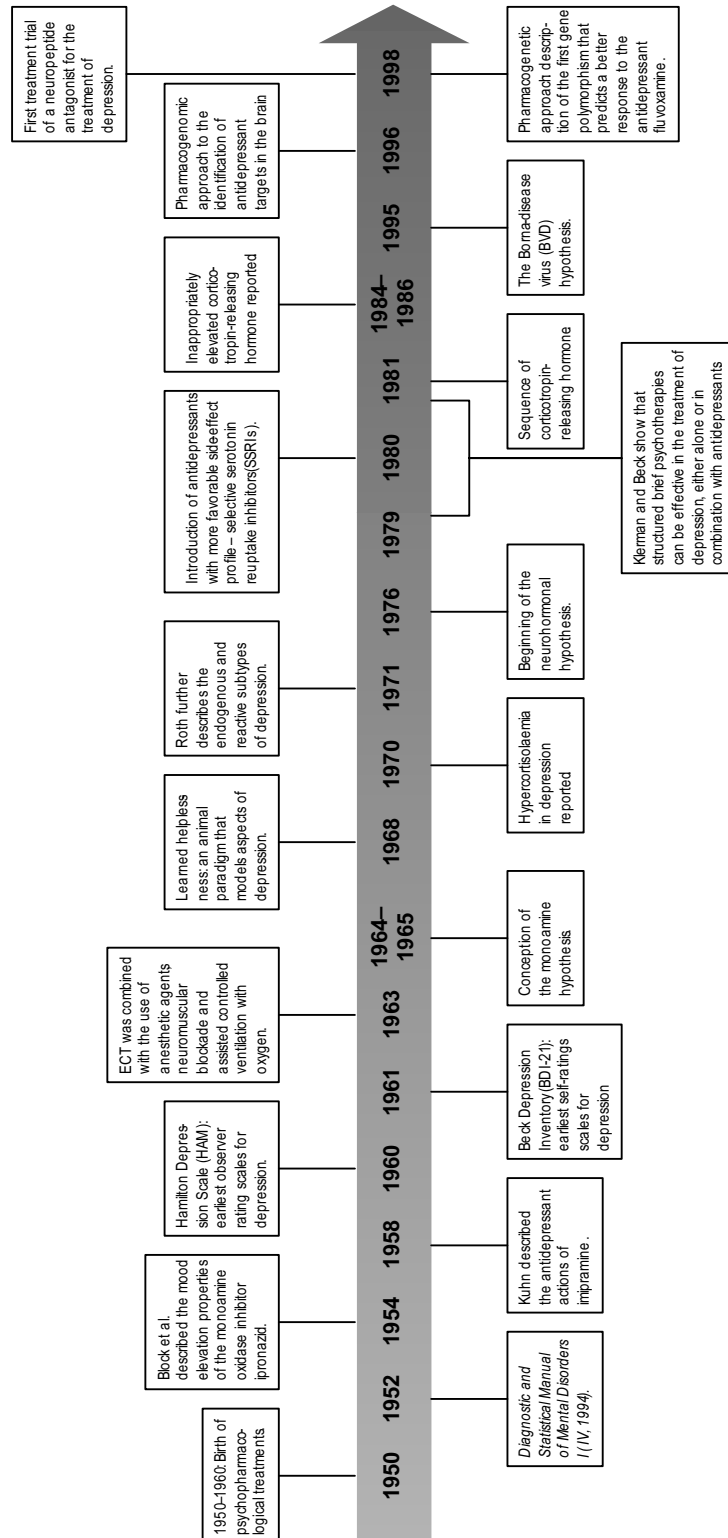


Figure 26.1 Cornerstones in the history of major depression (reproduced from ref. [3])

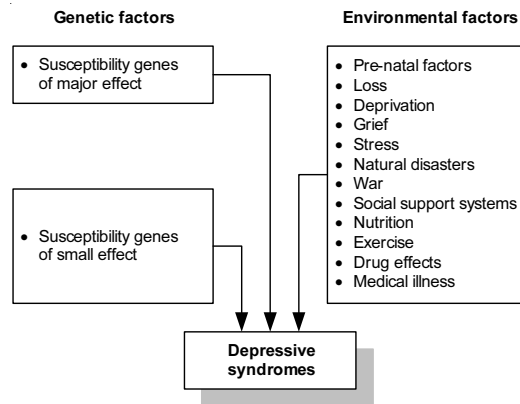


Figure 26.2 A conceptual approach to depression. Available evidence consistently indicates that neurobiological substrates underlying depression phenotypes are the outcome of a combination of genetic and environmental factors (reproduced from ref. [3]).

26.2 Epidemiology of Major Depression

26.2.1 Introduction

Epidemiology concerns the statistical relationships of diseases or disorders and their variations in different population subgroups. In the United States available national estimates are derived primarily from two large community surveys: the National Institutes of Mental Health Epidemiologic Catchment Area (ECA) Survey that was conducted from 1980–1985 (ECA) [7–9] and evaluated over 18,000 adults aged 18 to 54 years, and the National Comorbidity Surveys (NCS) that were conducted from 1990–1992 [9] and repeated in 2001–2002 (NCS-R) [10] in which about 8000 persons between 15 and 54 years of age were evaluated. Face-to-face interviews were conducted in both surveys. The ECA-DIS (Diagnostic Interview Schedule) assessed the DSM-III psychiatric diagnoses. An expanded version (University of Michigan) of the WHO’s composite International Diagnostic Interview (UM-CIDI) was used in the NCS and a sub-sample was confirmed using DSM-IV diagnostic criteria.

Interestingly, lifetime prevalence of depression was reported to be 5.2 in 100 in the ECA [11], and a decade later the NCS reported a much higher prevalence of 17.1. In two successive National Ambulatory Care Surveys the rates of depression increased from 1992–1993 to 1996–1997 among whites (10.9 to 11.3%), blacks (4.2 to 5.5%) and Hispanics (4.8 to 8.3%) [12]. In the United States and other countries, the prevalence of depression seems to be increasing among adults [13]. This perceived increase has led Gerald Klerman to call the present time “the age of

melancholia". This disparity in incidence has generated controversy, but it is believed that methodological differences contribute to it. However, it has been noted that there is a significant trend towards higher prevalence in each successive birth cohort compared to adults who were 60 years of age or older at the time of the survey [14].

According to a prospective study a significant proportion of untreated people with major depression will still have symptoms in 1 (40%) and 2 years (20%) [15].

The prevalence of dysthymic disorder is approximately 1.6 in 100 in individuals over 18 years of age [8]. The lifetime prevalence of dysthymic disorder has been estimated to be between 3 and 6% [9, 16].

26.2.2

Age of Onset

The first episode of major depression can occur at any age, but the most likely age of onset is in the mid- to late 20s and this is reasonably consistent among studies [10, 11]. Women seem to be younger at the age of onset (15–19 years) than men (25–29 years) [17]. There is a perception that the age of onset is younger among birth cohorts born more recently [10, 18]. Data from the NIMH Collaborative Program of the Psychobiology of Depression reveal that the cumulative probability of onset of depression by the age of 30 years in female relatives of patients with major depression was lower than 10% among individuals born before 1929, and increased dramatically to 60% among those individuals born between 1930 and 1949. The same trend was also observed in men. Analysis of ECA [19] and NCS data also confirmed that the prevalence of major depression seems higher among younger people [20].

At least some of this trend may be related to differences in reporting over this time period [21]. It is also important to note that until recently physicians and family members alike have been unwilling to recognize depression in children and adolescents, attributing mood changes to normal development. Fortunately, there has been a growing recognition that clinical depression can appear in children because it can increase the risk for suicide, the third leading cause of death among 10- to 24-year-olds [22–25]. Epidemiological data suggest that up to 1% of pre-school children, 2% of school age children, and 8% of adolescents may have major depression [22, 26].

Aging *per se* does not seem to be a risk factor for depression, although data from the ECA suggest that there is a decline in the prevalence of major depression with age but an increase in the prevalence of "minor depression" symptoms [27]. Recent data estimates that 8–20% and 20% of older adults living in the community and seen in primary care settings respectively, suffer from depression.

26.2.3

Previous History of Depression

The risk for developing a depressive episode is significantly higher in individuals with a prior history of depression. About 60% of individuals who experienced one

episode of depression will experience a second one [28]. A 15-year naturalistic observational prospective study [5, 6, 29] of the course of depression indicated that 85% of individuals with a prior history of major depression experienced a recurrence of symptoms over a period of 15 years.

Individuals with dysthymic disorder are also at higher risk for depression. In a given year about 40% of adults with dysthymia will meet criteria for another affective disorder [17]. Dysthymia of early onset (before the age of 21 years) was shown to increase the rate of depression in a 5-year follow-up study [30].

Certain personality traits or qualities, such as neuroticism and dependency, pessimism, helplessness, hopelessness, excessive worry, guilty, shame, self-blame, low self esteem and anxiety, are also thought to be risk factor for major depression [31–34].

26.2.4

Familial Factors

The risk of being depressed increases two- to three-fold in first-degree relatives of individuals with major depression when compared to controls [35]. Major depression seems to be a familial disorder that is mostly based on genetic influences, though the influence of the environment on specific individuals may be etiologically significant [36].

Relatives of individuals with early-onset recurrent major depression have a higher risk of depression (17.4%) [37] than relatives of individuals with a single episode and late age of onset (3.4%). Similar results were reported in other studies [32, 38, 39]. Disease severity also seems to be correlated with disease risk among relatives. Relatives of individuals with mild depression (14.7%) have a lower risk than relatives of individuals with severe depression (16.4%); relatives of control subjects had a rate of 5.1% (comparable to the general population) [40, 41].

26.2.5

Gender

Women are twice as affected by major depression than men [41–45]. This is the most consistent finding in cross-national studies and the ECA and NCS [11]. In any given year 6.5% (6.7 million) of women and 3.3% (3.2 million) of men suffer from depression [16]. The lifetime prevalence is estimated to be 25% for women against 12% for men [9, 14]. Prior to puberty there is no gender differences in the prevalence rates, but they start to diverge at the age of 10–14 years [46, 47].

There are no adequate explanations for the gender differences, but it is probable that men under-report depression, and mask their symptoms by the use of alcohol or drugs, which are more prevalent among men. It is also possible that an increase in awareness of depression among men will increase its detection.

It has also been proposed that social rather than biological differences are the key factors that lead to the predominance of depression in women [48, 49], and that the negative cognitive styles and low self-esteem which are more commonly

found among women may be attributed to their social and cultural roles [50–52]. However, it is hard to explain the reversal of sex differences in the prevalence of depression that has been documented among subjects over 55 years of age [53] on the basis of social factors. It is relevant to remember here that a history of childhood trauma, particularly sexual or physical abuse is one of the most important psychological risk factors for depression and exposure to sexual abuse is higher among girls than boys [54] (also see Chapter 2). In fact, it has been proposed that about 35% of gender-related differences in depression rates are associated with this single factor [55].

26.2.6

Adverse or Significant Life Events

Although some life events that are associated with the precipitation of a major depressive episode are not necessarily recognized as adverse events (such as a job promotion, geographical relocation or childcare responsibilities), the majority of acute and chronic psychosocial factors linked to depression are.

The main psychological factors associated with depression include poverty, childhood neglect or trauma (particularly sexual abuse), death of spouse or loved one, divorce, job loss, financial dependence or difficulties, combined work and domestic duties [52, 56, 57]. Adverse childhood events have been associated with the early onset of depression [32]. The importance of these factors varies with gender, age and ethnicity. Events related to family or close social networks represent a greater impact to women, while issues related to work, legal, and divorce matters affect more men [58, 59]. Increased incidence of depression has been noted when several life events occur simultaneous [60] in the month prior to the episode.

Marital status and social class are two factors that have been associated with onset and prevalence of depression. Divorced or separated compared to married or never married individuals have a two-fold increase in the prevalence of depression [44, 61, 62]; these conditions also increase the odds for the occurrence of a first depression episode [63].

Low income (less than \$20,000/year) increases the likelihood of major depression, and its prevalence has an inverse relationship with income levels, the higher the income the lower the prevalence of depression [20]. Psychosocial risk factors also include being homemakers or being disabled [64]. But adjusted odds ratios showed no significant association between depression and household income [20]; also in the ECA data, no association was found between socioeconomic status and major depression.

Poor social support [65, 66] and level of education [67, 68], stress and an increased number of recent life events [66, 68], unemployment, living alone, death of a close relative, and limited participation in recreational activities [67], and alcohol and drug use [68] have also been associated with a higher prevalence of depression.

26.2.7

Other Medical Illnesses

The prevalence of depression is estimated to be higher in primary care patients, as many as 16% had subsyndromal symptoms [69]. Between 5 and 10% of primary care patients meet DSM criteria for depression, and 7.8% meet criteria for dysthymia [70]. The rates of depression have been reported to be higher among patients with several medical illnesses, such as cardiovascular disease, AIDS, respiratory disorders, cancer, diabetes, and neurological disorders (particular Parkinson's disease and stroke) [33, 34]. There is a strong association between depression and increased ischemic heart disease morbidity and mortality [71–73].

It is important to note that several drugs have the potential ability to cause symptoms of depression [74–76].

26.2.8

Race, Ethnicity and Culture

The estimated prevalence of major depression is consistent among several countries (Table 26.2). Data derived from a large cross-cultural study of nine countries [11], using DSM-III diagnostic criteria uncovered a significant variation in the annual rates of adult major depression, from 0.8 (Taiwan) to 19 in 100 (Lebanon). Variations in the rates of depression were also found in studies of depression in different ethnic groups [12]. The National Ambulatory Care Survey found that 5% of African-American, 8% of Hispanic and 11% of white outpatients met ICD-9 criteria for

Table 26.2 Lifetime and annual rates and onset for major depression (ages 18–64 years)^{a)}

Country	Annual rate per 100 (SE)	Lifetime rate per 100 (SE)				Mean age at onset in years (SE)
		Overall	Females	Males	Female ratio	
United States	3.0 (0.18)	5.2 (0.24)	7.4 (0.39)	2.8 (0.26)	2.6 (0.11)	25.6 (0.30)
Edmonton, Alberta, Canada	5.2 (0.45)	9.6 (0.60)	12.3 (0.93)	6.6 (0.73)	1.9 (0.13)	24.8 (0.52)
Puerto Rico	3.0 (0.49)	4.3 (0.59)	5.5 (0.91)	3.1 (0.72)	1.8 (0.29)	29.5 (1.19)
Paris, France	4.5 (0.65)	16.4 (1.16)	21.9 (1.80)	10.5 (1.39)	2.1 (0.16)	29.2 (0.52)
West Germany ^{b)}	5.0 (1.13)	9.2 (1.50)	13.5 (2.46)	4.4 (1.56)	3.1 (0.39)	21.7 (1.18)
Florence, Italy	Not avail.	12.4 (1.33)	18.1 (2.16)	6.1 (1.40)	3.0 (0.26)	34.8 (1.12)
Beirut, Lebanon	Not avail.	19.0 (1.76)	23.1 (2.63)	14.7 (2.25)	1.6 (0.19)	25.2 (1.00)
Taiwan	0.8 (0.09)	1.5 (0.12)	1.8 (0.19)	1.1 (0.16)	1.6 (0.17)	29.3 (1.04)
Korea	2.3 (0.22)	2.9 (0.24)	3.8 (0.38)	1.9 (0.29)	2.0 (0.18)	29.3 (0.88)
Christchurch, New Zealand	5.8 (0.70)	11.6 (0.96)	15.5 (1.51)	7.5 (1.14)	2.1 (0.18)	27.3 (0.58)

^{a)} Figures standardized to US age and sex distribution.

^{b)} Data from former Federal Republic of Germany (West Germany) based on ages 26 to 64 years (SE, standard error).

Adapted with permission from ref. [11]. © (1996) American Medical Association.

major depression, although the ECA indicated similar age- and sex-adjusted 1-year rates of major depression for whites and Hispanics [77]. These observed variations in prevalence across ethnic and racial groups may be attributed to several factors, including differences in symptom presentation, cultural beliefs, socio-cultural factors, access to medical care, reluctance to identify or recognize symptoms or conditions that may impose a social stigma on the patients [78] (also see Chapter 39). But most of the variations related to race and ethnicity can be explained by educational and socioeconomic factors [79].

26.3

Conclusion

Major depression is a complex common clinical syndrome(s) of unknown etiology, which has been described for over 2000 years. Our understanding of this (these) disorder(s) has evolved throughout time. Presently, unbiased sampling provides us with a consensus of descriptive epidemiological characteristics that are prevalent in the main clinical syndrome(s) of depression; these data have supported some of the beliefs and hypotheses proposed about risk factors in depression. Studies based in clinical or psychiatric settings are more likely to be biased, and they also could represent different admixtures of clinical syndromes with similar symptomatology.

At present, there is consensus on the following characteristics of major depression:

1. Age of onset around mid 20s.
2. Two-fold increase in rates of occurrence among women when compared to men.
3. Differences in lifetime prevalence around the world.
4. Increased prevalence rates in several medical illnesses.
5. Strong association between depression and ischemic heart disease.
6. Increased rates when several life events have occurred within 1 month of the depressive episode.
7. Early life trauma is associated with early onset in women.
8. Familial forms have strong genetic susceptibility.

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References

- 1 SHORTER, E., *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac*. New York, NY: John Wiley & Sons, 1997.
- 2 JACKSON, S. W., *Melancholia & Depression*. New Haven, CT: Yale University Press, 1986.
- 3 WONG, M.-L., LICINIO, J., Research and treatment approaches to depression. *Nature Rev. Neurosci.* 2001, 2, 343–351.
- 4 HEALY, D., *The Antidepressant Era*. Boston, MA: Harvard University Press, 1998.
- 5 KELLER, M. B., BERNDT, E. R., Depression treatment: a lifelong commitment? *Psychopharmacol. Bull.* 2002, 36 (Suppl. 2), 133–141.
- 6 MUELLER, T. I., LEON, A. C., KELLER, M. B., SOLOMON, D. A., ENDICOTT, J., CORYELL, W., et al., Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am. J. Psychiatry* 1999, 156, 1000–1006.
- 7 REGIER, D. A., HIRSCHFELD, R. M., GOODWIN, F. K., BURKE, J. D., JR, LAZAR, J. B., JUDD, L. L., The NIMH Depression Awareness, Recognition, and Treatment Program: structure, aims, and scientific basis. *Am. J. Psychiatry* 1988, 145, 1351–1357.
- 8 NARROW, W. E., RAE, D. S., ROBINS, L. N., REGIER, D. A., Revised prevalence estimates of mental disorders in the United States: using a clinical significance criterion to reconcile 2 surveys' estimates. *Arch. Gen. Psychiatry* 2002, 59, 115–123.
- 9 KESSLER, R. C., MCGONAGLE, K. A., ZHAO, S., NELSON, C. B., HUGHES, M., ESHLEMAN, S., et al., Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch. Gen. Psychiatry* 1994, 51, 8–19.
- 10 KESSLER, R. C., BERGLUND, P., DEMLER, O., JIN, R., KORETZ, D., MERIKANGAS, K. R., et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003, 289, 3095–3105.
- 11 WEISSMAN, M. M., BLAND, R. C., CANINO, G. J., FARAVELLI, C., GREENWALD, S., HWU, H. G., et al., Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 1996, 276, 293–299.
- 12 SKAER, T. L., SCLAR, D. A., ROBISON, L. M., GALIN, R. S., Trends in the rate of depressive illness and use of anti-depressant pharmacotherapy by ethnicity/race: an assessment of office-based visits in the United States, 1992–1997. *Clin. Ther.* 2000, 22, 1575–1589.
- 13 MURRAY, C. J., LOPEZ, A. D., *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard University Press, 1996.
- 14 KESSLER, R. C., MCGONAGLE, K. A., SWARTZ, M., BLAZER, D. G., NELSON, C. B., Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J. Affect Disord.* 1993, 29 (2–3), 85–96.
- 15 KELLER, M. B., LAVORI, P. W., WUNDER, J., BEARDSLEE, W. R., SCHWARTZ, C. E., ROTH, J., Chronic course of anxiety disorders in children and adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 1992, 31, 595–599.
- 16 NARROW, W. E., REGIER, D. A., GOODMAN, S. H., RAE, D. S., ROPER, M. T., BOURDON, K. H., et al., A comparison of federal definitions of severe mental illness among children and adolescents in four communities. *Psychiatr. Serv.* 1998, 49, 1601–1608.
- 17 REGIER, D. A., NARROW, W. E., RAE, D. S., MANDERSCHIED, R. W., LOCKE, B. Z., GOODWIN, F. K., The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. *Arch. Gen. Psychiatry* 1993, 50, 85–94.
- 18 BURKE, K. C., BURKE JR., J. D., RAE, D. S., REGIER, D. A., Comparing age at onset of major depression and other psychiatric disorders by birth cohorts in five US community populations. *Arch. Gen. Psychiatry* 1991, 48, 789–795.
- 19 WICKRAMARATNE, P. J., WEISSMAN, M. M., LEAF, P. J., HOLFORD, T. R., Age, period and cohort effects on the risk of major depression: results from five

- United States communities. *J. Clin. Epidemiol.* **1989**, 42, 333–343.
- 20 BLAZER, D. G., Dysthymia in community and clinical samples of older adults. *Am. J. Psychiatry* **1994**, 151, 1567–1569.
 - 21 STASSEN, H. H., RAGAZ, M., REICH, T., Age-of-onset or age-cohort changes in the lifetime occurrence of depression? *Psychiatr. Genet.* **1997**, 7, 27–34.
 - 22 BIRMAHER, B., RYAN, N. D., WILLIAMSON, D. E., BRENT, D. A., KAUFMAN, J., Childhood and adolescent depression: a review of the past 10 years. Part II. *J. Am. Acad. Child Adolesc. Psychiatry* **1996**, 35, 1575–1583.
 - 23 BIRMAHER, B., RYAN, N. D., WILLIAMSON, D. E., BRENT, D. A., KAUFMAN, J., DAHL, R. E., et al., Childhood and adolescent depression: a review of the past 10 years. Part I. *J. Am. Acad. Child Adolesc. Psychiatry* **1996**, 35, 1427–1439.
 - 24 BIRMAHER, B., BRENT, D. A., BENSON, R. S., Summary of the practice parameters for the assessment and treatment of children and adolescents with depressive disorders: American Academy of Child and Adolescent Psychiatry. *J. Am. Acad. Child Adolesc. Psychiatry* **1998**, 37, 1234–1238.
 - 25 WEISSMAN, M. M., WOLK, S., GOLDSTEIN, R. B., MOREAU, D., ADAMS, P., GREENWALD, S., et al., Depressed adolescents grown up. *JAMA* **1999**, 281, 1707–1713.
 - 26 JELLINEK, M. S., SNYDER, J. B., Depression and suicide in children and adolescents. *Pediatr. Rev.* **1998**, 19, 255–264.
 - 27 ROMANOSKI, A. J., FOLSTEIN, M. F., NESTADT, G., CHAHAL, R., MERCHANT, A., BROWN, C. H., et al., The epidemiology of psychiatrist-ascertained depression and DSM-III depressive disorders: Results from the Eastern Baltimore Mental Health Survey Clinical Reappraisal. *Psychol. Med.* **1992**, 22, 629–655.
 - 28 AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Text Revision. Washington, DC: American Psychiatric Association, **2000**.
 - 29 PINCUS, H. A., PECHURA, C. M., ELINSON, L., PETTIT, A. R., Depression in primary care: linking clinical and systems strategies. *Gen. Hosp. Psychiatry* **2001**, 23, 311–318.
 - 30 HAYDEN, E. P., KLEIN, D. N., Outcome of dysthymic disorder at 5-year follow-up: the effect of familial psychopathology, early adversity, personality, comorbidity, and chronic stress. *Am. J. Psychiatry* **2001**, 158, 1864–1870.
 - 31 BECK, A. T., *Depression: Clinical, Experimental and Theoretical Aspects*. New York, NY: Harper and Row, **1967**.
 - 32 ALLOY, L. B., ABRAMSON, L. Y., WHITEHOUSE, W. G., HOGAN, M. E., TASHMAN, N. A., STEINBERG, D. L., et al., Depressogenic cognitive styles: predictive validity, information processing and personality characteristics, and developmental origins. *Behav. Res. Ther.* **1999**, 37, 503–531.
 - 33 HANKIN, B. L., ABRAMSON, L. Y., Development of gender differences in depression: an elaborated cognitive vulnerability-transactional stress theory. *Psychol. Bull.* **2001**, 127, 773–796.
 - 34 MULDER, R. T., Personality pathology and treatment outcome in major depression: a review. *Am. J. Psychiatry* **2002**, 159, 359–371.
 - 35 KLIERMAN, G. L., WEISSMAN, M. M., Increasing rates of depression. *JAMA* **1989**, 261, 2229–2235.
 - 36 SULLIVAN, P. F., NEALE, M. C., KENDLER, K. S., Genetic epidemiology of major depression: review and meta-analysis. *Am. J. Psychiatry* **2000**, 157, 1552–1562.
 - 37 BLAND, R. C., NEWMAN, S. C., ORN, H., Recurrent and nonrecurrent depression. A family study. *Arch. Gen. Psychiatry* **1986**, 43, 1085–1089.
 - 38 WEISSMAN, M. M., WICKRAMARATNE, P., MERIKANGAS, K. R., LECKMAN, J. F., PRUSOFF, B. A., CARUSO, K. A., et al., Onset of major depression in early adulthood. Increased familial loading and specificity. *Arch. Gen. Psychiatry* **1984**, 41, 1136–1143.
 - 39 KUPFER, D. J., FRANK, E., CARPENTER, L. L., NEISWANGER, K., Family history in recurrent depression. *J. Affect Disord.* **1989**, 17, 113–119.
 - 40 WEISSMAN, M. M., GERSHON, E. S., KIDD, K. K., PRUSOFF, B. A., LECKMAN, J. F., DIBBLE, E., et al., Psychiatric disorders in the relatives of probands with affective disorders. The Yale University – National Institute of Mental Health Collaborative

- Study. *Arch. Gen. Psychiatry* 1984, 41, 13–21.
- 41 ANESHENSEL, C. S., FRERICHS, R. R., CLARK, V. A., Family roles and sex differences in depression. *J. Health Soc. Behav.* 1981, 22, 379–393.
 - 42 BOYD, J. H., WEISSMAN, M. M., Epidemiology of affective disorders. A reexamination and future directions. *Arch. Gen. Psychiatry* 1981, 38, 1039–1046.
 - 43 KIVELA, S. L., PAHKALA, K., LAIPPALA, P., Prevalence of depression in an elderly population in Finland. *Acta Psychiatr. Scand.* 1988, 78, 401–413.
 - 44 CHO, M. J., NAM, J. J., SUH, G. H., Prevalence of symptoms of depression in a nationwide sample of Korean adults. *Psychiatry Res.* 1998, 81, 341–352.
 - 45 OHAYON, M. M., SCHATZBERG, A. F., Using chronic pain to predict depressive morbidity in the general population. *Arch. Gen. Psychiatry* 2003, 60, 39–47.
 - 46 KESSLER, R. C., WALTERS, E. E., Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depress. Anxiety* 1998, 7, 3–14.
 - 47 HANKIN, B. L., ABRAMSON, L. Y., MOFFITT, T. E., SILVA, P. A., MCGEE, R., ANGELL, K. E., Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. *J. Abnorm. Psychol.* 1998, 107, 128–1240.
 - 48 HARRIS, T., SURTEES, P., BANCROFT, J., Is sex necessarily a risk factor to depression? *Br. J. Psychiatry* 1991, 158, 708–712.
 - 49 MAIER, W., GANSICKE, M., GATER, R., REZAKI, M., TIEMENS, B., URZUA, R. F., Gender differences in the prevalence of depression: a survey in primary care. *J. Affect Disord.* 1999, 53, 241–252.
 - 50 JACK, D. C., *Silencing the Self: Women and Depression*. New York, NY: HarperCollins, 1993.
 - 51 KEARNEY-COOKE, A., Gender differences and self-esteem. *J. Gend. Specif. Med.* 1999, 2, 46–52.
 - 52 STOPPARD, J., *Understanding Depression: A Feminist Social Constructionist Approach*. New York, NY: Routledge, 2000.
 - 53 BEBBINGTON, P. E., DUNN, G., JENKINS, R., LEWIS, G., BRUGHA, T., FARRELL, M., et al., The influence of age and sex on the prevalence of depressive conditions: report from the National Survey of Psychiatric Morbidity. *Psychol. Med.* 1998, 28, 9–19.
 - 54 PINE, D. S., COHEN, J. A., Trauma in children and adolescents: risk and treatment of psychiatric sequelae. *Biol. Psychiatry* 2002, 51, 519–531.
 - 55 CUTLER, S. E., NOLEN-HOEKSEMA, S., Accounting for sex differences in depression through female victimization: childhood sexual abuse. *Sex Roles* 1991, 24, 425–438.
 - 56 BROWN, G. W., MORAN, P. M., Single mothers, poverty and depression. *Psychol. Med.* 1997, 27, 21–33.
 - 57 EATON, W. W., MUNTANER, C., BOVASSO, G., SMITH, C., Socioeconomic status and depressive syndrome: the role of inter- and intra-generational mobility, government assistance, and work environment. *J. Health Soc. Behav.* 2001, 42, 277–294.
 - 58 KENDLER, K. S., GARDNER, C. O., NEALE, M. C., PRESCOTT, C. A., Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? *Psychol. Med.* 2001, 31, 605–616.
 - 59 KENDLER, K. S., THORNTON, L. M., GARDNER, C. O., Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *Am. J. Psychiatry* 2001, 158, 582–586.
 - 60 KENDLER, K. S., ROY, M. A., Validity of a diagnosis of lifetime major depression obtained by personal interview versus family history. *Am. J. Psychiatry* 1995, 152, 1608–1614.
 - 61 WEISSMAN, M. M., Advances in psychiatric epidemiology: rates and risks for major depression. *Am. J. Public Health* 1987, 77, 445–451.
 - 62 PAHKALA, K., KESTI, E., KONGAS-SAVIARO, P., LAIPPALA, P., KIVELA, S. L., Prevalence of depression in an aged population in Finland. *Soc. Psychiatry Psychiatr. Epidemiol.* 1995, 30, 99–106.
 - 63 CORYELL, W., ENDICOTT, J., KELLER, M., Major depression in a nonclinical

- sample. Demographic and clinical risk factors for first onset. *Arch. Gen. Psychiatry* **1992**, 49, 117–125.
- 64 KESSLER, R. C., Epidemiology of women and depression. *J. Affect Disord.* **2003**, 74, 5–13.
 - 65 OXMAN, T. E., BERKMAN, L. F., KASL, S., FREEMAN, D. H., JR, BARRETT, J., Social support and depressive symptoms in the elderly. *Am. J. Epidemiol.* **1992**, 135, 356–368.
 - 66 PAYKEL, E. S., Life events, social support and depression. *Acta Psychiatr. Scand. Suppl.* **1994**, 377, 50–58.
 - 67 AL-SHAMMARI, S. A., AL-SUBAIE, A., Prevalence and correlates of depression among Saudi elderly. *Int. J. Geriatr. Psychiatry* **1999**, 14, 739–747.
 - 68 PATTEN, S. B., SEDMAK, B., RUSSELL, M. L., Major depression: prevalence, treatment utilization and age in Canada. *Can. J. Clin. Pharmacol.* **2001**, 8, 133–138.
 - 69 WILLIAMS JR., J. W., KERBER, C. A., MULROW, C. D., MEDINA, A., AGUILAR, C., Depressive disorders in primary care: prevalence, functional disability, and identification. *J. Gen. Intern. Med.* **1995**, 10, 7–12.
 - 70 SPITZER, R. L., KROENKE, K., LINZER, M., HAHN, S. R., WILLIAMS, J. B., DEGRUY 3RD, F. V., et al., Health-related quality of life in primary care patients with mental disorders. Results from the PRIME-MD 1000 Study. *JAMA* **1995**, 274, 1511–1517.
 - 71 ROOSE, S. P., Depression, anxiety, and the cardiovascular system: the psychiatrist's perspective. *J. Clin. Psychiatry* **2001**, 62 (Suppl. 8), 19–22; discussion 23.
 - 72 MUSSELMAN, D. L., EVANS, D. L., NEMEROFF, C. B., The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch. Gen. Psychiatry* **1998**, 55, 580–592.
 - 73 GLASSMAN, A. H., SHAPIRO, P. A., Depression and the course of coronary artery disease. *Am. J. Psychiatry* **1998**, 155, 4–11.
 - 74 PATTEN, S. B., LOVE, E. J., Drug-induced depression. *Psychother. Psychosom.* **1997**, 66, 63–73.
 - 75 REUS, V., Mental disorders. In BRAUNWALD, E., HAUSER, S. L., FAUCI, A. S., LONGO, D. L., KASPER, D. L., JAMESON, J. L. (Eds.), *Harrison's Principles of Internal Medicine*, 15th ed. New York, NY: McGraw Hill, **2001**.
 - 76 Anon. Drugs that cause psychiatric symptoms. *Med. Lett. Drugs Ther.* **2002**, 44, 59–62.
 - 77 OQUENDO, M. A., ELLIS, S. P., GREENWALD, S., MALONE, K. M., WEISSMAN, M. M., MANN, J. J., Ethnic and sex differences in suicide rates relative to major depression in the United States. *Am. J. Psychiatry* **2001**, 158, 1652–1658.
 - 78 LIN, K. M., Biological differences in depression and anxiety across races and ethnic groups. *J. Clin. Psychiatry* **2001**, 62 (Suppl. 13), 13–19; discussion 20–21.
 - 79 HIRSCHFELD, R. M., WEISSMAN, M. M., Risk factors for major depression and bipolar disorder. In DAVIS, K. L., CHARNEY, D., COYLE, J. T., NEMEROFF, C. (Eds.), *Neuropsychopharmacology: The Fifth Generation of Progress*. Nashville, TN: American College of Neuropsychopharmacology, **2002**.

27

Major Depression and Animals Models

Ma-Li Wong

Abstract

Animal models have been helpful to facilitate understanding of the pathophysiology of human diseases and development of relevant new therapies. In this chapter we will discuss scientific and ethical issues relevant to the use of animal models which were developed in order to understand a common complex disorder such as depression. How can an animal model for major depression be developed when this condition is considered to be the quintessential human disorder?

Depression affects sophisticated cognitive functions that are thought to be fundamentally human and which we maintain as absent in animals. Manifestations of major depression include decreased self-esteem, negativism, suicidality, and depression. Therefore, animal models can only reproduce some features of depression; furthermore, there is no unanimously accepted paradigm. Advances in genetics have already greatly improved our ability to understand human diseases. Genetically modified mice have facilitated and accelerated our capacity to model several human diseases. The characterization of behavioral phenotypes in genetically modified mice, generated by genetic engineering (such as knockout, knockdown, point mutation, random mutation or transgenic technologies) is expected to revolutionize our ability to model and to understand key features of common complex diseases.

27.1

Introduction

Animal models that have focused on reproducing an entire disease state (global models) of psychiatric disorders have been problematic. Therefore, researchers have departed from a position of trying to find “schizophrenic”, “depressed” or “autistic” animals and endeavored to attain the more practical goals of reproducing specific phenotypic components of psychiatric disorders [1–3]. The lack of a universally accepted animal model for major depression presents severe limitations

to our ability to advance the understanding of the pathophysiology of this disorder and the development of strategies for drug discovery [4].

Animal models generally replicate some characteristics of depression in a paradigm of stress or separation. Their relevance to the human condition is enhanced by our knowledge that antidepressant drugs represent effective treatment approaches for a significant proportion of depressed patients. Consequently, antidepressants are tested in animal paradigms to test their ability to ameliorate features of depression. One can argue that animal research in depression has been primarily psychopharmacological research, but this scenario is likely to change with the use of models based on genetic engineering. Genetic engineering has the potential to expand the number of models and behavioral phenotypes we study. Thus, mouse models will likely dominate the field and gradually supplant the use of more traditional rat models.

In this chapter we will describe the criteria for the development of animal models and briefly discuss the impact of ethical issues in depression research using animal models. We will not focus on specific models, but rather give an overview of the available models.

27.2

Historical Perspective

It is probably impossible to extricate our notions of the use of animals in psychiatric research from our recollections of the work on “conditioned reflex” and “conditioning” first described by Ivan Pavlov, the 1904 Nobel Laureate in Physiology or Medicine. He used dogs as experimental animals to study the relationship between salivation and digestion. Pavlov’s research into the physiology of digestion and the discovery of conditioned reflexes, which he regarded as an elementary psychological phenomenon [5], paved the way for the objective study of psychic activity.

Pavlov deduced three principles for the theory of reflexes: (1) determinism, (2) analysis and synthesis, and (3) structure. The development of these principles has greatly helped to strengthen the scientific basis of medicine and the discovery of the laws that control the functioning of living organisms. Pavlov’s work was also essential to our understanding of the basic laws that govern the activity of the cortex and cerebral hemispheres [6].

Experiments in Pavlov’s laboratory by Shenger-Kerstovnikova suggested that dogs involved in solving a series of increasingly complex and contradictory discrimination tasks eventually developed “experimental neurosis” [7]. Pavlov’s work indicated that abnormal behavior could be produced and studied by using a two-stage procedure:

- In stage 1, an animal was trained to learn a specific response to a particular situation.
- In stage 2, the environment was changed to produce a conflict with the trained response.

These approaches were based upon the presumed etiology based on intrapsychic conflict of human abnormal behavior [8]. Models following those concepts prevailed in the field for many years and they continue to be used to date. But these strategies present several problems as they attempted to reproduce global models of psychiatric disorders for testing experimental interventions. Further complications arise because these models were developed in a period in which ethical concerns in animal research were essentially non-existent.

27.3

Criteria for the Development of Animal Models

The basic assumption that makes the use of animal models possible, is founded on the existence of an analogy in physiological and behavioral characteristics among several animal species, thus inferences can be made across species to help understand the human condition. The prevalent notion is that a useful animal model should lead to informative predictions about the human disorders and if it does not, the model should be abandoned. Therefore, valuable models should be reliable and predictive in relation to the human condition.

Several reviews have discussed the criteria for the evaluation of animal models [9–13]. Validation criteria, which are relevant standards for the assessment of any model, have been applied to evaluate animal models. Their implications are discussed in the following paragraphs; most animal models meet some of these criteria, and they can be ranked according to how well they meet one or more of the criteria described below.

27.3.1

Reliability

Variables under study should be consistent and stable. Reliable and reproducible models are essential for research. As such, our ability to reproduce the event under most similar conditions and the effects of manipulations and their measurement should be evident and consistent. It should be noted that it is expected that biological systems have a small degree of variability between- and within-subjects.

27.3.2

Validity

Different types of validity criteria can be applied to animal models [14–18]. These would include construct, etiological, face, predictive, convergent and discriminant validity. In a recently article Willner and Mitchell reviewed the validity of animal models for predisposition to depression [19]. The creation of several forms of validations provides convergent corroboration for the hypothesized cross-species analogy. Clearly, models that meet the criteria for multiple types of validity have

greater value in modeling the human condition. In addition to these considerations, ethical issues have required that investigators perform stringent assessment of the validity of animal models to determine whether the harm inflicted on the animals during the course of the experimental procedures is justified.

27.3.2.1 Construct Validity

Construct validity is a criterion that assesses whether a model is based on a sound theoretical rationale. The application of this criterion in models for depression presumes that it is possible to construct psychopathology theories which can be applicable to non-human animals. It may appear that the construct validity would be the most important property of an animal model [15, 17], however this criterion reflects our limited understanding of the underlying processes or mechanisms in major depression. The construct validity of a certain model could be based on neurobiological, etiological (also called etiological validity [20]) or psychological/behavioral mechanisms. Therefore, this criterion will constantly change to capture the evolution of our scientific theories.

Two models described to have construct validity based on behavioral phenomena are learned helplessness [21] and anhedonia [18] (failure to perform rewarded behavior, as measured in chronic mild stress models).

27.3.2.2 Etiological Validity

This criterion is a type of construct validity and assesses whether the etiology of the phenomenon under study is identical in the animal model and in humans [20, 22]. The evaluation of the etiological validity of an animal model faces very similar problems to those described for construct validity. Although a variety of factors are implicated in the etiology of major depression (such as genetic influences, medical illness, medications, psychological stress, and adverse childhood experiences), our understanding of how they affect the physiological processes modulating mood is inadequate. Accordingly, etiological validity is limited to the hypothesis of possible etiology. Because the etiology of depression is unknown, we cannot require that a model for depression has etiological validity, but rather, we could develop animal models and test their etiological validity. This seems to be a reasonable strategy for testing genetically engineered animals. It is hoped that the combination of genetic and molecular biology approaches will advance our ability to generate and test etiologically based models for depression.

27.3.2.3 Face Validity

This criterion measures how well the characteristic behavior of the animal model reproduces the human condition in a broad variety of symptoms and signs [9]. A number of comparisons between the model and the condition modeled may significantly decrease the problems related to subjective arguments [16, 21, 23]. There are several considerations to be taken into account:

1. Even when the etiology of a condition is known, two species may exhibit different symptoms.

2. Similarity of core symptoms of a disease has more relevance than the resemblance of secondary symptoms.
3. Not all symptoms of depression can be modeled by animals; for instance, we cannot model symptoms that are expressed verbally (e.g. feelings of worthlessness, suicidal ideation, demoralization, depressed mood, etc).
4. Some core symptoms, for example dysthymia, are present in other psychiatric conditions (such as schizophrenia).
5. Antidepressants ameliorate depressive symptoms after chronic usage (ranging from 2 to 8 weeks), therefore an animal model that has face validity should have a delayed onset of therapeutic response to antidepressant treatment.
6. As tolerance to the antidepressant effects do not occur in the clinical setting, the response in the model should be sustained until the termination of antidepressant treatment.
7. There should not be any major divergence between the model and the disease it supposedly models.
8. Specificity of the model should be investigated; symptoms addressed should not be general features of several psychopathological conditions.

27.3.2.4 Predictive Validity

This criterion refers to the ability of the model to produce results which are predictive of those that would occur in the situation being modeled [24]. The practical application of predictive validity is to assess the effects of potential therapeutic treatments: the model has predictive validity if it successfully differentiates between effective and ineffective treatments. Therefore, an animal model for depression should be tested for a range of treatments that are known to be effective (e.g. TCA, MAOI, ECT, etc.) and ineffective, and predictive validity would be enhanced if potency in the model were correlated with clinical potency. A significant positive correlation between behavioral effects and clinical potency of antidepressants has been demonstrated in the “behavioral despair” test (also called forced swim test or Porsolt’s test) [21] and it has also been shown that there is a significant negative correlation between the clinical potency of antidepressants and their ability to desensitize beta-receptors [25].

27.3.2.5 Convergent and Discriminant Validity

For the assessment of animal models for depression, these criteria could be considered as subsidiary. Convergent validity refers to the degree to which a test correlates with other tests that endeavor to measure the same phenomenon. Discriminant validity assesses the degree to which a test measures aspects of a construct that are different from those assessed by other tests [14].

27.4

Ethical Issues in Animal Research

Ethical issues concerning the justification for using animals in research have been debated extensively by contemporary philosophers [26–28]. Presently, there is robust agreement that animals matter morally and that when carrying out animal research scientists must take the welfare of the animals into account. Detailed discussion on ethical implications about the use of animals in research is beyond the scope of this chapter. Readers are referred to recent reviews for a more in-depth understanding of ethical issues [8, 29–32]. In the following paragraphs, we will discuss some ethical issues that have impacted the use of animal models in depression research.

Animal research is covered under the United States Animal Welfare Act (AWA), which requires that minimum standards of care and treatment be provided for certain animals bred for commercial sale, used in research, transported commercially, or exhibited to the public (<http://www.aphis.usda.gov/ac/publications.html>). In the United States, hypothetically any investigative procedure (with the exception of performing surgery with non-anesthetic paralytic agents) can be approved if the argument for human benefit is reasonably convincing.

The elementary wisdom justifying the use of animals for experimentation purposes is that the results of such endeavors should be of benefit to the human species and also possibly to animal species [8]. The use of animal models in research has been ethically and morally defended by the commonly shared intuition that normal adult humans have more highly-developed abilities (more sophisticated cognitive functions) which make possible a greater number of interests and produce greater levels of satisfaction, reflective thought and self-consciousness, thereby, arguably, making human lives more valuable because their complex cognitive abilities enhance the various ways that a person may experience pleasure or harm. But since we accept that major depression involves complex thought processes and emotions which we believe to be inherent to the human condition, this line of thought thus precludes the development of global animal models for depression. It then becomes evident that global models suffer from intrinsic validity problems. This then undoubtedly leads to the consolidation of the rationale for the development of partial models in which various features of depression are modeled.

Research activities have become progressively more influenced by ethical and moral considerations, as several ethical theories have been applied to the use of animals in scientific work over the past several decades. While debates on the ethical justification of animal use continues to lack clarity [31–34], it is of scientific importance that researchers expand their knowledge of bioethics and critically evaluate the use of animals from both a scientific and an ethical perspective [35,36].

Thus, to ensure that optimum animal welfare and high quality science shape future developments, researchers involved in formulating new animal models for depression have been faced with the daunting task of meeting the scientific challenges involved in unraveling a common complex disorder with cognitive, systemic, behavioral and affective manifestations and of meeting complex ethical

requirements. There is no doubt that sensitivity and respect are essential elements that should guide the utilization of animals for a good cause and that the proposals of Russell and Burch [37], also referred to as the “three Rs”, should be followed. Consequently, “alternative” methods supporting replacement, reduction or refinement principles are in actuality more scientifically valid and advanced methods.

Animal research has undoubtedly made an enormous contribution to the advancement of biomedical science. Morrison has recently argued unambiguously in support of animal research [38] and concluded his lecture on biomedical ethics by outlining his arguments as follows:

- “(1) Our first obligation is to our fellow humans;*
- (2) All human beings are persons;*
- (3) Animals are not little persons;*
- (4) We have a great obligation to the animals under our control; and*
- (5) Good science requires good animal care, but bureaucracy does not necessarily equate with increased welfare.”*

Morrison’s assertions should be viewed with caution, as they do not reflect the lack of clarity in the ethical debate [38]. Bioethics is likely to become more complex since developments in genetic engineering have extended ethical considerations [29] beyond the usual debate of animal welfare. Genetic engineering is a sophisticated scientific process that is complex and costly. It may produce unexpected consequences concerning harm to humans, non-human animals and to the environment.

It is unlikely that we will stop using animal in biomedical research in the near future. Ethical obligation and duty require that we acknowledge that animals matter morally and that their welfare be considered in our experimental designs. Researchers must become more aware of issues that impact the validation of models and the relevant characteristics of the animal species they select to use. Ethical issues may indeed provide opportunities for reassurance that sound science and optimum animal welfare will strengthen future scientific developments.

27.5

The Use of Animal Models in the Study of Major Depression

Even though there are several intrinsic limitations, a number of animal models have been developed for depression and they are summarized in Table 27.1. Approaches based on the creation of global disease models are scientifically problematic. One problem emerges from the argument that central symptoms for major depression are frequently defined by subjective language which is difficult to translate into the non-verbal behavior of animals. We are unable to recognize symptoms such as depression, suicidality, negativism or decreased self-esteem in animals. Another issue that arises from our limited understanding of the pathophysiology of the disease is that once our understanding of major depression evolves, what once appeared to be an overall model then becomes inadequate.

Table 27.1 Animal models of major depression (reproduced from [4])

Model	Rational	Description	Phenotype reproduced	Predictive validity
Uncontrollable stress models: Learned helplessness model (LHM) [47–49] Behavioral despair (BD) [50, 51] Tail suspension test (TST) [52–54]	Exposure to uncontrollable stress produces performance deficits in subsequent learning tasks that are not seen in subjects exposed to identical stressors that are under the subjects' control.	LHM: Rats or mice exposed to uncontrollable stress, e.g. uncontrollable foot shock. BD is a variant of LHM: Rats or mice are forced to swim in a confined environment (a.k.a. forced swim test or Porsolt's test). TST is theoretically similar to BD: Mice are suspended by their tails for 6 min; the amount of time they spend immobile is recorded.	Loss of appetite and weight, decreased locomotor activity, and poor performance in both appetitively and aversively motivated tasks.	Pharmacological treatments clinically effective in depression are effective in reducing the behavioral and "physical" abnormalities seen in animals exposed to uncontrollable stress. These models have high degree of predictive validity in terms of pharmacological isomorphism.
Reward models: Intracranial self-stimulation (ICSS) [55] Sucrose preference [56–58] Place preference [59]	Stress induces abnormalities in reward processes. These paradigms are not considered models of an entire syndrome, but rather provide operational measures of anhedonia, a core feature of depression and a negative symptom of schizophrenia.	ICSS: brief electrical self-stimulation of specific brain sites, which is very reinforcing. In reward models the rate of responding and/or the psychophysically defined threshold(s) may be used to measure the reward value of the stimulation. The readouts to stress paradigm, such as chronic mild stress, are used to change the response to reward models. Amphetamine withdrawal seems to be a suitable substrate for inducing depression-like symptoms in rodents.	Anhedonia is the markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.	Stress-induced alterations in ICSS behavior was reversed by antidepressant treatment. Anhedonic effect of stress was reversed by antidepressant treatment, but not by anti-psychotic, anxiolytic, amphetamine, or morphine treatment, indicating good predictive validity in terms of pharmacological isomorphism.

Table 27.1 (continued)

Model	Rational	Description	Phenotype reproduced	Predictive validity
Olfactory bulbectomy [60, 61]	Olfactory bulbs are extensions of the rostral telencephalon and constitute 4% of the total brain mass in adult rats. Extensive connections with the limbic and higher brain centers implicating this model in a wide range of effects other than anosmia alone.	Bilateral removal of olfactory bulbs of rodents (mainly rats).	Behavioral, neurochemical, neuroendocrine, and neuroimmune alterations seem to be comparable to changes in depression.	Reliable prediction of response to antidepressants in rats.
Chronic mild stress (CMS) [62, 63]	Exposure to mild unpredictable stressors induces long-term changes resembling those found in depressed patients.	CMS has two major effects: CMS depresses the consumption of sucrose solutions and also decreases brain reward function (see above).	Behavioral, neurochemical, neuroimmune, and neuroendocrine alterations resembling those observed in depression.	Anhedonia-like behaviors are reversed by chronic but not acute antidepressant treatment. Poor reliability of results in rats has limited the utilization of this model.
Drug withdrawal [64–66]	Withdrawal from drugs of abuse reduces brain reward function.	Amphetamine withdrawal seems to be a substrate for inducing depression-like phenotypes. Effects can be monitored by ICSS, sucrose preference, BD, TST, LHM.	Anhedonia is the markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.	Anhedonia-like behaviors are reversed by chronic but not acute antidepressant treatment.
Maternal deprivation [67–69]	Development of the HPA axis is under maternal regulation. Separating mother and pups for 24 h results in activation of the HPA axis.	Litters are separated from their mother for many hours (24 h) before testing and kept warm but without any available food or water.	HPA axis alterations.	Limited testing of antidepressants has been conducted.

Table 27.1 (continued)

Model	Rational	Description	Phenotype reproduced	Predictive validity
Neonatal clomipramine [70]	Clomipramine increases monoaminergic availability at the synaptic level and suppresses REM sleep.	Rat pups are treated from postnatal day 5 to 21 with clomipramine 15 mg/kg, s.c., twice daily.	Behavioral changes during adulthood, circadian disturbances and alterations in sexual behavior.	Limited testing of antidepressants has been conducted.
Genetic models: Selective animal breeding	Rats are selectively bred for hypo- or hyper-sensitivity of specific receptor subtypes whose altered function has been hypothesized to be involved in the etiology of depression.	Cholinergic–noradrenergic neurotransmitter imbalance (Flinders Sensitive Line rats, FSL) [71]; the 8-OH-DPAT line of rats [72]; Fawn-Hooded (FH/Wjd) [73]; Rouen “depressed” mice [74, 75].	Animals are more susceptible to stress-induced behavioral disturbances.	Increased immobility in the forced swim test and foot shock responds to antidepressants.
Genetic models: Transgenic animals	Transgenic mice (knockout or overexpressors) that exhibit depression or antidepressant-related behavior.	Serotonin system [76–88], noradrenergic system [89–92], monoamine oxidase [93–95], opioid [96], GABA [97, 98], glutamate [99, 100], substance P system [101–104], HPA axis [105–108], galanin [109], immunological [110, 111], intracellular signaling molecules and transcription factors [112–116], other neurotransmitter or receptors [117–124].	Phenotype is variable and each model has been accessed by one or more of the paradigms listed above (such as BD, TST, LHM, CMS).	Phenotypes can be depression-like or antidepressant-related.

Table 27.1 (continued)

Model	Rational	Description	Phenotype reproduced	Predictive validity
Other useful tests:	These tests address specific psychiatric symptoms.	EEG characterization [74, 125]; energy expenditure [126]; nesting behavior [127]; social avoidance or withdrawal [128, 129]; swimming [130] treadmill/running wheel [131];	Fatigue or loss of energy can be assessed by these tests; social withdrawal can also be a measure of anxiety.	These tests measure changes in behavior/signs that are not necessarily specific for depression.
		Attention [132]; spatial memory [133]; working memory [134].	Decreased ability to think or concentrate.	Same as above.
		Prenatal stress [135].	May reproduce stress or conditions that influence behavioral or physiological changes during adulthood.	Same as above.
		Novelty suppressed feeding [136].	May reflect anxiety.	Behavioral effects following chronic treatment.
		Resident intruder [137].	May reflect social stress or anxiety.	Change in agonistic behavior during the course of antidepressant drug treatment.
		LPS-induced immunological activation [138].	May reproduce neuro-immune or neuroendocrine changes that occur during stress.	Sensitive to tricyclic antidepressant.

Also, the same attributes that make non-human primates attractive for research also triggers questions about the ethical justification of using them.

Rather than attempting to reproduce complete disorders, newer experimental approaches aim to produce models of specific components of the psychiatric condition under study, such as the signs or symptoms [20]. These partial models which focus on duplicating features of the overall human clinical phenomena are also referred to as “simulacra” [39]. Comprehensive examination of the fundamental mechanisms of specific syndromal signs increases the ability to evaluate validity issues. Simulacra models can only meet validity criteria if extensive human clinical information is available and animal scientists can properly target their research models.

Novel technologies that enable scientists to manipulate the mouse genome has brought a plethora of resources; inbred strains and mutant stocks are available for genetic studies in mice at reasonable housing costs and short generation times. The applications of genetic engineering in the mouse have recently been reviewed in the October 2001 issue of *Nature Reviews Genetics*. The mouse is certainly not a perfect model for every disease, but the ability to manipulate its genome, to observe the resulting phenotypic consequences using cellular, electrophysiological molecular approaches and to perform genetic mapping in that model organism, have made mice models very valuable for research. Genetic manipulations for the generation of new behavioral and neurological mutations can be achieved by three complementary methodologies: target mutagenesis, gene-trap mutagenesis and N-ethyl-N-nitrosourea (ENU) mutagenesis. The mutant locus can be determined by positional cloning and QTL (quantitative trait locus) analysis [40] (for a broad review of mouse models of human disorders see [41]).

Mouse models of single-gene Mendelian disorders have already led to invaluable advances in biomedical research. Their potential to help us gain insight into the pathophysiology of common complex disorders, such as major depression, seems even greater. But unexpected results have already been found; we have learned lessons from the discovery that phenotype in mice and humans can be different even when they have the same genotype. For example a genetic enzyme deficiency in mice may lead to no phenotypic change or to a change that is quite different from the metabolic disorder manifested in man by the same enzyme deficiency [42]. Interestingly, these differences have been very informative, as we have become more knowledgeable about the consequences of altered biochemical and physiological pathways. Several important factors need to be taken into consideration when trying to define a causal relationship between specific behavior and its underlying electrophysiological, biochemical, cellular and neuropathological mechanisms [40]. These factors include:

- Pleiotropy: a single gene which can cause many distinctive and apparently unrelated phenotypic characteristics
- Confounding effects of genetic background
- Confounding effects of environmental factors
- Issues with experimental design

Mouse models have already been created for the study of Alzheimer's and Huntington diseases [43–45]. Mutations in several other genes which cause alterations in human behavior have already been studied in the mouse. It is hoped that the study of these mouse strains will enhance our understanding of the molecular mechanisms that underlie certain human conditions. For instance, mutations in the collection of genes which cause X-linked mental retardation can give us insight into genetically heterogeneous, nonspecific forms of mental retardation [46].

Will we be able to find particular genes or a set of genes that exclusively mediate certain behaviors? It is anticipated that identification and characterization of several behavioral mutants will allow us to address this vital question in neurobiology. Mouse models that reproduce endophenotypes of complex psychiatric and behavioral disorders will provide the means with which to investigate the mechanisms of action of therapeutic agents, gain insight into pathophysiological mechanisms and facilitate the development of novel pharmacological approaches.

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References

- 1 FREEDMAN, R., ADLER, L. E., LEONARD, S., Alternative phenotypes for the complex genetics of schizophrenia. *Biol. Psychiatry* **1999**, *45*, 551–558.
- 2 LEBOYER, M., BELLIVIER, F., NOSTEN-BERTRAND, M., JOUVENT, R., PAULS, D., MALLET, J., Psychiatric genetics: search for phenotypes. *Trends Neurosci.* **1998**, *21*, 102–105.
- 3 TARANTINO, L. M., BUCAN, M., Dissection of behavior and psychiatric disorders using the mouse as a model. *Hum. Mol. Genet.* **2000**, *9*, 953–965.
- 4 WONG, M. L., LICINIO, J., From monoamines to genomic targets: a paradigm shift for drug discovery in depression. *Nature Rev. Drug Discov.* **2004**, *3* (2), 136–151.
- 5 PAVLOV, I. P., The scientific investigation of the psychical faculties or processes in the higher animals (The Huxley lecture, 1906). *Lancet* **1906**, 911–915.
- 6 *Nobel Lectures, Physiology or Medicine 1901–1921*. Amsterdam: Elsevier Publishing Company, **1967**.
- 7 SHENGER-KRESTOVNIKOVA, N. R., Contributions to the question of differentiation of visual stimuli and the limits of differentiation by the visual analyzer of the dog. *Bull. Lesgaft Inst. Petrograd* **1921**, *3*, 1–43.
- 8 GLUCK, J. P., BELL, J., Ethical issues in the use of animals in biomedical and psychopharmacological research. *Psychopharmacology (Berl.)* **2003**, *171* (1), 6–12.
- 9 MCKINNEY JR., W. T., BUNNEY JR., W. E., Animal model of depression. I. Review of evidence: implications for research. *Arch. Gen. Psychiatry* **1969**, *21*, 240–248.
- 10 HINDE, R. A., The use of differences and similarities in comparative psychopathology. In SERBAN, G., KLING, A. (Eds.), *Animal Models in Psychobiology*. New York: Plenum Press, **1976**, 187–202.
- 11 MATTHYSSE, S., Animal models in psychiatric research. *Prog. Brain Res.* **1986**, *65*, 259–270.
- 12 SEGAL, D. S., GEYER, M. A., Animal models of psychopathology. In JUDD,

- L. L., GROVES, P. M. (Eds.), *Psychobiological Foundations of Clinical Psychiatry*. Philadelphia: JB Lippincott, 1985.
- 13 MARKOU, A., WEISS, F., GOLD, L. H., CAINE, S. B., SCHULTEIS, G., KOOB, G. F., Animal models of drug craving. *Psychopharmacology* 1993, 112, 163–182.
- 14 CAMPBELL, D. T., FISKE, D. W., Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychol. Bull.* 1959, 56, 81–105.
- 15 CRONBACH, L. J., MEEHL, P. E., Construct validity in psychological tests. *Psychol. Bull.* 1955, 52, 281–302.
- 16 MOSIER, C. I., A critical examination of the concepts of face validity. *Educ. Psychol. Measurement* 1947, 7, 191–205.
- 17 WILLNER, P., The validity of animal models of depression. *Psychopharmacology (Berl.)* 1984, 83, 1–16.
- 18 WILLNER, P., Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. *Psychopharmacology (Berl.)* 1997, 134, 319–329.
- 19 WILLNER, P., MITCHELL, P. J., The validity of animal models of predisposition to depression. *Behav. Pharmacol.* 2002, 13, 169–188.
- 20 GEYER, M. A., MARKOU, A., Animals models of psychiatric disorders. In BLOOM, F. E., KUPFER, D. (Eds.), *Psychopharmacology: Fourth Generation of Progress*. New York: Raven, 1995, 787–798.
- 21 WILLNER, P., Validation criteria for animal models of human mental disorders: learned helplessness as a paradigm case. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 1986, 10, 677–690.
- 22 MCKINNEY, W. T., Animal models of depression: an overview. *Psychiatr. Dev.* 1984, 2, 77–96.
- 23 ABRAMSON, L. Y., SELIGMAN, M. E. P., Modelling psychopathology in the laboratory: History and rationale. In MASER, J. D., SELIGMAN, M. E. P. (Eds.), *Psychopathology: Animal Models*. San Francisco: Freeman, 1977, 1–26.
- 24 RUSSELL, R. W., Extrapolation from animals to man. In STEINBERG, H. (Ed.), *Animal Behaviour and Drug Action*. London: Churchill, 1964, 410–418.
- 25 WILLNER, P., The ability of antidepressant drugs to desensitize beta-receptors is inversely correlated with their clinical potency. *J. Affect Disord.* 1984, 7, 53–58.
- 26 CLARKE, D. D., CLARKE, D. M., Analysis: an introduction to ethical concepts. Definition and ethical decisions. *J. Med. Ethics* 1977, 3, 186–188.
- 27 MIDGLEY, M., *Animals and Why they Matter*. London: Duckworth, 1984.
- 28 SINGER, P., *Animal Rights*, 2nd ed. New York: Random House, 1990.
- 29 ALMOND, B., Commodifying animals: ethical issues in genetic engineering of animals. *Health Risk Soc.* 2000, 2, 95–105.
- 30 RUSSOW, L. M., DONNELLEY, S., DRESSER, R., VANDEBERG, J. L., WILLIAMS-BLANGERO, S., WOLFLE, T. L., Bioethics, animal research, and ethical theory. *Ilar J.* 1999, 40, 15–21.
- 31 DE GRAZIA, D., The moral status of animals and their use in research: a philosophical review. *Kennedy Inst. Ethics J.* 1991, 1, 48–70.
- 32 BEAUCHAMP, T. L., Opposing views on animal experimentation: do animals have rights? *Ethics Behav.* 1997, 7, 113–121.
- 33 ROLLIN, B., *The Unheeded Cry: Animal Consciousness, Animal Pain and Science*. New York: Oxford University, 1989.
- 34 GLUCK, J. P., DiPASQUALE, T., Introduction and overview. In GLUCK, J. P., DiPASQUALE, T., ORLANS, F. B. (Eds.), *Applied Ethics in Animal Research: Philosophy, Regulation, and Laboratory Applications*. West Lafayette: Purdue, 2002, 1–11.
- 35 GLUCK, J. P., KUBACKI, S. R., Animals in biomedical research: the undermining effect of the rhetoric of the besieged. *Ethics Behav.* 1991, 1, 157–173.
- 36 GOODMAN, S., CHECK, E., The great primate debate. *Nature* 2002, 417, 684–687.
- 37 RUSSELL, W., BURCH, R., *The Principles of Humane Experimental Technique*. London: Methuen, 1959.
- 38 MORRISON, A. R., Developing an ethical view on the use of animals in biomedical research. Fourth Walter C. Randall Lecture on Biomedical Ethics. *Physiologist* 2002, 45, 135, 139–144.
- 39 MCCLEARN, G. E., Genetics and alcoholism simulacra. *Alcohol Clin. Exp. Res.* 1979, 3, 255–258.

- 40 BUCAN, M., ABEL, T., The mouse: genetics meets behaviour. *Nature Rev. Genet.* **2002**, 3, 114–123.
- 41 CRAIGEN, W. J., Mouse Models of human genetic disorders. In SCRIVER, C. R., BEAUDET, A. L., VALLE, D., SLY, W. S., CHILDS, B., KINZER, K. W., et al. (Eds.), *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. New York: McGraw-Hill, **2001**.
- 42 ELSEA, S. H., LUCAS, R. E., The mouse-trap: what we can learn when the mouse model does not mimic the human disease. *Ilar J.* **2002**, 43, 66–79.
- 43 YAMAMOTO, A., LUCAS, J. J., HEN, R., Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell* **2000**, 101, 57–66.
- 44 CHAPMAN, P. F., FALINSKA, A. M., KNEVETT, S. G., RAMSAY, M. F., Genes, models and Alzheimer's disease. *Trends Genet.* **2001**, 17, 254–261.
- 45 CHEN, G., CHEN, K. S., KNOX, J., INGLIS, J., BERNARD, A., MARTIN, S. J., et al., A learning deficit related to age and beta-amyloid plaques in a mouse model of Alzheimer's disease. *Nature* **2000**, 408, 975–979.
- 46 CHELLY, J., MANDEL, J. L., Monogenic causes of X-linked mental retardation. *Nature Rev. Genet.* **2001**, 2, 669–680.
- 47 MAIER, S. F., Learned helplessness and animal models of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1984**, 8, 435–446.
- 48 SELIGMAN, M. E., BEAGLEY, G., Learned helplessness in the rat. *J. Comp. Physiol. Psychol.* **1975**, 88, 534–541.
- 49 VOLLMAYR, B., HENN, F. A., Learned helplessness in the rat: improvements in validity and reliability. *Brain Res. Brain Res. Protoc* **2001**, 8, 1–7.
- 50 PORSOLT, R. D., BERTIN, A., JALFRE, M., "Behavioural despair" in rats and mice: strain differences and the effects of imipramine. *Eur. J. Pharmacol.* **1978**, 51, 291–294.
- 51 WEST, A. P., Neurobehavioral studies of forced swimming: the role of learning and memory in the forced swim test. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1990**, 14, 863–877.
- 52 PORSOLT, R. D., CHERMAT, R., LENEGRE, A., AVRIL, I., JANVIER, S., STERU, L., Use of the automated tail suspension test for the primary screening of psychotropic agents. *Arch. Int. Pharmacodyn. Ther.* **1987**, 288, 11–30.
- 53 BAI, F., LI, X., CLAY, M., LINDSTROM, T., SKOLNICK, P., Intra- and interstrain differences in models of "behavioral despair". *Pharmacol. Biochem. Behav.* **2001**, 70, 187–192.
- 54 MAYORGA, A. J., LUCKI, I., Limitations on the use of the C57BL/6 mouse in the tail suspension test. *Psychopharmacology (Berl.)* **2001**, 155, 110–112.
- 55 SHIZGAL, P., Toward a cellular analysis of intracranial self-stimulation: contributions of collision studies. *Neurosci. Biobehav. Rev.* **1989**, 13, 81–90.
- 56 MATTHEWS, K., FORBES, N., REID, I. C., Sucrose consumption as an hedonic measure following chronic unpredictable mild stress. *Physiol. Behav.* **1995**, 57, 241–248.
- 57 FORBES, N. F., STEWART, C. A., MATTHEWS, K., REID, I. C., Chronic mild stress and sucrose consumption: validity as a model of depression. *Physiol. Behav.* **1996**, 60, 1481–1484.
- 58 HARRIS, R. B., ZHOU, J., YOUNGBLOOD, B. D., SMAGIN, G. N., RYAN, D. H., Failure to change exploration or saccharin preference in rats exposed to chronic mild stress. *Physiol. Behav.* **1997**, 63, 91–100.
- 59 VAN DER KOOP, D., Place conditioning: A simple and effective method for assessing the motivational properties of drugs. In BOZARTH, M. A. (Ed.), *Methods of Assessing the Reinforcing Properties of Abused Drugs*. New York: Springer Verlag, **1987**, 229–240.
- 60 KELLY, J. P., WRYNN, A. S., LEONARD, B. E., The olfactory bulbectomized rat as a model of depression: an update. *Pharmacol. Ther.* **1997**, 74, 299–316.
- 61 HOZUMI, S., NAKAGAWASAI, O., TAN-NO, K., NIJIMA, F., YAMADERA, F., MURATA, A., et al., Characteristics of changes in cholinergic function and impairment of learning and memory-related behavior induced by olfactory bulbectomy. *Behav. Brain Res.* **2003**, 138, 9–15.
- 62 KATZ, R. J., ROTH, K. A., CARROLL, B. J., Acute and chronic stress effects on open field activity in the rat: implications for a

- model of depression. *Neurosci. Biobehav. Rev.* **1981**, 5, 247–251.
- 63 WILLNER, P., MUSCAT, R., PAPP, M., Chronic mild stress-induced anhedonia: a realistic animal model of depression. *Neurosci. Biobehav. Rev.* **1992**, 16, 525–534.
 - 64 KOKKINIDIS, L., ZACHARKO, R. M., ANISMAN, H., Amphetamine withdrawal: a behavioral evaluation. *Life Sci.* **1986**, 38, 1617–1623.
 - 65 ANRAKU, T., IKEGAYA, Y., MATSUKI, N., NISHIYAMA, N., Withdrawal from chronic morphine administration causes prolonged enhancement of immobility in rat forced swimming test. *Psychopharmacology (Berl.)* **2001**, 157, 217–220.
 - 66 CRYAN, J. F., HOYER, D., MARKOU, A., Withdrawal from chronic amphetamine induces depressive-like behavioral effects in rodents. *Biol. Psychiatry* **2003**, 54, 49–58.
 - 67 MATTHEWS, K., ROBBINS, T. W., Early experience as a determinant of adult behavioural responses to reward: the effects of repeated maternal separation in the rat. *Neurosci. Biobehav. Rev.* **2003**, 27, 45–55.
 - 68 LADD, C. O., OWENS, M. J., NEMEROFF, C. B., Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology* **1996**, 137, 1212–1218.
 - 69 PRYCE, C. R., FELDON, J., Long-term neurobehavioural impact of the postnatal environment in rats: manipulations, effects and mediating mechanisms. *Neurosci. Biobehav. Rev.* **2003**, 27, 57–71.
 - 70 VOGEL, G., NEILL, D., HAGLER, M., KORS, D., A new animal model of endogenous depression: a summary of present findings. *Neurosci. Biobehav. Rev.* **1990**, 14, 85–91.
 - 71 OVERSTREET, D. H., The Flinders sensitive line rats: a genetic animal model of depression. *Neurosci. Biobehav. Rev.* **1993**, 17, 51–68.
 - 72 OVERSTREET, D. H., Behavioral characteristics of rat lines selected for differential hypothermic responses to cholinergic or serotonergic agonists. *Behav. Genet.* **2002**, 32, 335–348.
 - 73 REZVANI, A. H., PARSIAN, A., OVERSTREET, D. H., The Fawn-Hooded (FH/Wjd) rat: a genetic animal model of comorbid depression and alcoholism. *Psychiatr. Genet.* **2002**, 12, 1–16.
 - 74 EL YACOUBI, M., BOUALI, S., POPA, D., NAUDON, L., LEROUX-NICOLLET, I., HAMON, M., et al., Behavioral, neurochemical, and electrophysiological characterization of a genetic mouse model of depression. *Proc. Natl. Acad. Sci. USA* **2003**, 100, 6227–6232.
 - 75 VAUGEOIS, J. M., ODIEVRE, C., LOISEL, L., COSTENTIN, J., A genetic mouse model of helplessness sensitive to imipramine. *Eur. J. Pharmacol.* **1996**, 316, R1–R2.
 - 76 RAMBOZ, S., OOSTING, R., AMARA, D. A., KUNG, H. F., BLIER, P., MENDELSON, M., et al., Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. *Proc. Natl. Acad. Sci. USA* **1998**, 95, 14476–14481.
 - 77 HEISLER, L. K., CHU, H. M., BRENNAN, T. J., DANA, J. A., BAJWA, P., PARSONS, L. H., et al., Elevated anxiety and antidepressant-like responses in serotonin 5-HT1A receptor mutant mice. *Proc. Natl. Acad. Sci. USA* **1998**, 95, 15049–15054.
 - 78 PARKS, C. L., ROBINSON, P. S., SIBILLE, E., SHENK, T., TOTH, M., Increased anxiety of mice lacking the serotonin1A receptor. *Proc. Natl. Acad. Sci. USA* **1998**, 95, 10734–10739.
 - 79 BOUTREL, B., MONACA, C., HEN, R., HAMON, M., ADRIEN, J., Involvement of 5-HT1A receptors in homeostatic and stress-induced adaptive regulations of paradoxical sleep: studies in 5-HT1A knock-out mice. *J. Neurosci.* **2002**, 22, 4686–4692.
 - 80 MAYORGA, A. J., DALVI, A., PAGE, M. E., ZIMOV-LEVINSON, S., HEN, R., LUCKI, I., Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B) receptor mutant mice. *J. Pharmacol. Exp. Ther.* **2001**, 298, 1101–1107.
 - 81 KNOBELMAN, D. A., HEN, R., BLENDY, J. A., LUCKI, I., Regional patterns of compensation following genetic deletion of either 5-hydroxytryptamine(1A) or 5-hydroxytryptamine(1B) receptor in the mouse. *J. Pharmacol. Exp. Ther.* **2001**, 298, 1092–1100.
 - 82 KNOBELMAN, D. A., HEN, R., LUCKI, I., Genetic regulation of extracellular serotonin by 5-hydroxytryptamine(1A)

- and 5-hydroxytryptamine(1B) auto-receptors in different brain regions of the mouse. *J. Pharmacol. Exp. Ther.* **2001**, 298, 1083–1091.
- 83 DE GROOTE, L., OLIVIER, B., WESTENBERG, H. G., The effects of selective serotonin reuptake inhibitors on extracellular 5-HT levels in the hippocampus of 5-HT(1B) receptor knockout mice. *Eur. J. Pharmacol.* **2002**, 439, 93–100.
 - 84 MALAGIE, I., DAVID, D. J., JOLLIET, P., HEN, R., BOURIN, M., GARDIER, A. M., Improved efficacy of fluoxetine in increasing hippocampal 5-hydroxytryptamine outflow in 5-HT(1B) receptor knock-out mice. *Eur. J. Pharmacol.* **2002**, 443, 99–104.
 - 85 HOLMES, A., YANG, R. J., MURPHY, D. L., CRAWLEY, J. N., Evaluation of antidepressant-related behavioral responses in mice lacking the serotonin transporter. *Neuropsychopharmacology* **2002**, 27, 914–923.
 - 86 LI, Q., WICHEMS, C., HEILS, A., VAN DE KAR, L. D., LESCH, K. P., MURPHY, D. L., Reduction of 5-hydroxytryptamine (5-HT)(1A)-mediated temperature and neuroendocrine responses and 5-HT(1A) binding sites in 5-HT transporter knock-out mice. *J. Pharmacol. Exp. Ther.* **1999**, 291, 999–1007.
 - 87 GOBBI, G., MURPHY, D. L., LESCH, K., BLIER, P., Modifications of the serotonergic system in mice lacking serotonin transporters: an in vivo electrophysiological study. *J. Pharmacol. Exp. Ther.* **2001**, 296, 987–995.
 - 88 MANNOURY LA COUR, C., BONI, C., HANOUN, N., LESCH, K. P., HAMON, M., LANFUMEY, L., Functional consequences of 5-HT transporter gene disruption on 5-HT(1a) receptor-mediated regulation of dorsal raphe and hippocampal cell activity. *J. Neurosci.* **2001**, 21, 2178–2185.
 - 89 CRYAN, J. F., DALVI, A., JIN, S. H., HIRSCH, B. R., LUCKI, I., THOMAS, S. A., Use of dopamine-beta-hydroxylase-deficient mice to determine the role of norepinephrine in the mechanism of action of antidepressant drugs. *J. Pharmacol. Exp. Ther.* **2001**, 298, 651–657.
 - 90 SCHRAMM, N. L., McDONALD, M. P., LIMBIRD, L. E., The alpha(2a)-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety. *J. Neurosci.* **2001**, 21, 4875–4882.
 - 91 SALLINEN, J., HAAPALINNA, A., MACDONALD, E., VIITAMAA, T., LAHDESMÄKI, J., RYBNIKOVA, E., et al., Genetic alteration of the alpha2-adrenoceptor subtype c in mice affects the development of behavioral despair and stress-induced increases in plasma corticosterone levels. *Mol. Psychiatry* **1999**, 4, 443–452.
 - 92 HALLER, J., BAKOS, N., RODRIGUIZ, R. M., CARON, M. G., WETSEL, W. C., LIPOSITS, Z., Behavioral responses to social stress in noradrenaline transporter knockout mice: effects on social behavior and depression. *Brain Res. Bull.* **2002**, 58, 279–284.
 - 93 EVRARD, A., MALAGIE, I., LAPORTE, A. M., BONI, C., HANOUN, N., TRILLAT, A. C., et al., Altered regulation of the 5-HT system in the brain of MAO-A knock-out mice. *Eur. J. Neurosci.* **2002**, 15, 841–851.
 - 94 CASES, O., SEIF, I., GRIMSBY, J., GASPAR, P., CHEN, K., POURNIN, S., et al., Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. *Science* **1995**, 268, 1763–1766.
 - 95 GRIMSBY, J., TOTTH, M., CHEN, K., KUMAZAWA, T., KLAIDMAN, L., ADAMS, J. D., et al., Increased stress response and beta-phenylethylamine in MAOB-deficient mice. *Nature Genet.* **1997**, 17, 206–210.
 - 96 FILLIOL, D., GHOZLAND, S., CHLUBA, J., MARTIN, M., MATTHES, H. W., SIMONIN, F., et al., Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. *Nature Genet.* **2000**, 25, 195–200.
 - 97 STORK, O., JI, F. Y., KANEKO, K., STORK, S., YOSHINOBU, Y., MORIYA, T., et al., Postnatal development of a GABA deficit and disturbance of neural functions in mice lacking GAD65. *Brain Res.* **2000**, 865, 45–58.
 - 98 SCHULER, V., LUSCHER, C., BLANCHET, C., KLIX, N., SANSIG, G., KLEBS, K., et al., Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA(B) responses in mice lacking GABA(B(1)). *Neuron* **2001**, 31, 47–58.

- 99 MIYAMOTO, Y., YAMADA, K., NODA, Y., MORI, H., MISHINA, M., NABESHIMA, T., Lower sensitivity to stress and altered monoaminergic neuronal function in mice lacking the NMDA receptor epsilon 4 subunit. *J. Neurosci.* **2002**, *22*, 2335–2342.
- 100 CRYAN, J. F., KELLY, P. H., NEIJT, H. C., SANSIG, G., FLOR, P. J., VAN DER PUTTEN, H., Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. *Eur. J. Neurosci.* **2003**, *17*, 2409–2417.
- 101 RUPNIAK, N. M., CARLSON, E. J., WEBB, J. K., HARRISON, T., PORSOLT, R. D., ROUX, S., et al., Comparison of the phenotype of NK1R^{-/-} mice with pharmacological blockade of the substance P (NK1) receptor in assays for antidepressant and anxiolytic drugs. *Behav. Pharmacol.* **2001**, *12*, 497–508.
- 102 SANTARELLI, L., GOBBI, G., BLIER, P., HEN, R., Behavioral and physiologic effects of genetic or pharmacologic inactivation of the substance P receptor (NK1). *J. Clin. Psychiatry* **2002**, *63* (Suppl. 11), 11–17.
- 103 FROGER, N., GARDIER, A. M., MORATALLA, R., ALBERTI, I., LENA, I., BONI, C., et al., 5-hydroxytryptamine (5-HT)_{1A} auto-receptor adaptive changes in substance P (neurokinin 1) receptor knock-out mice mimic antidepressant-induced desensitization. *J. Neurosci.* **2001**, *21*, 8188–8197.
- 104 BILKEI-GORZO, A., RACZ, I., MICHEL, K., ZIMMER, A., Diminished anxiety- and depression-related behaviors in mice with selective deletion of the Tac1 gene. *J. Neurosci.* **2002**, *22*, 10046–10052.
- 105 MONTKOWSKI, A., BARDEN, N., WOTJAK, C., STEC, I., GANSTER, J., MEANEY, M., et al., Long-term antidepressant treatment reduces behavioural deficits in transgenic mice with impaired glucocorticoid receptor function. *J. Neuroendocrinol.* **1995**, *7*, 841–845.
- 106 GROENINK, L., DIRKS, A., VERDOUW, P. M., SCHIPHOLT, M., VEENING, J. G., VAN DER GUGTEN, J., et al., HPA axis dysregulation in mice overexpressing corticotropin releasing hormone. *Biol. Psychiatry* **2002**, *51*, 875–881.
- 107 VAN GALEN, M. M., STENZEL-POORE, M. P., HOLSBOER, F., STECKLER, T., Effects of transgenic overproduction of CRH on anxiety-like behaviour. *Eur. J. Neurosci.* **2002**, *15*, 2007–2015.
- 108 BALE, T. L., VALE, W. W., Increased depression-like behaviors in corticotropin-releasing factor receptor-2-deficient mice: sexually dichotomous responses. *J. Neurosci.* **2003**, *23*, 5295–5301.
- 109 HOLMES, A., YANG, R. J., CRAWLEY, J. N., Evaluation of an anxiety-related phenotype in galanin overexpressing transgenic mice. *J. Mol. Neurosci.* **2002**, *18*, 151–165.
- 110 YAMADA, K., IIDA, R., MIYAMOTO, Y., SAITO, K., SEKIKAWA, K., SEISHIMA, M., et al., Neurobehavioral alterations in mice with a targeted deletion of the tumor necrosis factor-alpha gene: implications for emotional behavior. *J. Neuroimmunol.* **2000**, *111*, 131–138.
- 111 CALAPAI, G., CRUPI, A., FIRENZUOLI, F., INFERRERA, G., CILIBERTO, G., PARISI, A., et al., Interleukin-6 involvement in antidepressant action of Hypericum perforatum. *Pharmacopsychiatry* **2001**, *34* (Suppl. 1), S8–S10.
- 112 SVENNINGSSON, P., TZAVARA, E. T., WITKIN, J. M., FIENBERG, A. A., NOMIKOS, G. G., GREENGARD, P., Involvement of striatal and extrastriatal DARPP-32 in biochemical and behavioral effects of fluoxetine (Prozac). *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 3182–3187.
- 113 ZHANG, H. T., HUANG, Y., JIN, S. L., FRITH, S. A., SUVARNA, N., CONTI, M., et al., Antidepressant-like profile and reduced sensitivity to rolipram in mice deficient in the PDE4D phosphodiesterase enzyme. *Neuropsychopharmacology* **2002**, *27*, 587–595.
- 114 CAO, B. J., LI, Y., Reduced anxiety- and depression-like behaviors in Emx1 homozygous mutant mice. *Brain Res.* **2002**, *937*, 32–40.
- 115 SAARELAINE, T., HENDOLIN, P., LUCAS, G., KOPONEN, E., SAIRANEN, M., MACDONALD, E., et al., Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.* **2003**, *23*, 349–357.
- 116 RAHMAN, Z., SCHWARZ, J., GOLD, S. J., ZACHARIOU, V., WEIN, M. N., CHOI, K. H., et al., RGS9 modulates dopamine

- signaling in the basal ganglia. *Neuron* **2003**, *38*, 941–952.
- 117 EL YACOUBI, M., LEDENT, C., PARMENTIER, M., COSTENTIN, J., VAUGEIS, J. M., Adenosine A2A receptor knockout mice are partially protected against drug-induced catalepsy. *Neuroreport* **2001**, *12*, 983–986.
 - 118 DRAGO, J., MCCOLL, C. D., HORNE, M. K., FINKELSTEIN, D. I., ROSS, S. A., Neuronal nicotinic receptors: insights gained from gene knockout and knockin mutant mice. *Cell Mol. Life Sci.* **2003**, *60*, 1267–1280.
 - 119 MARTIN, M., LEDENT, C., PARMENTIER, M., MALDONADO, R., VALVERDE, O., Involvement of CB1 cannabinoid receptors in emotional behaviour. *Psychopharmacology (Berl.)* **2002**, *159*, 379–387.
 - 120 GAVIOLI, E. C., MARZOLA, G., GUERRINI, R., BERTORELLI, R., ZUCCHINI, S., DE LIMA, T. C., et al., Blockade of nociceptin/orphanin FQ-NOP receptor signalling produces antidepressant-like effects: pharmacological and genetic evidences from the mouse forced swimming test. *Eur. J. Neurosci.* **2003**, *17*, 1987–1990.
 - 121 TSCHENETT, A., SINGEWALD, N., CARLI, M., BALDUCCI, C., SALCHNER, P., VEZZANI, A., et al., Reduced anxiety and improved stress coping ability in mice lacking NPY-Y2 receptors. *Eur. J. Neurosci.* **2003**, *18*, 143–148.
 - 122 HOLMES, A., HOLLON, T. R., GLEASON, T. C., LIU, Z., DREILING, J., SIBLEY, D. R., et al., Behavioral characterization of dopamine D5 receptor null mutant mice. *Behav. Neurosci.* **2001**, *115*, 1129–1144.
 - 123 OKUYAMA, S., SAKAGAWA, T., SUGIYAMA, F., FUKAMIZU, A., MURAKAMI, K., Reduction of depressive-like behavior in mice lacking angiotensinogen. *Neurosci. Lett.* **1999**, *261*, 167–170.
 - 124 STORK, O., WELZL, H., WOLFER, D., SCHUSTER, T., MANTEI, N., STORK, S., et al., Recovery of emotional behaviour in neural cell adhesion molecule (NCAM) null mutant mice through transgenic expression of NCAM180. *Eur. J. Neurosci.* **2000**, *12*, 3291–3306.
 - 125 CHEETA, S., RUIGT, G., VAN PROOSDIJ, J., WILLNER, P., Changes in sleep architecture following chronic mild stress. *Biol. Psychiatry* **1997**, *41*, 419–427.
 - 126 NONOGAKI, K., ABDALLAH, L., GOULDING, E. H., BONASERA, S. J., TECOTT, L. H., Hyperactivity and reduced energy cost of physical activity in serotonin 5-HT(2C) receptor mutant mice. *Diabetes* **2003**, *52*, 315–320.
 - 127 BALLARD, T. M., PAULY-EVERS, M., HIGGINS, G. A., OUAGAZZAL, A. M., MUTEL, V., BORRONI, E., et al., Severe impairment of NMDA receptor function in mice carrying targeted point mutations in the glycine binding site results in drug-resistant nonhabituating hyperactivity. *J. Neurosci.* **2002**, *22*, 6713–6723.
 - 128 HALLER, J., BAKOS, N., Stress-induced social avoidance: a new model of stress-induced anxiety? *Physiol. Behav.* **2002**, *77*, 327–332.
 - 129 DIXON, A. K., HUBER, C., LOWE, D. A., Clozapine promotes approach-oriented behavior in male mice. *J. Clin. Psychiatry* **1994**, *55* (Suppl. B), 4–7.
 - 130 DUNN, A. L., CRNIC, L. S., Repeated injections of interferon-alpha A/D in Balb/c mice: behavioral effects. *Brain Behav. Immun.* **1993**, *7*, 104–111.
 - 131 GRIPPO, A. J., BELTZ, T. G., JOHNSON, A. K., Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiol. Behav.* **2003**, *78*, 703–710.
 - 132 VAN GAALLEN, M. M., STENZEL-POORE, M., HOLSBOER, F., STECKLER, T., Reduced attention in mice overproducing corticotropin-releasing hormone. *Behav. Brain Res.* **2003**, *142*, 69–79.
 - 133 CONTARINO, A., DELLU, F., KOOB, G. F., SMITH, G. W., LEE, K. F., VALE, W., et al., Reduced anxiety-like and cognitive performance in mice lacking the corticotropin-releasing factor receptor 1. *Brain Res.* **1999**, *835*, 1–9.
 - 134 ESTAPE, N., STECKLER, T., Cholinergic blockade impairs performance in operant DNMTF in two inbred strains of mice. *Pharmacol. Biochem. Behav.* **2002**, *72*, 319–334.
 - 135 MACCARI, S., DARNAUDERY, M., MORLEY-FLETCHER, S., ZUENA, A. R., CINQUE, C., VAN REETH, O., Prenatal stress and long-term consequences: implications of glucocorticoid hormones. *Neurosci. Biobehav. Rev.* **2003**, *27*, 119–127.

- 136 SANTARELLI, L., SAXE, M., GROSS, C., SURGET, A., BATTAGLIA, F., DULAWA, S., et al., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **2003**, 301, 805–809.
- 137 MITCHELL, P. J., REDFERN, P. H., Potentiation of the time-dependent, antidepressant-induced changes in the agonistic behaviour of resident rats by the 5-HT1A receptor antagonist, WAY-100635. *Behav. Pharmacol.* **1997**, 8, 585–606.
- 138 DUNN, A. J., SWIERGIEL, A. H., The reductions in sweetened milk intake induced by interleukin-1 and endotoxin are not prevented by chronic antidepressant treatment. *Neuroimmunomodulation* **2001**, 9, 163–169.

28

Loss and Deprivation: From Animal Models to Clinical Presentation

Kristin M. Penza, Christine Heim and Charles B. Nemeroff

Abstract

Loss early in life has long been known to be a risk factor for major depression and several other psychiatric disorders in adulthood. The long-lasting effects of early parental loss are likely mediated by the effects of early-life adversity on neural systems involved in the mediation of stress and emotion. Preclinical studies in rodents and non-human primates demonstrate that loss early in life produces marked behavioral, physiological, and neurobiological changes that persist into adulthood. Many of these effects correspond to classical features of depression. Recent clinical studies have shown that early adversity in humans is associated with similar neurobiological changes. This chapter describes and compares the behavioral and biological findings in both animal paradigms and human research on early loss and deprivation. Potential mediators of the relationship between early loss and depression, as well as treatment implications, are discussed.

28.1**Introduction**

Loss early in life has long been known to precipitate major depression. Freud (1957) and Bowlby (1973) described the potential impact of loss of a loved one on development of psychopathology. Bowlby (1980) particularly discussed the relevance of early parental loss on the development of later pathological behavior and noted similar behavioral responses among children and laboratory animals. Recent decades of animal research on rodents and non-human primates have demonstrated behavioral, physiological, and neurobiological changes in response to loss early in life. Many of these effects correspond to those found among depressed patients exposed to parental loss in childhood. Because behavioral and biological effects of early loss likely produce changes in multiple regulatory systems (Hofer, 1996), careful scrutiny of the effects of early life stress should allow for the discovery of

several affected regulatory systems. Animal models of loss are particularly useful because they provide for experimental control of loss features and a correspondingly close observation of the neurobiological and behavioral sequelae that are obviously unavailable in clinical research. Perhaps the most prominent animal model of loss relevant to major depressive disorder (MDD) has been maternal separation (MS) in postnatal laboratory animals. This chapter will focus on and compare and contrast the behavioral and biological findings of both animal model paradigms and human research on early loss and deprivation as well as discuss potential mediators in the relationship of early loss to depression, and treatment implications.

28.2

Animal Models of Loss and Deprivation: Maternal Separation

Overwhelming evidence from animal studies supports the idea that early loss results in long-term effects on behavior and neurobiology, particularly the development of hypersensitivity to stressors encountered later in life (Hofer, 1987; Plotsky and Meaney, 1993). Animal models of loss and deprivation are predominantly derived from a paradigm in which the postnatal infant animal is separated from the dam for periods of 3 to 6 h daily, the MS paradigm. Behavioral and neurobiological changes due to early loss, such as MS, are likely mediated by alterations in multiple regulatory systems (Hofer, 1996). Animal models in research are particularly useful for elucidating which physiological systems are altered and they have had particular utility in psychiatry and behavioral sciences (Willner, 1991).

28.2.1

Behavioral Changes

Some of the earliest observations of the effects of MS on non-human primates include changed vocalization patterns, which occur immediately following separations (Levine, Haltmeyer, Karas, and Denenberg, 1967; Reite, Short, Seiler, and Pauley, 1981). Similar MS reactions have been observed in Bonnet and pigtail monkey infants. The infants go through a two-stage “agitation-depression” behavioral reaction with accompanying physiological changes. After the mother is removed from the social group, increased activity and coo vocalizations are observed immediately. Delayed changes on days 2 through 4 include decreases in time of play; and, particularly for pigtail monkey infants, evidence of a depressed phase occurs with an increase in slouch behavior and prominent postural collapse (Reite, Kaemingk, and Boccia, 1989; Reite et al., 1981). Social deprivation is perhaps the most extreme form of MS, involving deprivation of any maternal and/or peer contact, precluding the formation of attachment relationships (for a review, see Gilmer and McKinney, 2003). Long-term behavioral effects of social deprivation include self-injurious behaviors, repetitive idiosyncratic behavior, increased time huddling, inappropriate aggressive behaviors, psychomotor retardation, and inappropriate sexual and parenting behaviors (Gilmer and McKinney, 2003; McKinney, 1974).

These behaviors are similar to those found in children separated from a parent, usually a mother, at a young age. Specifically, after separation from parents, temporarily (2–3 weeks) nursery-reared children, will immediately protest through screaming or crying, temper tantrums, and uncooperative behavior. After several days, they may demonstrate hostility, biting another child or favorite object from home; eventually they may become detached and withdrawn, seemingly in a state of despair (Bowlby, 1973). In addition to provoking agitated and depressive behaviors, MS also affects cognitive function. Nursery-reared monkeys display cognitive difficulties in acquiring the delayed non-matching to sample task, as well as impaired object reversal learning, compared to normal controls (Sanchez, Hearn, Do, Rilling, and Herndon, 1998). These cognitive deficits are also correlated with decreases in corpus callosum size (Sanchez et al., 1998). Socially deprived monkeys exhibit increased errors on odd object discrimination and extinction deficits including increased perseverance on non-reward tasks and inability to ignore irrelevant stimuli (Beauchamp, Gluck, Fouty, and Lewis, 1991; Gilmer and McKinney, 2003; Gluck and Pearce, 1977).

In rat studies, a single episode of MS produces sleep disturbances, increased activity and stress in rat pups as young as 2 weeks old (Hofer, 1987). Behavioral changes associated with MS also include slowed learning and less stable memory (Novakova, Koldovsky, Faltin, Hahn, and Flandera, 1962). Development of anhedonia, the inability to experience pleasure in activities that were formerly enjoyable, has also been observed among MS rats. Anhedonia is one of the cardinal features of MDD, perhaps the most pathognomonic sign of the disorder. Anhedonia has been described in MS rats, as measured by a reduction in sucrose (or saccharine) solution ingestion. MS rats (separated for 180 min daily on postnatal days 2 through 14) have been noted to drink 35% less sucrose solution, compared to handled rats and MS rats separated for briefer periods (two groups: brief handling twice weekly and 15 min daily; Ladd, Huot, Thrivikraman, Nemeroff, Meaney, and Potsky, 2000). A similar result was observed in overnight food-deprived rats; the following day the MS rats drank less sweetened solution in a 60-min period (Plotsky and Meaney, 1993). This may demonstrate anhedonia; however, a recent study on non-human primates calls this distinction into question. Paul, English, and Halaris (2000) reported finding that maternally deprived monkeys ingested less sweetened water and consumed more bitter water than controls. The authors suggested that the effect might represent a general attenuated responsiveness to stimuli, rather than a specific reduction in responsiveness to appetitive stimuli properties (Paul et al., 2000). Whether this observation represents a reduction in perceived valence of stimuli in general, or an example of anhedonia, it is clear that MS has altered responsiveness to positive and negative gustatory valence. Future research using other sensory stimuli (e.g. visual) may clarify whether this is anhedonia or attenuated responsiveness due to MS.

Anxiety is often part of the symptom complex of MDD, and anxiety disorders frequently occur in comorbidity with MDD. Among MS laboratory rats, heightened anxiety has been observed in behavioral tests of anxiety such as defensive withdrawal, elevated plus maze, open field exploration, acoustic startle reflex, and novelty induced

suppression of appetitive behavior (for a detailed review of these tests, see Ladd et al., 2000; Ladd, Owens, and Nemeroff, 1996; Plotsky and Meaney, 1993). In the defensive withdrawal test, MS rats demonstrate a greater latency to enter the open field, a greater time in the darkened cylinder, and increased freezing in the open field, compared to briefly handled rats (Caldji, Francis, Sharma, Plotsky, and Meaney, 2000). This suggests that relative to control rats, the MS and socially deprived rats experience more anxiety or fearfulness in novel places. During an elevated plus maze task, MS rats spent less time in open arms than briefly handled rats, also suggesting increased anxiety or fear (Holson, Scallet, Ali, and Turner, 1991; Jones, Robbins, and Marsden, 1989; Ladd et al., 2000; Wright, Upton, and Marsden, 1991). Acoustic startle tests provide evidence of heightened fear among MS rats as they demonstrate an enhanced startle response in a high decibel range (110–120 dB), compared to briefly handled animals (Caldji et al., 2000). Lastly, novelty-induced suppression of appetitive behavior measures behavior upon presentation of food in a novel environment. Among rats that were food-deprived for 24 h and then presented with food, MS rats demonstrated a greater latency to approach and eat the food and spent less time eating than briefly handled rats (Caldji et al., 2000). These tests collectively demonstrate increased anxious and fearful behavior among MS rats, which persists into adulthood. MS stress, experienced during the period of caregiver–offspring interactions, appears to affect later perceptions of threat and behavioral responses to threat (Ladd et al., 2000).

In contrast to the effects of MS, postnatal “handling” (typically involving brief, 15-min maternal separation and handling by technicians during postnatal weeks 2–3) appears to be related to improved stress coping (Hilakivi-Clarke, Turkka, Lister, and Linnoila, 1991; Levine et al., 1967; Meaney et al., 1994). As adults, handled rats demonstrate less fearfulness in novel environments (Meaney et al., 1991). Short MS does not appear to provoke enduring anxious or fearful behaviors, and may be protective against anxiety, for example, by promoting slow wave sleep in adulthood (Kaneko, Riley, and Ehlers, 1994).

Although addictive behavior is not part of the symptom criteria of a MDD episode, comorbid substance and/or alcohol abuse or dependence frequently does occur. The available data suggests that MS in rats also increases addictive behaviors. For example, Matthews, Robbins, Everitt, and Caine (1999) reported finding that among repeated maternally separated rats (6 h per separation on postnatal days 5–20), females increased self-administration of cocaine (at a dose of .03 mg), compared to control rats. Huot, Thrivikraman, Meaney, and Plotsky (2001) reported that MS rats (180-min separations on postnatal days 2–14) drank significantly more of an ethanol–sucrose solution and less of a sweetened solution than non-MS or briefly handled rats. There were also correlations between ethanol consumption, plasma corticosterone concentrations, and behavioral measures of anxiety. Ethanol consumption was positively correlated with the corticosterone response to air-puff startle and negatively correlated with time spent in an open arm of an elevated plus maze (Huot et al., 2001). These recent studies suggest that the regulatory systems affected by MS may include physiological or neurochemical systems involved in addictive behaviors. This area indicates an important example of how animal models

of behavior, in this case loss, can help formulate hypotheses about human research and can facilitate further exploration of those hypotheses.

28.2.2

Biological Changes

Many biological changes have been associated with MS stress in laboratory animals. Basic physiological changes due to MS in monkeys include immediate decreases in overall REM sleep, and delayed changes 2–4 days later including decreased heart rate and body temperature, and increased heart rate responses to novel situations (Champoux, Coe, Schanberg, Kuhn, and Suomi, 1989; Lubach, Kittrell, and Coe, 1992; Reite et al., 1981). Impaired immune functioning has been detected among infant monkeys with social deprivation, including decreases in ratio of helper to suppressor T cells and increases in natural killer cell number and activity (Boccia, Scanlan, Laudenslager, Berger, Hijazi, and Reite, 1997; Coe, Lubach, Ershler, and Klopp, 1989; Lewis, Gluck, Petitto, Hensley, and Ozer, 1999). Interestingly, the detrimental effects of MS on immune functioning appear to be protected by the presence of social support figures during the separation period. Boccia et al. (1997)

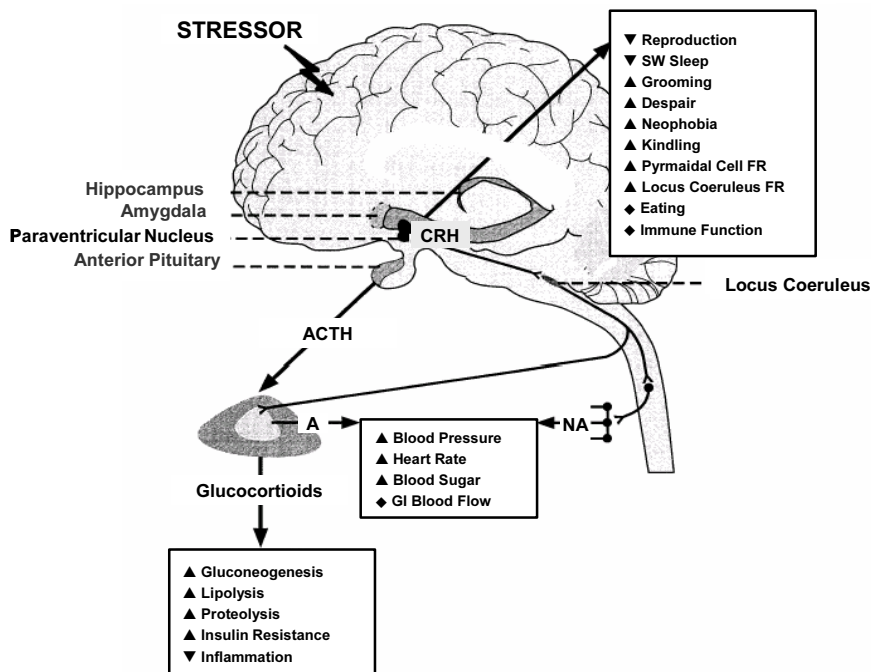


Figure 28.1 The hypothalamic–pituitary–adrenal (HPA) axis and the effects of central corticotropin-releasing factor (CRF). Triangles indicate an increase; inverted triangles, a decrease, and diamonds, bi-directional changes. ACTH, adrenocorticotropin; GI, gastrointestinal; FR, firing rate; SW, slow wave. From Arborelius et al. (1999).

reported that Bonnet macaques with juvenile attachment figures (e.g. friends) were somewhat buffered by not demonstrating impaired lymphocyte activation by mitogens or natural cytotoxicity which was observed among MS monkeys without juvenile attachments (Boccia et al., 1997).

MS affects neurocircuitry of the amygdala and associated limbic areas, well known to be associated with fearful behavior. Fear is at least partly mediated by corticotropin-releasing factor (CRF) projections from the central nucleus of the amygdala to brainstem areas, particularly the locus coeruleus (LC; Gray, 1990; Koegler-Muly, Owens, Ervin, Kilts, and Nemeroff, 1993; Ladd et al., 2000). MS rats exhibited both increased CRF messenger RNA expression and CRF concentrations in the central nucleus of the amygdala, compared to non-MS and briefly handled rats (Plotsky and Mearney, 1993, 1996). Increased CRF peptide concentration has also been found in the LC and paraventricular nucleus (PVN) of MS rats (Plotsky and Meaney, 1996). In addition to affecting CRF neurotransmission, many of the neurobiological effects of MS involve neurocircuitry of other critical components of the hypothalamic–pituitary–adrenal (HPA) axis. CRF and the HPA axis affect a number of other biological (e.g. immunological) and behavioral systems (see Figure 28.1). MS has been associated with long-term alterations in HPA axis functioning.

28.2.2.1 HPA Axis

It is well established that HPA axis responses to stress are altered by MS among laboratory animals (for a detailed review, see Arborelius, Owens, Plotsky, and Nemeroff, 1999; Ladd et al., 2000). In rats, maternal separation paradigms are usually comprised of 3 to 6-h separations per day for 1–3 weeks beginning in the first two weeks of life. Ladd et al. (1996) reported that MS resulted in long-term effects on the development of hypothalamic and extrahypothalamic CRF neural systems and subsequent responses to stress. As adults, MS rats demonstrated increases in basal and stress-induced adrenocorticotrophin hormone (ACTH) concentrations. In addition, MS rats exhibited increases in CRF concentration in the median eminence and reductions in the density of CRF binding sites in the anterior pituitary (Ladd et al., 1996; Plotsky and Meaney, 1993). MS rats also displayed impaired glucocorticoid-mediated negative feedback as observed after administration of the synthetic glucocorticoid dexamethasone (Plotsky and Meaney, 1993), down-regulation of hippocampal glucocorticoid receptors (GR) and upregulation of the mineralocorticoid (MR) system (Ladd, Huot, Thirivikraman, and Plotsky, 1998). CRF mRNA expression is increased in other areas including the parvocellular PVN (pPVN), central nucleus of the amygdala, and bed nucleus of the stria terminalis in MS rats (Plotsky and Mearney, 1993).

Compared to physical stressors, psychological stressors appear to exert a greater impact on neuroendocrine stress responsivity in MS rats. ACTH and corticosterone responses to the air-puff startle, a psychological stressor, are greatly increased in MS rats, compared to non-MS rats, and with their responses to physical stressors (e.g. cold, hemorrhage; Engelmann et al., 1996). Interestingly, brief handling has an opposite effect when compared to MS on HPA axis activity and CRF mRNA expression and CRF content. Adult rats exposed to brief handling in infancy have

lower levels of median eminence CRF and hypothalamic CRF mRNA than controls (Plotsky and Meaney, 1993). HPA axis alterations secondary to MS among non-human primates are similar to those described in rodents exposed to MS. Particularly, dysregulated HPA axis responses to stress and CSF CRF concentrations are elevated among monkeys as a result of MS (Champoux et al., 1989; Clarke, 1993) and adverse early rearing conditions (Coplan et al., 1996, 2001; Matthew et al., 2002). The CRF changes associated with MS, along with corresponding fearful behaviors, can be reversed in rats following administration of the selective serotonin reuptake inhibitor (SSRI) antidepressant paroxetine (Ladd et al., 2000). Paroxetine administration in MS rats also reduces ethanol consumption and eliminates alterations in HPA axis responsiveness (Huot et al., 2001).

28.2.2.2 Neuroanatomical and Neurochemical Changes

Both neuroanatomical and neurochemical changes have been detected among non-human primates reared under social deprivation or MS conditions. Development of specific brain structures and neurotransmitter systems appear to be detrimentally impacted by loss of parental attachment. Neuroanatomical effects of MS on rhesus monkeys include decreased corpus callosum size (mid-sagittal sections), compared to normally reared control monkeys (Sanchez et al., 1998). Changes in the morphology of the basal ganglia and dentate gyrus granule layer of the hippocampus have also been reported among socially-deprived infant monkeys (Martin, Spicer, Lewis, Gluck, and Cork, 1991).

Reported neurochemical effects of MS include those on norepinephrine (NE), dopamine (DA), γ -aminobutyric acid (GABA)/benzodiazepine (BZ), and neuropeptide Y (NPY) systems. Non-human primates exposed to social deprivation as infants exhibit reduced cerebrospinal fluid (CSF) NE concentrations, differential responses to yohimbine, hypersensitivity to D-amphetamine, and DA receptor supersensitivity (Coplan, Rosenblum, Friedman, Bassoff, and Gorman, 1992; Kraemer, Ebert, Lake, and McKinney, 1984; Kraemer, Ebert, Schmict, and McKinney, 1989; Lewis, Gluck, Beauchamp, Keresztury, and Mailman, 1990). Research on rodents has also revealed several changes in NE, GABA, NPY, and BZ receptors. Liu, Caldji, Sharma, Plotsky, and Meaney (2000) reported that longer-term MS rats (180-min separations) displayed heightened NE at baseline and in response to restraint, compared to briefly handled (15-min separations) and non-handled animals. Restraint responses in NE corresponded to increases in ACTH among the MS rats, suggesting that NE levels may be at least partly responsible for activating the HPA axis during restraint stress (Liu et al., 2000). GABAergic systems may contribute to the behavioral and neuroendocrine effects of MS, as GABA systems have been shown to mediate fearful behaviors in novel situations (Bodnoff, Suranyi-Cadotte, Quirion, and Meaney, 1989; File, 1995; Wilson, 1996) and to mediate stress responses to psychosocial, not physical, stressors (Malizia, Coupland, and Nutt, 1995; Bhatnagar, Shank, and Meaney, 1995). Benzodiazepines act at least in part by inhibition of CRF circuits in the amygdala (Owens, Vargas, Knight, and Nemeroff, 1991; Ladd et al., 2000; Skelton, Nemeroff, Knight, and Owens, 2000). Ladd et al. (2000) reported that expression of the $\gamma 2$ subunit of GABA_A receptors

was reduced in MS versus briefly handled rats, important because this particular receptor subunit is involved in BZ binding activity. Both MS rats and rat genetic strains that model depressive behaviors exhibit decreased hippocampal NPY concentrations. Among MS rats, dorsal hippocampal NPY concentrations are lower in female compared to male rats, and are increased in the hypothalamus of both sexes (Jimnez-Vasquez, Math, Thomas, Riley, and Ehlers, 2001). NPY levels are also decreased in the frontal cortex of male rats exposed to MS. Mathé (1999) hypothesizes that anhedonia is a consequence of decreased NPY in the frontal cortex because administration of drugs of abuse and increases in alcohol preference are both related to decreases in NPY concentrations in the frontal cortex (Ehlers et al., 1998; Wahlestedt and Heilig, 1995). Furthermore, electroconvulsive therapy (ECT) ameliorates anhedonia and this effect may be due to increases in frontal cortex NPY after ECT treatment (Mathé, 1999).

28.3

Human Experiences of Loss: Early Parental Death and Early Parental Separation

A majority of the literature on the effects of early loss as a risk factor for depression focuses on a human parallel of laboratory animal MS research, early loss of a parent. Specifically, early parental death and separation have been most intensively studied. However, reported findings have been inconsistent. One of the most important reasons for discrepancies in the literature stems from the collapsing of early parental death and early parental separation into one category (Tennant, 1988). In the following sections, the extant literature on the effects of parental death and separation on later development of depression is considered, followed by a discussion of potential mediators of the effect of parental loss on adult depression.

28.3.1

Early Parental Death

The immediate effects of early parental death (EPD) on children can be devastating, predicting high levels of psychopathology, particular MDD (Elizur and Kaffman, 1983). However, reported findings on the long-term effects of EPD have been mixed, with some studies reporting an association of EPD with later depression (Mireault and Bond, 1992; Pfohl, Stangl, and Tsuang, 1983) and other studies reporting finding no such association (Canetti et al., 2000; Hallstrom, 1987; Kendler Neale, Kessler, Heath, and Eaves, 1992; Oakley-Browne, Joyce, Wells, Bushnell, and Hornblow, 1995a; Roy, 1983; see Table 28.1).

Many studies have failed to detect a direct effect of EPD on later development of adulthood depression for EPD occurring before the ages of 15 to 17 years (Bifulco, Brown, and Harris, 1987; Birtchnell, 1980; Favarelli, Saccgetti, Ambonetti, Conte, Pallanti, and Vita, 1986; Hallstrom, 1987; Perris, Holmgren, Von Knorring, and Perris, 1986; Ragan and McGlashan, 1986; Roy, 1983; Tennant, Bebbington, and Hurry, 1980). Age of onset of adult depression is also unrelated to EPD (Perris

Table 28.1 Summary of study effects of early parental death and early parental separation

	<i>Age range</i>	<i>Sample</i>	<i>Effect</i>
Death			
Pfohl et al. (1983)	< 10 years	Depression, schizophrenia bipolar disorder, <i>N</i> = 347	↑
Kendler et al. (1999)	< 17 years	Twin pairs, <i>N</i> = 7188	↑
Agid et al. (1999)	< 17 years	MDD patients, controls, <i>N</i> = 306	↑
Hallstrom (1987)	< 17 years	Community survey, <i>N</i> = 460	↓
Canetti et al. (2000)	< 16 years	Israeli adolescents, <i>N</i> = 844	↓
Kendler et al. (1992)	< 17 years	Female twins, <i>N</i> = 1018 pairs	↓
Roy (1983)	< 17 years	Depressed patients, controls, <i>N</i> = 300	↓
Separation			
Hallstrom (1987)	< 17 years	Community survey, <i>N</i> = 460	↑
Kendler et al. (1992)	< 17 years	Female twins, <i>N</i> = 1018 pairs	↑
Canetti et al. (2000)	< 16 years	Israeli adolescents, <i>N</i> = 844	↑
Kendler et al. (2002a)	< 17 years	Twin pairs, <i>N</i> = 7188	↑
Oakley-Browne et al. (1995a)	< 15 years	Women with a history of MDD, never-depressed women, <i>N</i> = 146	↑
Roy (1983)	< 17 years	Depressed patients, controls, <i>N</i> = 300	↓

Note:

↑ = increased proportion of EP loss among participants with MDD;

↓ = no effect of increased EP loss among participants with MDD.

et al., 1986). Lastly, characteristics of the parental death are also not related to adult depression, including sex of the deceased parent, age of subject at parental death, how the parent died, forewarning of the death, subject's sex, interaction of subject sex with parent sex, participation in mourning activities, and witnessing the death (Luecken, 2000; Roy, 1983). EPD occurs less often in our society than early parental separation (EPS), such as divorce, which is more common. However, a direct comparison of subjects with and without EPD would afford more power to detect an effect.

Using this approach, Luecken (2000) compared 30 college students who had experienced EPD before age 16 years to 31 control participants. She discovered an interaction of loss by EPD with family relationships in predicting depression scores, as measured by the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, and Erbaugh, 1961). There was no main effect of EPD, only an interaction effect such that the effect of EPD was significant specifically among those who experienced poor quality family relationships characterized by low levels of affection, low levels of family support, and high levels of family conflict. Family relationship charac-

teristics that were protective against depression following EPD included supportiveness among family members, open expression of feelings, and low levels of conflict and anger. An interaction was also discovered predicting social support; those with EPD and low-levels of family relationships experienced less adulthood social support (Luecken, 2000). These findings suggest that the family environment, potentially both before and after a parental death, may constitute an essential variable in predicting a mourning child's immediate and long-term risk of developing psychopathology. Indeed, previous authors contended that examinations of early parental loss without considering the child's relationship with the surviving parent are missing the most critical variable (Bowlby, 1980; Tennant, 1988).

Using a similar method to Luecken (2000), Canetti et al. (2000) compared subjects with EPD and control subjects from intact families. The authors reported finding no significant differences in MDD and other psychological disorders, well-being, social support, or parental bonding when comparing those with and without EPD. However, effects of EP separation were significant in predicting depressive symptoms.

28.3.2

Early Parental Separation

Parental separation occurs far more frequently than parental death, as divorce is fairly common in our society (Canetti et al., 2000). In contrast to the generally negative findings on the direct effects of EPD, findings reported in the early parent separation (EPS) literature indicate a more clear and definitive link with later depression in adulthood (see Table 28.1). In addition, mediation effects emerge comparable to those detected in EPD research. Specifically, the family environment after the loss has been implicated. However, many more definitional and methodological inconsistencies exist within EPS research. For example, EPS studies can

Table 28.2 Summary of studies finding mediating factors influencing the effect of early parental loss on adult depression

<i>Study</i>	<i>Loss</i>	<i>Age range</i>	<i>Mediator</i>
Mireault and Bond (1992)	Death	< 17 years	Perceived vulnerability to future loss
Luecken (2000)	Death	< 16 years	Quality of family relationships
Saler and Skolnick (1992)	Death	< 18 years	Empathic, warm, and autonomy-promoting surviving parent
Bifulco et al. (1992)	Death or separation	< 17 years	Lack of maternal care prior to loss (aberrant separation or maternal death before the age of 6 years); lack of maternal care after loss
Oakley-Browne et al. (1995b)	Death or separation	< 15 years	Maternal care

differ with regard to type of separation (divorce, drafting to war duty, childhood institutionalism), permanence of separation (permanent, temporary), duration of separation (1 month to 5 years), and gender of parental separation (maternal or paternal). Also, there is often a lack of representativeness of patient groups via socio-economic status (SES), ethnicity, race, and the decade of birth (Birtchnell, 1972; Furukawa, Ogura, Hirai, Fujihara, Kitamura, and Takahashi, 1999). However, despite these inconsistencies, the concatenation of findings on this area point to a clear association of EPS with increased vulnerability to adult depression.

Some studies collapse EPD and EPS into the same “early parental loss” variable. Many of these studies report clear associations of EP loss with adulthood depression. For example, in a survey of more than 8000 respondents, Kessler, Davis, and Kendler (1997) found early parental loss events (death or separation) to be associated with an increase in mood disorders (more than anxiety disorders), even after controlling for comorbidities and other adversities (e.g. parental psychopathology, interpersonal traumas such as rape, and natural disasters). No sex differences were found in this association. However, these findings may be predominantly due to the large effect of EPS, as compared to EPD. Oakley-Browne et al. (1995a) reported that in a community survey of adult women, aggregated parental loss (due to death, separation, or divorce) was a weak predictor of lifetime MDD. Kendler et al. (2002a) studied more than 7000 twin pairs and found that the time for increased risk of MDD to decay to baseline was far greater for EPS (29–35 years), as compared to EPD (12–15 years).

Kendler et al. (1992) reported that EPS, not EPD, before the age of 17 years increased risk for MDD, generalized anxiety disorder (GAD), panic disorder (PD), and phobias. However, they also reported that familial parental bonding and social support each tempered the effect of EPS on psychiatric symptoms. When controlling for either parental bonding or family social support, the previously significant differences in psychiatric symptoms between adolescents with EPS and those from intact families disappeared. Canetti et al. (2000) reported that compared to controls, Israeli adolescents who experienced separation (any 5-year period before the age of 16 years) from one or both parents demonstrated higher prevalence rates of MDD and other psychiatric symptoms. In addition to increased symptoms, participants reporting previous EPS also reported less life satisfaction, less family support, and feeling less cared for and more controlled by parents (Canetti et al., 2000). Even among healthy controls without MDD, EP loss, including separation, is associated with other characteristics that likely constitute vulnerabilities to both psychiatric and physical illness including lower incomes, more physical illnesses, more lifetime cigarette smoking, more frequent divorce, and a greater likelihood of living alone (Agid et al., 1999).

28.3.3

Mediators of the Effects of Early Parental Loss on Adult Depression

As noted above, many authors have described the significant impact of family quality factors in mediating the effects of EPS on adulthood depression (see Table 28.2).

In particular, the quality of parental care subsequent to EPS appears to affect susceptibility to later psychopathology, especially MDD (Bifulco et al., 1987, 1992; Breier, Kelsoe, Kirwin, Beller, Wolkowitz, and Pickar, 1988; Harris, Brown, and Bifulco, 1986). Supportive family relationships and positive parental qualities in the remaining parent such as empathy, warmth, and promoting autonomy in the child are protective against later reporting of depressive symptoms (Luecken, 2000; Saler and Skolnick, 1992).

Kendler, Gardner, and Prescott (2002b) reported that early parental loss (death or separation before the age of 17 years) among 1900 twins uniquely predicted only low levels of education. However, path analysis revealed an increased susceptibility to adult MDD associated with childhood adversities including disturbed family environment, childhood sexual abuse, and early parental loss (Kendler et al., 2002b). Oakley-Browne, Joyce, Wells, Bushnell, and Hornblow (1995b) studied depressed and never-depressed women and measured varied childhood adversities (before the age of 15 years) including permanent parental separation (divorce, death), temporary parental separation (1 month or more), quality of parental relationships, and leaving school. After controlling for other variables, only low maternal care predicted recent and lifetime MDD ($OR = 4.1$ for MDD; Oakley-Browne et al., 1995b). This suggests that the effects of both temporary and permanent separations are influenced by parental, especially maternal, relationships after the loss. Breier et al. (1988) also reported evidence of a mediator role for quality of care after early parental loss. After failing to find any differences in EPS or EPD among those with a history of adult psychopathology and healthy controls, Breier et al. (1988) discovered that “Home Life and Personal Adaptation” (HAPA; Breier et al., 1988) scores predicted adult psychopathology in 80% of participants. The group with adult psychopathology reported HAPA scores indicating detrimental home environments, particularly non-supportive relationships with the remaining parent in which the subject felt burdened by the parent’s need for emotional support. The group without psychopathology reported protective parent qualities subsequent to EPS including having at least one caretaker who met their childhood needs either “very” or “extremely” satisfactorily (Breier et al., 1988).

Childhood adversities including early parental loss are also associated with later hardships including low educational attainment, increased lifetime traumas, and low social support for recent adversities (Kendler et al., 2002b). Indeed several stressful adult events such as premarital pregnancy, marital separation or divorce, and negative self-evaluation have all been suggested to be linked to lack of quality parental care and affect later incidence of adult depression (Bifulco et al., 1987). Poor parental care in childhood is related to later lack of intimacy in marriage in adulthood for women (Harris et al., 1986), and those with poor parenting histories experience more potentially stressful life events overall (Bifulco et al., 1987). Adult losses of ideals and significant relationships might evoke the negative memories of childhood loss and poor care, provoking an episode of MDD (Bowlby, 1980, 1988).

28.3.4

Clinical Psychobiology of Early Loss

Neuroendocrine changes closely approximating those found in MS paradigms in laboratory animals have been observed among adults with a history of early parental loss and other childhood adversities. For example, Gunnar, Morison, Chisholm, and Schuder (2001) reported markedly increased daytime cortisol levels among Romanian orphans (orphaned for 8 months or more in the first year of life) as compared to early-adopted orphans (adopted after less than 4 months as orphans) and non-orphaned Canadian children. The Romanian orphans had, however, been exposed to gross deprivation of basic needs (Gunnar et al., 2001), likely experiencing less than adequate parental care, including meeting emotional and physical needs, as well as nutritional deficits. This study probably most closely parallels many of the MS paradigms in animals, but, these naturalistic types of studies are obviously rare for ethical reasons.

Most of the data on long-term neuroendocrine stress system changes secondary to early adverse experience comes from studies on adults with childhood physical and sexual abuse experiences. Heim et al. (2000) observed markedly increased cortisol responses to a laboratory stressor among depressed women who retrospectively reported childhood physical and sexual abuse histories. Moreover, heightened ACTH responses to stress were noted among women with abuse histories, with or without syndromal major depression (Heim et al., 2000). In a separate study, Heim, Newport, Bonsall, Miller, and Nemeroff (2001) examined ACTH responses to hormonal challenge tests. In response to administered CRF, depressed women, with or without childhood abuse, exhibited blunted ACTH responses, abused women without MDD exhibited elevated ACTH responses to CRF (Heim et al., 2001). These differential responses have been reported among previously published studies on patients with depression and PTSD. Blunted ACTH responses to CRF have been reported among patients with melancholic depression and combat-related PTSD (Holsboer, Gerken, Stalla, and Mueller, 1985; Maes, Claes, Vandewouder, and Schotte, 1992; Smith et al., 1989). However, elevated ACTH response to CRF challenge tests have been reported among patients with PTSD and with mixed types of childhood and adulthood traumas (Rasmusson et al., 2001). A possible explanation for this discrepancy, in addition to differences in the characteristics of the study groups, is that an initial neuroendocrine stress response sensitization, due to early life stress, may evolve into blunted pituitary responsiveness with ongoing stress (Heim et al., 2001). Blunted ACTH responsiveness is likely due to CRF receptor down-regulation secondary to hypersecretion of CRF associated with exposure to chronic stress (Heim et al., 2001). Newport et al. (2003) reported evidence to partly support this contention. Among women with and without MDD and/or a history of childhood abuse, central CRF hypersecretion was associated with blunted ACTH responses (Newport et al., 2003). Newport and colleagues (2004) recently reported an interaction effect of early life stress and psychiatric status on responses to a low-dose dexamethasone suppression test (DST). Women with histories of childhood abuse and either a diagnosis of MDD or PTSD demonstrated

greater cortisol suppression compared to abused women without current psychopathology and women with no abuse histories. Also, women with MDD or PTSD and childhood abuse exhibited greater corticotropin suppression, compared to healthy controls and non-depressed, abused women (Newport, Heim, Bonsall, Miller, and Nemeroff, 2004). This evidence suggests that the enhanced glucocorticoid feedback is related to the combined state of psychiatric illness with early life trauma history (Newport et al., 2004). HPA alterations due to early life stress may be further impaired by severe recent stress in adulthood. Adulthood traumas are associated with elevated ACTH responses to psychosocial stress, after accounting for the variance due to early life stress (Heim, Newport, Wagner, Wilcox, Miller, and Nemeroff, 2002). Concordant with the aforementioned findings, elevated cerebrospinal fluid CRF concentrations were recently measured in adults reporting high levels of preschool stress (Carpenter et al 2003).

Neuroanatomical changes have been reported as a consequence of childhood abuse experiences. Reduced corpus callosum and under-development of the left neocortex, hippocampus, and amygdala have been reported in children with a history of physical or sexual abuse (Teicher, Ito, Glod, Andersen, Dumont, and Ackerman, 1997; Teicher, Andersen, Polcari, Anderson, Navalta, and Kim, 2003). Among adults with MDD in the Heim et al. (2000) study, those reporting childhood physical and/or sexual abuse histories had an 18% smaller mean left hippocampal volume than non-abused depressed subjects and a 15% smaller mean left hippocampal volume than healthy controls (Vythilingam et al., 2002). The effect was not observed in depressed women without a history of childhood abuse.

28.4

Animal Models and Clinical Findings: Parallels and Treatment Implications

The results from clinical and pre-clinical laboratory animal research have together provided a greatly increased understanding of the effects of early loss on the vulnerability to adult psychiatric disorders, particularly depression. Although there is a considerably larger literature on the neurobiological alterations in animals after early life adverse events, parallels between animal MS models and EP loss can be drawn. Behaviors in response to loss include agitation and protest, followed by withdrawn behavior indicating despair among laboratory animals (McKinney, 1974; Reite et al., 1981) and nursery-reared children (Bowlby, 1973). Research on rats exposed to MS reveals associations with states indicative of depression, or typically comorbid with depression such as anxiety, anhedonia, and addictive behaviors (Huot et al., 2001; Ladd et al., 2000; Matthews et al., 1999). Many of the HPA axis changes found in laboratory animals exposed to MS have been detected among adults with histories of early life adversities, particularly childhood abuse. Increases in stress-induced ACTH have been detected among MS animals (Ladd et al., 1996) and humans reporting retrospective childhood abuse (Heim et al., 2000). Blunted ACTH responses in depressed women, with or without early life abuse likely reflect pituitary CRF receptor down-regulation potentially due to CRF

hypersecretion, as seen in animal models of MS (Ladd et al., 1996). Antidepressant medications used to treat depression, such as fluoxetine (Hollon, Thase, and Markowitz, 2002) can normalize HPA axis changes in humans (DeBellis, Gold, Geraciotti, Listwak, and Kling, 1993; Inder, Prickett, Mulder, Donald, and Joyce, 2001) and serve a protective function for MS animals (Lee et al., 2001). In parallel with the animal literature on changed morphology in the dentate gyrus layer of the hippocampus after MS (Martin et al., 1991), Vythilingam and colleagues (2002) reported finding decreased hippocampal volume size among depressed women with a history of childhood abuse, compared with non-abused depressed and healthy subjects. Figure 28.2 illustrates some of the parallel changes in animal models and human research due to early parental loss. Some seminal questions remain. For example, Hofer (1996, p. 573) has asked “What exactly is lost in maternal separation?” Speculations include attachment bonds, adequate nutrition, and cognitive representations or memories of the parental figure. These are areas that should be addressed in future research.

Effective treatments may exist for children experiencing adversity and depression including play therapy, doll play, group art activities, and games (Webb, 1999), although controlled, methodologically sound studies are lacking. These treatment methods involving non-direct communication may be particularly important for children because they often lack both the coping mechanisms of adults, as well as adequate family support to deal with a crisis such as parental loss (Webb, 1999). A review on treatment efficacy with children and adolescents suggests that individual and group CBT and family therapy following the death of a parent might be particularly effective (Moore and Carr, 2000). However, these methods are more likely to be successful with older children who are capable of abstract reasoning and problem solving.

Treatment of adult MDD has largely focused on psychotherapy, primarily cognitive behavioral therapy (CBT) or interpersonal therapy (IPT), and antidepressant pharmacotherapy. Several classes of effective antidepressants are now available; the most commonly prescribed are the selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine, paroxetine, sertraline, escitalopram, fluvoxamine, and citalopram), dual serotonin/norepinephrine reuptake inhibitors (e.g. venlafaxine and milnacipran), or antidepressants with other mechanisms of action (e.g. mirtazepine, nefazodone, orazadine, and bupropion). Typically, studies on the efficacy of psychotherapeutic and pharmacological treatments have reported equivalent results for non-psychotic mild to moderate forms of depression (Hollon et al., 2002; Rush and Thase, 1998), although most investigators view antidepressants and electroconvulsive therapy (ECT) to be superior in severe depression. In a landmark study, patients with chronic MDD (longer than 2 years) apparently responded better to a combination of psychotherapy and antidepressant therapy (Keller et al., 2000).

Examination of the treatment efficacy for MDD as a function of early loss represents a much-needed area of future research. The extant literature would on the surface suggest that pharmacotherapy and psychotherapy should each potentially be effective in treating MDD associated with early loss. Psychopharmacological treatment has been shown to protect against many of the long-term neurobiological

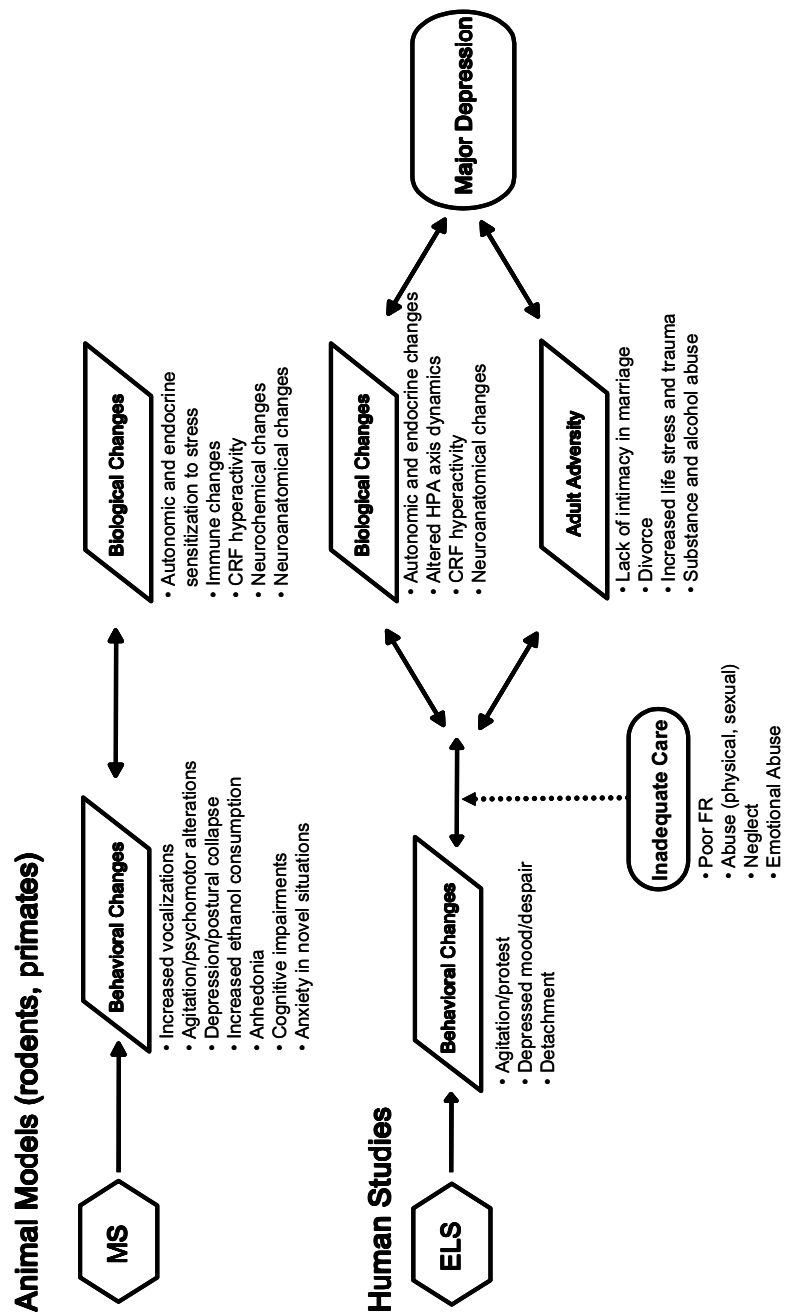


Figure 28.2 Comparison of animal model and human research findings on the effects of early loss. CRF, corticotropin releasing factor; ELS, Early Life Stress; FR, family relationships; MS, Maternal Separation; HPA, hypothalamic–pituitary–adrenal axis; dotted line indicates mediator variable.

consequences of early loss (e.g. MS) in laboratory animals. Lee et al. (2001) reported that fluoxetine treatment of MS rat pups prevented the significant decrement in cell proliferation and apoptosis in the dentate gyrus observed in the vehicle-treated MS rat pups. Fluoxetine treatment in depressed adults can normalize HPA axis hyperactivity and CSF CRF concentrations associated with MDD (De Bellis et al., 1993; Inder et al., 2001). A recent study by Nemeroff and colleagues (2003) examined the effects of antidepressants (nefazodone), psychotherapy (Cognitive Behavioral Analysis System of Psychotherapy (CBASP)), and their combination on patients with chronic MDD from the Keller et al. (2000) study, as a function of the presence or absence of childhood trauma. The CBASP psychotherapy regime was more effective than antidepressant monotherapy in treating MDD patients with a history of childhood trauma before the age of 15 years, including parental loss (either death or separation), physical abuse, sexual abuse, and neglect. The treatment effects of the combination of nefazodone and CBASP was not significantly better than the treatment effects due to CBASP alone (Nemeroff et al., 2003). Although clearly needing replication, this finding suggests that MDD related to early adversity, including EP loss, may respond better to psychotherapy than antidepressants, and holds promise for many with chronic MDD, which can remain resistant to treatment with antidepressant medication. Whether similar results will be obtained when comparing psychotherapy and SSRIs or SNRIs remains to be determined.

28.5 Discussion

The writings of Freud and Bowlby are often cited for their prescient theories of the importance of early life trauma, particularly early parental loss, in the development of adult psychopathology. Now, decades later, there is ample evidence that early parental loss adversely affects neurobiological systems and behavior, and increases the incidence of later life adversities, MDD, and other related disorders. Animal models of depression using MS as a method to provoke depressive behaviors and neurobiological changes, which have been found to accompany MDD (e.g. alterations in HPA axis responses to stress), have been useful. Although there is a considerably larger literature on the neurobiological alterations in animals after early life adverse events, future research on early parental loss in humans must more carefully define the biological consequences. With regard to the human literature on early loss, findings predominately concern clinical characteristics (e.g. disorders) and mediators of the link between early loss and later psychopathology. Genetic factors likely play a contributing role as well. Thus, Caspi et al. (2003) recently reported seminal evidence that a polymorphism of the serotonin transporter gene moderated the effect of stressful life events on the development of depressive symptoms.

Parental separation is a robust predictor of poor later adjustment in both animals and humans. Many of the neurobiological alterations due to MS in laboratory animals have been demonstrated in MDD and among women who report retrospective histories of childhood abuse. In predicting psychopathology in adulthood,

in contrast to the mixed literature cited on EPD, EPS appears to robustly predict adulthood MDD. This may be due to a perceived negative meaning for the child and more difficulty in accepting and coping with a separation compared to a death (Canetti et al., 2000). Children may take on personalized reasons for the separation, whereas they may feel less responsible in the event of EPD. Alternatively, the effects of EPS may operate indirectly, through mediator variables such as parental warmth and care by the surviving parent (Bifulco et al., 1992; Oakley-Browne et al., 1995b; Saler and Skolnick, 1992). Problems related to divorce may compound parental stress and result in poorer quality care of offspring. These stressors may include reduced family income, mother (or father) starting work, and a new parental partner may be introduced to the home (Tennant, 1988). Continuing parental conflict and loss of contact with the separated parent may also occur. Parental acrimony after separation is also related to behavioral problems in children (Shaw and Emery, 1987). A prolonged effect of EP separation may increase vulnerability to disorders later in life. EPS interacts with recent stressful life events to increase vulnerability to alcohol abuse and psychiatric disorders, whereas EPD apparently does not (Landerman, George, and Blazer, 1991).

What about the role of protective and ameliorative processes in the responses to early loss or deprivation? Protective, or resiliency, factors are believed to buffer the effects of loss. For example, in response to loss, social support can ameliorate depressive symptoms (Brown, Andrews, Harris, Adler, and Bridge, 1986). Ladd et al. (2000) suggested that social buffering can mute the neurobiological effects of early adverse experiences in rats. Francis, Diorio, Plotsky, and Meaney (2002) reported that altered behavioral and HPA axis responses to stress due to MS were reversed by environmental enrichment during the peri-pubertal period. However, CRF mRNA expression remained unaltered. The authors concluded that the mechanism by which environmental enrichment acted was by compensation for, rather than reversal of, the neural effects of early life stress (Francis et al., 2002).

Early loss and deprivation may increase appetitive or addictive behaviors. Findings reported in animal models using MS support the link between early deprivation or loss (e.g. abuse in the form of neglect) and appetitive or addictive behavior. Boccia et al. (1997) reported finding that rat infants show increases in feeding behavior, as part of the depressive phase of their response to MS. Huot et al. (2001) and Matthews et al. (1999) reported increased self-administration of ethanol and cocaine (respectively) among MS rats.

Early adversity may be associated with specific clinical features of MDD. Levitan et al. (1998) reported that childhood physical or sexual abuse predicted MDD with reversed neurovegetative symptoms (increased appetite, weight gain, hypersomnia), so-called atypical depression. Matza, Revicki, Davidson, and Stewart (2003) studied atypical MDD characterized by reversed vegetative symptoms of hypersomnia and hyperphagia. They compared patients with and without reversed vegetative symptoms. Compared to those without atypical MDD, the atypical MDD group was characterized by a greater percentage of women, earlier age of onset, higher rates of most MDD symptoms, and high levels of childhood neglect and sexual abuse. These results may explain why patients with MDD defined by reversed neurovegetative

symptoms typically have a chronic course of illness (Asnis, McGinn, and Sanderson, 1995; Kendler et al., 1996), earlier ages of onset, and frequent episodes (Horwath, Johnson, Weissman, and Horning, 1992; Kendler et al., 1996). These findings suggest that an atypical MDD subgroup may exist, which is comprised mostly of women with childhood adversity histories, potentially including early parental loss.

In summary, exciting findings relating to humans with early parental loss parallel much of the early loss (e.g. MS) literature relating to laboratory animals. Future research will help to further illuminate the direct and mediator roles of early parental loss and other adversities (e.g. abuse, adult adversity) in the development of psychopathology and altered neurobiological stress systems. Buffering mechanisms of stress, such as social support and quality parental care after loss, may also be further defined. Clinical research addressing these issues will help answer the open questions and contribute toward the recognition of distinct depressive symptoms or syndromes due to early-life stress, as well as the development of treatment protocols specific to pathological states related to early stress.

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References

- AGID, O., SHAPIRA, B., ZISLIN, J., RITSNER, M., HANIN, B., MURAD, H., TROUDART, T., BLOCH, M., HERESCO-LEVY, U., LERER, B., Environment and vulnerability to major psychiatric illness: A case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Mol. Psychiatry* **1999**, *4*, 163–172.
- ARBORELUIS, L., OWENS, M. J., PLOTSKY, P. M., NEMEROFF, C. B., The role of corticotropin-releasing factor in depression and anxiety disorders. *J. Endocrinol.* **1999**, *160*, 1–12.
- ASNIS, G. M., MCGINN, L. K., SANDERSON, W. C., Atypical depression: clinical aspects and noradrenergic function. *Am. J. Psychiatry* **1995**, *152*, 31–36.
- BEAUCHAMP, A. J., GLUCK, J. P., FOUTY, H. E., LEWIS, M. H., Associative processes in differentially reared rhesus monkeys (*Macaca mulatta*): blocking. *Dev. Psychobiol.* **1991**, *21*, 355–364.
- BECK, A. T., WARD, C. H., MENDELSON, M., MOCK, J., ERBAUGH, J., An inventory for measuring depression. *Arch. Gen. Psychiatry* **1961**, *4*, 561–571.
- BHATNAGAR, S., SHANK, N., MEANEY, M. J., Hypothalamic–pituitary–adrenal function in handled and non-handled rats in response to chronic stress. *J. Neuroendocrinol.* **1995**, *7*, 107–119.
- BIFULCO, A. T., BROWN, G. W., HARRIS, T. O., Childhood loss of parent, lack of adequate parental care and adult depression: a replication. *J. Affect Disord.* **1987**, *12*, 115–128.
- BIFULCO, A., HARRIS, T., BROWN, G. W., Mourning or early inadequate care: Reexamining the relationship of maternal loss in childhood with adult depression and anxiety. *Dev. Psychopathology* **1992**, *4*, 433–449.
- BIRCHNELL, J., The interrelationship between social class, early parent death, and mental illness. *Psychol. Med.* **1972**, *2*, 166–175.
- BIRCHNELL, J., Women whose mothers died in childhood: an outcome study. *Psychol. Med.* **1980**, *10*, 699–713.
- BOCCIA, M. L., SCANLAN, J. M., LAUDENSLAGER, M. L., BERGER, C. L., HIJAZI, A. S., REITE, M. L., Juvenile friends, behavior, and immune responses to separation in Bonnet macaque infants. *Physiol. Behav.* **1997**, *61*, 191–198.
- BODNOFF, S. R., SURANYI-CADOTTE, B. E., QUIRION, R., MEANEY, M. J., Role of the central benzodiazepine receptor system in behavioral habituation to novelty. *Behav. Neurosci.* **1989**, *103*, 209–212.
- BOWLBY, J., Separation: anxiety and anger. In *Attachment and Loss*, Volume II. New York: Basic Books, **1973**.
- BOWLBY, J., Loss: sadness and depression. In *Attachment and Loss*, Volume III. New York: Basic Books, **1980**.
- BOWLBY, J., *A Secure Base: Parent–Child Attachment and Healthy Human Development*. New York, NY: Basic Books, **1988**.
- BREIER, A. B., KELSOE, J. R., KIRWIN, P. D., BELLER, S. T., WOLKOWITZ, O. M., PICKAR, D., Early parental loss and development of adult psychopathology. *Arch. Gen. Psychiatry* **1988**, *45*, 987–993.
- BROWN, G. W., ANDREWS, B., HARRIS, T., ADLER, Z., BRIDGE, L., Social support, self-esteem, and depression. *Psychol. Med.* **1986**, *16*, 813–831.
- CALDI, C., FRANCIS, D., SHARMA, S., PLOTSKY, P. M., MEANEY, M. J., The effects of early rearing environment on the development of GABA_A and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacology* **2000**, *22*, 219–229.
- CANETTI, L., BACHAR, E., BONNE, O., AGID, O., LERER, B., D-NOUR, A. K., SHALEV, A. Y., The impact of parental death versus separation from parents on the mental health of Israeli adolescents. *Compr. Psychiatry* **2000**, *41*, 360–368.

- CARPENTER, L. L., TYRKA, A. R., MCDUGGLE, C. J., MALISON, R. T., OWENS, M. J., NEMEROFF, C. B., PRICE, L. H., Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. *Neuropsychopharmacology*. Dec. 31, **2003** [E-pub ahead of print].
- CASPI, A., SUGDEN, K., MOFFITT, T. E., TAYLOR, A., CRAIG, I. W., HARRINGTON, H., MCCLAY, J., MILL, J., MARTIN, J., BRAITHWAITE, A., POULTON, R., Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **2003**, *301*, 386–389.
- CHAMPOUX, M., COE, C. L., SCHANBERG, S. M., KUHN, C. M., SUOMI, S. J., Hormonal effects of early rearing conditions in the infant rhesus monkey. *Am. J. Primatol.* **1989**, *19*, 111–117.
- CLARKE, A. S., Social rearing effects on HPA axis activity over early development and in response to stress in rhesus monkeys. *Dev. Psychobiol.* **1993**, *26*, 43–46.
- COE, C. L., LUBACH, G. R., ERSHLER, W. B., KLOPP, R. G., Influence of early rearing on lymphocyte proliferation responses in juvenile rhesus monkeys. *Brain Behav. Immun.* **1989**, *3*, 47–60.
- COPLAN, J. D., ANDREWS, M. W., ROSENBLUM, L. A., OWENS, M. J., FRIEDMAN, S., GORMAN, J. M., NEMEROFF, C. B., Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 1619–1623.
- COPLAN, J. D., ROSENBLUM, L. A., FRIEDMAN, S., BASSOFF, T. B., GORMAN, J. M., Behavioral effects of oral yohimbine in differentially reared nonhuman primates. *Neuropsychopharmacology* **1992**, *6*, 31–37.
- COPLAN, J. D., SMITH, E. L., ALTEMUS, M., SCHARF, B. A., OWENS, M. J., NEMEROFF, C. B., GORMAN, J. M., ROSENBLUM, L. A., Variable foraging demand rearing: sustained elevations in cisternal cerebrospinal fluid corticotropin-releasing factor concentrations in adult primates. *Biol. Psychiatry* **2001**, *50*, 200–204.
- DE BELLIS, M. D., GOLD, P. W., GERACIOTI JR., T. D., LISTWAK, S. J., KLING, M. A., Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *Am. J. Psychiatry* **1993**, *150*, 656–657.
- EHLERS, C. L., LI, T. K., LUMENG, L., HWANG, B., SOMES, C., JIM, NEZ, P., MATH, A. A., Neuropeptide Y (NPY) levels in ethanol-naïve alcohol preferring and non-preferring rats and in Wistars following ethanol exposure. *Alcohol Clin. Exp. Res.* **1998**, *22*, 1778–1782.
- ELIZUR, E., KAFFMAN, M., Factors influencing the severity of childhood bereavement reactions. *Am. J. Orthopsychiatry* **1983**, *53*, 668–676.
- ENGELMANN, M., THRIVIKRAMAN, K. V., SU, Y., NEMEROFF, C. B., MONTKOWSKI, A., LANDGRAF, R., HOLDSBOER, F., PLOTSKY, P. M., Endocrine and behavioral effects of airpuff-startle in rats. *Psychoneuroendocrinology* **1996**, *21*, 391–400.
- FAVARELLI, C., SACCHETTI, E., AMBONETTI, A., CONTE, G., PALLANTI, S., VITA, A., Early life events and affective disorder revisited. *Br. J. Psychiatry* **1986**, *148*, 288–295.
- FILE, S. E., Animal models of different anxiety states. In BIGGIO, G., COSTA, E. (Eds.), *GABAA Receptors and Anxiety: From Neurobiology to Treatment*. Raven Press: New York, **1995**, 93–113.
- FRANCIS, D., DIORIO, J., PLOTSKY, P. M., MEANEY, M. J., Environmental enrichment reverses the effects of maternal separation on stress reactivity. *J. Neurosci.* **2002**, *22*, 7840–7843.
- FREUD, S., Mourning and melancholia. In STRACHEY, J., FREUD, A. (Eds.), *The Standard Edition of the Complete Psychological Works of Sigmund Freud*. Hogarth Press: Toronto, **1957**, 243–258.
- FURUKAWA, T. A., OGURA, A., HIRAI, T., FUJIHARA, S., KITAMURA, T., TAKAHASHI, K., Early parental separation experiences among patients with bipolar disorder and major depression: A case-control study. *J. Affect Disord.* **1999**, *52*, 85–91.
- GILMER, W. S., MCKINNEY, W. T., Early experience and depressive disorders: human and non-human primate studies. *J. Affective Disord.* **2003**, *75*, 97–113.
- GLUCK, J. P., PEARCE, H. E., Acquisition and extinction of an operant response in

- differentially reared rats. *Dev. Psychobiol.* **1977**, *10*, 143–149.
- GRAY, T. S., The organization and possible function of amygdaloid corticotropin-releasing factor pathways. In DeSouza, E. B., Nemeroff, C. B. (Eds.), *Corticotropin-releasing Factor: Basic and Clinical Studies of a Neuropeptide*. CRC Press: Boca Raton, **1990**, 53–68.
- GUNNAR, M. R., MORISON, S. J., CHISHOLM, K., SCHUDER, M., Salivary cortisol levels in children adopted from Romanian orphanages. *Dev. Psychopathol.* **2001**, *13*, 611–628.
- HALLSTROM, T., The relationships of childhood socio-demographic factors and early parental loss to major depression in adult life. *Acta Psychiatr. Scand.* **1987**, *75*, 212–216.
- HARRIS, T., BROWN, G. W., BIFULCO, A., Loss of parent in childhood and adult psychiatric disorder: the role of lack of adequate parental care. *Psychol. Med.* **1986**, *16*, 641–659.
- HEIM, C., NEWPORT, D. J., BONSALE, R., MILLER, A. H., NEMEROFF, C. B., Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *Am. J. Psychiatry* **2001**, *158*, 575–581.
- HEIM, C., NEWPORT, D. J., HEIT, S., GRAHAM, Y. P., WILCOX, M., BONSALE, R., MILLER, A. H., NEMEROFF, C. B., Pituitary–adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* **2000**, *284*, 592–597.
- HEIM, C., NEWPORT, D. J., WAGNER, D., WILCOX, M. M., MILLER, A. H., NEMEROFF, C. B., The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: A multiple regression analysis. *Depress. Anxiety* **2002**, *15*, 117–125.
- HILAKIVI-CLARKE, L. A., TURKKA, J., LISTER, R. G., LINNOILA, M., Effects of early postnatal handling on brain beta-adrenoceptors and behavior in tests related to stress. *Brain Res.* **1991**, *542*, 286–292.
- HOFFER, M. A., Early social relationships: A psychobiologist's view. *Child Dev.* **1987**, *58*, 633–647.
- HOFFER, M. A., On the nature and consequences of early loss. *Psychosom. Med.* **1996**, *58*, 570–581.
- HOLLON, S. D., THASE, M. E., MARKOWITZ, J. C., Treatment and prevention of depression. *Psychol. Sci. Publ. Interest* **2002**, *3*, 39–77.
- HOLSBOER, F., GERKEN, A., STALLA, G. K., MUELLER, O. A., ACTH, cortisol and corticosterone output after ovine corticotropin-releasing factor challenge during depression and after recovery. *Biol. Psychiatry* **1985**, *20*, 276–286.
- HOLSON, R. R., SCALLET, A. C., ALI, S. F., TURNER, B. B., Isolation stress: revisited: Isolation-rearing effects depend on animal care methods. *Physiol. Behav.* **1991**, *49*, 107–118.
- HORWATH, E., JOHNSON, J., WEISSMAN, M. M., HORNIG, C. D., The validity of major depression with atypical features based on a community study. *J. Affect. Disord.* **1992**, *26*, 117–125.
- HUOT, R. L., THRIVIKRAMAN, K. V., MEANEY, M. J., PLOTSKY, P. M., Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment. *Psychopharmacology* **2001**, *158*, 366–373.
- INDER, W. J., PRICKETT, T. C. R., MULDER, R. T., DONALD, R. A., JOYCE, P. R., Reduction in basal afternoon plasma ACTH during early treatment of depression with fluoxetine. *Psychopharmacology* **2001**, *156*, 73–78.
- JIMENEZ-VASQUEZ, P. A., MATH, A. A., THOMAS, J. D., RILEY, E. P., EHLERS, C. L., Early maternal separation alters neuropeptide Y concentrations in selected brain regions in adult rats. *Dev. Brain Res.* **2001**, *131*, 149–152.
- JONES, G. H., ROBBINS, T. W., MARSDEN, C. A., Isolation-rearing retards the acquisition of schedule-induced polydipsia in rats. *Physiol. Behav.* **1989**, *45*, 71–77.
- KANEKO, W. M., RILEY, E. P., EHLERS, C. L., Behavioral and electrophysiological effects of early repeated maternal separation. *Depression* **1994**, *2*, 34–53.
- KELLER, M. B., MCCULLOUGH, J. P., KLEIN, D. N., ARNOW, B., DUNNER, D. L., GELENBERG, A. J., MARKOWITZ, J. C., NEMEROFF, C. B., RUSSELL, J. M., THASE, M. E., TRIVEDI, M. H., ZAJECKA, J., A comparison of nefazodone, the

- cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N. Engl. J. Med.* **2000**, 342, 1462–1470.
- KENDLER, K. S., GARDNER, C. O., PRESCOTT, C. A., Toward a comprehensive developmental model for major depression in women. *Am. J. Psychiatry* **2002b**, 159, 1133–1145.
- KENDLER, K. S., NEALE, M. C., KESSLER, R. C., HEATH, A. C., EAVES, L. J., Childhood parental loss and adult psychopathology in women: a twin study perspective. *Arch. Gen. Psychiatry* **1992**, 49, 109–116.
- KENDLER, K. S., NEALE, M. C., PRESCOTT, C. A., KESSLER, R. C., HEATH, A. C., COREY, L. A., EAVES, L. J., Childhood parental loss and alcoholism in women: a causal analysis using a twin-family design. *Psychol. Med.* **1996**, 26, 79–95.
- KENDLER, K. S., SHETH, K., GARDNER, C. O., PRESCOTT, C. A., Childhood parental loss and risk for first-onset of major depression and alcohol dependence: the time-decay of risk and sex differences. *Psychol. Med.* **2002a**, 32, 1187–1194.
- KESSLER, R. C., DAVIS, C. G., KENDLER, K. S., Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. *Psychol. Med.* **1997**, 27, 1101–1119.
- KOGLER-MULY, S. M., OWENS, M. J., ERVIN, G. N., KILTS, C. D., NEMEROFF, C. B., Potential corticotropin-releasing factor pathways in the rat brain as determined by bilateral electrolytic lesions of the central amygdaloid nucleus and the paraventricular nucleus of the hypothalamus. *J. Neuroendocrinol.* **1993**, 5, 95–98.
- KRAEMER, G. W., EBERT, M. H., LAKE, C. R., MCKINNEY, W. T., Hypersensitivity to d-amphetamine several years after early social deprivation in rhesus monkeys. *Psychopharmacology* **1984**, 82, 266–271.
- KRAEMER, G. W., EBERT, M. H., SCHMIDT, D. E., MCKINNEY, W. T., A longitudinal study of the effect of different social rearing conditions on cerebrospinal fluid norepinephrine and biogenic amine metabolites in rhesus monkeys. *Neuropsychopharmacology* **1989**, 2, 175–189.
- LADD, C. O., HUOT, R. L., THRIVIKRAMAN, K. V., NEMEROFF, C. B., MEANEY, M. J., PLOTSKY, P. M., Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Prog. Brain Res.* **2000**, 122, 81–102.
- LADD, C. O., OWENS, M. J., NEMEROFF, C. B., Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology* **1996**, 139, 1212–1218.
- LANDERMAN, R., GEORGE, L. K., BLAZER, D. G., Adult vulnerability for psychiatric disorders: interactive effects of negative childhood experiences and recent stress. *J. Nerv. Ment. Dis.* **1991**, 179, 656–663.
- LEE, H. J., KIM, J. W., YIM, S. V., KIM, M. J., KIM, S. A., KIM, Y. J., KIM, C. J., CHUNG, J. H., Fluoxetine enhances cell proliferation and prevents apoptosis in dentate gyrus of maternally separated rats. *Mol. Psychiatry* **2001**, 6, 725–728.
- LEVINE, S., HALTMEYER, G. C., KARAS, G. G., DENENBERG, V. H., Physiological and behavioral effects of infantile stimulation. *Physiol. Behav.* **1967**, 2, 55–59.
- LEVITAN, R. D., PARIKH, S. V., LESAGE, A. D., HEGADOREN, K. M., ADAMS, M., KENNEDY, S. H., GOERING, P. N., Major depression in individuals with a history of childhood physical or sexual abuse: relationship to neurovegetative features, mania, and gender. *Am. J. Psychiatry* **1998**, 155, 1746–1752.
- LEWIS, M. H., GLUCK, J. P., BEAUCHAMP, A. J., KERESZTURY, M. F., MAILMAN, R. B., Long-term effects of early social isolation in *Macaca mulatta*: changes in dopamine receptor function following apomorphine challenge. *Brain Res.* **1990**, 513, 67–73.
- LEWIS, M. H., GLUCK, J. P., PETITTO, J. M., HENSLEY, L. L., OZER, H., Early social deprivation in nonhuman primates: long-term effects on survival and cell-mediated immunity. *Soc. Biol. Psychiatry* **1999**, 47, 119–126.
- LIU, D., CALDJI, C., SHARMA, S., PLOTSKY, P. M., MEANEY, M. J., Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinephrine release in the hypothalamic paraventricular nucleus. *J. Neuroendocrinol.* **2000**, 12, 5–12.
- LUBACH, G. R., KITTRELL, M. W., COE, C. L., Maternal influences on body temperature in the infant primate. *Physiol. Behav.* **1992**, 51, 987–994.

- LUECKEN, L. J., Attachment and loss experiences during childhood are associated with adult hostility, depression, and social support. *J. Psychosom. Res.* **2000**, *49*, 85–91.
- MAES, M., CLAES, M., VANDEWOUDE, M., SCHOTTE, C., Adrenocorticotropin hormone, beta-endorphin and cortisol responses to oCRF in melancholic patients. *Psychol. Med.* **1992**, *22*, 317–329.
- MALIZIA, A. L., COUPLAND, N. J., NUTT, D. J., Benzodiazepine receptor function in anxiety disorders. In BIGGO, E., SANNA, F., COSTA, E. (Eds.), *GABAA Receptors and Anxiety: From Neurobiology to Treatment*. Raven Press: New York, **1995**, 115–133.
- MARTIN, L. J., SPICER, D. M., LEWIS, M. H., GLUCK, J. P., CORK, L. C., Social deprivation of infant rhesus monkeys alters the chemoarchitecture of the brain in subcortical regions. *J. Neurosci.* **1991**, *11*, 3344–3358.
- MATHEW, S. J., COPLAN, J. D., SMITH, E. L., SCHARF, B. A., OWENS, M. J., NEMEROFF, C. B., MANN, J. J., GORMAN, J. M., ROSENBLUM, L. A., Cerebrospinal fluid concentrations of biogenic amines and corticotropin-releasing factor in adolescent non-human primates as a function of the timing of adverse early rearing. *Stress* **2002**, *5*, 185–193.
- MATTHEWS, K., ROBBINS, T. W., EVERITT, B. J., CAINE, S. B., Repeated neonatal maternal separation alters intravenous cocaine self-administration in adult rats. *Psychopharmacology* **1999**, *141*, 123–134.
- MATHÉ, A. A., Neuropeptides and electroconvulsive treatment. *J. ECT* **1999**, *15*, 60–75.
- MATZA, L. S., REVICKI, D. A., DAVIDSON, J. R., STEWART, W., Depression with atypical features in the National Comorbidity Survey. *Arch. Gen. Psychiatry* **2003**, *60*, 817–826.
- McKINNEY, W. T., Primate social isolation. Psychiatric implications. *Arch. Gen. Psychiatry* **1974**, *31*, 422–426.
- MEANEY, M. J., MITCHELL, J. B., AITKEN, D. H., BHATNAGAR, S., BODNOFF, S. R., INY, L. F., SARRIEAU, A., The effects of neonatal handling on the development of the adrenocortical response to stress: implications for neuropathology and cognitive deficits in later life. *Psychoneuroendocrinology* **1991**, *16*, 85–103.
- MEANEY, M. J., TANNENBASUM, B., FRANCIS, D., BHATNAGAR, S., SHANKS, N., VIAU, V., O'DONNELL, D., PLOTSKY, P. M., Early environmental programming hypothalamic–pituitary–adrenal responses to stress. *The Neurosciences* **1994**, *6*, 247–259.
- MIREAULT, G. C., BOND, L. A., Parental death in childhood: perceived vulnerability, and adult depression and anxiety. *Am. J. Orthopsychiatry* **1992**, *62*, 517–524.
- MOORE, M., CARR, A., Depression and Grief. In CARR, A. (Ed.), *What works with children and adolescents: A critical review of psychological interventions with children, adolescents, and their families*. Florence, KY, US, Taylor & Francis/Routledge, **2000**, 203–232.
- NEMEROFF, C. B., HEIM, C. M., THASE, M. E., KLEIN, D. N., RUSH, A. J., SCHATZBERG, A. F., NINAN, P. T., McCULLOUGH, J. P., WEISS, P. M., DUNNER, D. L., ROTHBAUM, B. O., KORNSTEIN, S., KEITNER, G., KELLER, M. B., Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 14293–14296.
- NEWPORT, D. J., HEIM, C., BONSALE, R., MILLER, A. H., NEMEROFF, C. B., Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse. *Biol. Psychiatry* **2004**, *55*, 10–20.
- NEWPORT, D. J., HEIM, C., OWENS, M. J., RITCHIE, J. C., RAMSEY, C. H., BONSALE, R., MILLER, A. H., NEMEROFF, C. B., Cerebrospinal fluid corticotropin-releasing factor (CRF) and vasopressin concentrations predict pituitary response in the CRF stimulation test: a multiple regression analysis. *Neuropsychopharmacology* **2003**, *28*, 569–576.
- NOVAKOVA, V., KOLDOVSKY, O., FALTIN, J., HAHN, P., FLANDERA, V., Effect of early and late waning on learning in adult rats. *Nature* **1962**, *193*, 280.
- OAKLEY-BROWNE, M. A., JOYCE, P. R., WELLS, J. E., BUSHNELL, J. A., HORNBLow, A. R., Disruptions in childhood parental care as risk factors for major depression in adult women. *Aust. NZ J. Psychiatry* **1995a**, *29*, 437–448.

- OAKLEY-BROWNE, M. A., JOYCE, P. R., WELLS, J. E., BUSHNELL, J. A., HORNBLow, A. R., Adverse parenting and other childhood experience as risk factors for depression in women aged 18–44 years. *J. Affect Disord.* **1995b**, 34, 13–23.
- OWENS, M. J., VARGAS, M. A., KNIGHT, D. L., NEMEROFF, C. B., The effects of alprazolam on corticotropin-releasing factor neurons in the rat brain: acute time course, chronic treatment and abrupt withdrawal. *J. Pharm. Exp. Ther.* **1991**, 258, 349–356.
- PAUL, I. A., ENGLISH, J. A., HALARIS, A., Sucrose and quinine intake by maternally-deprived and control rhesus monkeys. *Behav. Brain Res.* **2000**, 112, 127–134.
- PERRIS, C., HOLMGREN, S., VON KNORRING, L., PERRIS, H., Parental loss by death in the early childhood of depressed patients and of their healthy siblings. *Brit. J. Psychiatry* **1986**, 148, 165–169.
- PFOHL, B., STANGL, D., TSUANG, M. T., The association between early parental loss and diagnosis in the Iowa 500. *Arch. Gen. Psychiatry* **1983**, 40, 965–967.
- PLOTSKY, P. M., MEANEY, M. J., Early, post-natal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Mol. Brain Res.* **1993**, 18, 195–200.
- PLOTSKY, P. M., MEANEY, M. J., Neonatal rearing conditions alter HPA axis function, central CRF mRNA, CSF CRF levels, and behavior: reversal by SSRI treatment. Abstract for the 26th ISPNE Congress, Casais, Portugal, **1996**.
- RAGAN, P. V., MCGLASHAN, T. H., Childhood parental death and adult psychopathology. *Am. J. Psychiatry* **1986**, 143, 153–157.
- RASMUSSEN, A., LIPSCHITZ, D. S., WANG, S., HU, S., VOJVODA, D., BREMNER, J. D., SOUTHWICK, S. M., CHARNEY, D. S., Increased pituitary and adrenal reactivity in premenopausal women with post-traumatic stress disorder. *Biol. Psychiatry* **2001**, 50, 965–977.
- REITE, M., KAEMINGK, K., BOCCIA, M. L., Maternal separation in bonnet monkey infants: Altered attachment and social support. *Child Dev.* **1989**, 60, 473–480.
- REITE, M., SHORT, R., SEILER, C., PAULEY, J. D., Attachment, loss, and depression. *J. Child Psychol. Psychiatry* **1981**, 22, 141–169.
- ROY, A., Early parental death and adult depression. *Psychol. Med.* **1983**, 13, 861–865.
- RUSH, A. J., THASE, M. E., In MAJ, M., SARTORIUS, N. (Eds.), *Psychotherapies for depressive disorders: A review. WPA Series: Evidence and Experience in Psychiatry* (2nd edn., Vol. 1). Wiley: Chichester, UK, **1998**, 161–206.
- SALER, L., SKOLNICK, N., Childhood parental death and depression in adulthood: roles of surviving parent and family environment. *Am. J. Orthopsychiatry* **1992**, 62, 504–516.
- SANCHEZ, M. M., HEARN, E. F., DO, D., RILLING, J. K., HERNDON, J. G., Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Res.* **1998**, 812, 38–49.
- SHAW, D. S., EMERY, R. E., Parental conflict and other correlates of the adjustment of school-aged children whose parents have separated. *J. Abnorm. Child Psychol.* **1987**, 15, 269–281.
- SKELTON, K. H., NEMEROFF, C. B., KNIGHT, D. L., OWENS, M. J., Chronic administration of the triazolobenzodiazepine alprazolam produces opposite effects on corticotropin-releasing factor and urocortin neuronal systems. *J. Neurosci.* **2000**, 20, 1240–1248.
- SMITH, M. A., DAVIDSON, M. A., RITCHIE, J. C., KUDLER, H., LIPPER, S., CHAPPELL, P., NEMEROFF, C. B., The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. *Biol. Psychiatry* **1989**, 26, 349–355.
- TEICHER, M. H., ANDERSEN, S. L., POLCARI, A., ANDERSON, C. M., NAVAITA, C. P., KIM, D. M., The neurobiological consequences of early stress and childhood maltreatment. *Neurosci. Biobehav. Rev.* **2003**, 27, 33–44.
- TEICHER, M. H., ITO, Y., GLOD, C. A., ANDERSEN, S. L., DUMONT, N., ACKERMAN, E., Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. *Ann. NY Acad. Sci.* **1997**, 821, 160–175.
- TENNANT, C., Parental loss in childhood: its effect in adult life. *Arch. Gen. Psychiatry* **1988**, 45, 1045–1050.

- TENNANT, C., BEBBINGTON, P., HURRY, J., Parental death in childhood and risk of adult depressive disorders. *Psychol. Med.* **1980**, *10*, 289–299.
- VYTHILINGAM, M., HEIM, C., NEWPORT, J., MILLER, A. H., ANDERSON, E., VERMETTEN, E., BRONEN, R., STAIB, L., CHARNEY, D. S., NEMEROFF, C. B., BREMNER, J. D., Childhood trauma associated with smaller hippocampal volume in major depression. *Am. J. Psychiatry* **2002**, *159*, 2072–2080.
- WAHLESTEDT, C., HEILIG, M., Neuropeptide Y and related peptides. In BLOOM, F. E., KUPFER, D. J. (Eds.), *Psychopharmacology: The Fourth Generation of Progress*. Raven Press: New York, **1995**, 543–551.
- WEBB, N. B., In Play Therapy With Children. In WEBB, N. B. (Ed.), *Crisis: Individual, Group, and Family Treatment* (2nd edn.), New York, NY, US, Guilford Press, **1999**.
- WILLNER, P., Animal models as simulations of depression. *Trends Pharmacol. Sci.* **1991**, *12*, 131–136.
- WILSON, M. A., GABA physiology: modulation by benzodiazepines and hormones. *Crit. Rev. Neurobiol.* **1996**, *10*, 1–37.
- WRIGHT, I. K., UPTON, N., MARSDEN, C. A., Resocialisation of isolation-reared rats does not alter their anxiogenic profile on the elevated X-maze model of anxiety. *Physiol. Behav.* **1991**, *50*, 1129–1132.

29

Neurogenomics of Depression

Klaus Peter Lesch

Abstract

Depression is an etiologically heterogeneous group of brain disorders with complex genetics and obscure neurobiology. Definitions of clinical phenotypes are not rooted in their neurobiology and animal models of behavioral despair have considerable limitations. Nevertheless, investigation of the subtle alterations in gene expression, the correlations between genotype and brain activity, and the environmental variables interacting with genetic variants currently strengthen research on the genetics of depression. Although the post-genomic era is still in its infancy, several milestones have already been reached: variation in gene expression was confirmed to play a predominant role in individual differences in most traits including personality and behavior; gene \times environment interactions were established in humans and the nonhuman primate model; gene–phenotype correlations were substantiated by functional neuroimaging; and the notion that both genes and environmental factors impact on brain development. It is increasingly being appreciated that these milestones set the stage for susceptibility to depression. Given the etiological and psychobiological complexity of mood disorders, it is not surprising that the identification of vulnerability genes and elucidation of their interaction with environmental stressors is extremely difficult and continues to be among the last challenges of genomics, behavioral neurosciences and psychiatry.

29.1

Introduction

Depression is an etiologically heterogeneous group of brain disorders that are characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor, and emotional processes. Affected individuals differ remarkably in the profile of clinical features, severity, and course of illness as well as response to drug treatment and reintegration efforts. Genetic epidemiology has assembled convincing evidence to show that mood disorders including depression are

substantially influenced by genetic factors and that the genetic component is highly complex, polygenic, and epistatic. Because the mode of inheritance of depression is complex, it has been concluded that multiple genes of modest effect, in interaction with each other and in conjunction with environmental events, produce vulnerability to the disorder. Investigation of gene \times environment interactions in humans and nonhuman primates as well as gene inactivation and overexpression studies in mice further intensify the identification of genes that are essential for development and plasticity of brain systems related to depression.

29.2

Family Studies and Gene \times Environment Interaction

Epidemiological studies of unipolar major depression have revealed a population prevalence of 2–19% and an age-adjusted risk for first-degree relatives of 5–25% [1, 2]. In a meta-analysis of five large and rigorously selected family studies of major depression familial proclivity for this disease was demonstrated by a relative risk of 2.8 for affected subjects versus first-degree relative status [3]. Early age of onset and multiple episodes of depression seems to increase the familial aggregation and different affective disorders are often present in the same family [4]. Relatives of patients with bipolar disorder also have an increased risk of unipolar depression and affective disorders tend to co-exist with anxiety in many families [5–7].

Twin and family-based studies have accrued considerable evidence that a complex genetic mechanism is involved in the vulnerability to depressive disorders (for review see [8, 9]). Compared with the general population, relatives of depressed individuals have at least a three-fold increase in their risk of developing a major depressive disorder. In general, twin studies of depressive adults suggest that genes and specific environmental factors are critical, and that shared environmental factors, although important in less severe subtypes of depression, are possibly of less significance [10–13]. The heritability of unipolar depression appears to be remarkable, with estimates between 40 and 70%. Depression-associated genetic factors are largely shared with generalized anxiety disorder, while environmental determinants seem to be distinct [14–16]. This notion is consistent with recent models of emotional disorders which view depression and anxiety as sharing common vulnerabilities but differing on dimensions including, for instance, focus of attention or psychosocial liability. Although life events may precipitate depression, examination of familial liability along with social adversity reveals that environmental effects tend to be contaminated by genetic influences [16, 17]. The predisposition to suffer life events is likely influenced by shared family environment and some events may be associated with genetic factors.

While genetic research has typically focused either on depression-related traits or on major depressive disorders, with few investigations evaluating the genetic and environmental relationship between the two, it is crucial to answer the question of whether a certain quantitative trait etiopathogenetically influences the disorder or whether the trait is a syndromal dimension of the disorder. This concept also

supports the hypothesis that a genetic predisposition, coupled with early stress, in critical stages of development may result in a phenotype that is neurobiologically vulnerable to stress and may lower an individual's threshold for developing depression on additional stress exposure.

29.3 Molecular Genetics

Linkage analysis in extended pedigrees is a practical approach for identifying disease genes for monogenic diseases displaying a Mendelian mode of inheritance. In these studies, highly polymorphic genetic markers which are present throughout the genome allow the identification of the chromosomal region containing the disease-relevant genetic variation. Despite meiotic recombination events, marker alleles that remain close to the disease-causing variant tend to co-segregate with the disease within a family. Since mood disorders including depression are believed to be etiologically heterogeneous, different susceptibility genes may be operative in different families and, because large families with monogenetic inheritance of depressive disorders are rare, they are unlikely to be representative of the majority of cases. Although a rare disease-causing mutation in a single gene would not explain most cases, identification of such a major gene effect may facilitate the investigation of the poorly-understood pathophysiology of mood disorders.

Differential psychopathologic ascertainment aiming at the delineation of a distinct clinical subtype (e.g. early age of onset, stress reactivity, suicidality) may increase the probability of identifying a truly monogenic family. In addition to the mode of inheritance, the analysis requires assumptions to be made regarding the penetrance of the variant and the frequency of the susceptibility allele in the general population. For affective disorders, as well as for many other complex diseases, these parameters are not known. Therefore nonparametric methods are preferred, such as the affected pedigree member method, which investigates pairs of affected relatives, in most cases siblings (ASP; see Chapter 30). Since siblings share on average 50% of their alleles, pairs of siblings affected by the same disorder will have increased allele sharing for markers close to the disease gene. This method is independent of whether the disease is dominant, recessive, or non-Mendelian.

Bipolar disorder, a serious affective disorder with a lifetime risk of approximately 1%, in which individuals suffer from episodes of extreme depression and mania, is by far the most frequently studied mood disorder using linkage analysis. In the majority of families, bipolar disorder is now thought to be influenced by multiple genes, as well as environmental influences [18, 19]. Gene \times gene and gene \times environment interactions therefore complicate attempts to understand the etiology of this complex disorder. Locus heterogeneity is also thought to be present, in which several distinct genes contribute to the disorder, perhaps even within the same family.

Chapters 30 and 31 focus on genetic approaches to depression. Here, a brief summary of the facts follow to facilitate integration with the concepts discussed in the present chapter.

Past linkage studies in unipolar depression suffered from poor design and small numbers of families [20, 21], whereas two state-of-the-art genome-wide linkage scans have recently been published and several others are presently in progress. Zubenko and associates [22] reported several chromosomal loci that may influence the development of recurrent major depressive disorder in 81 families. The highest maximum lod score observed occurred at D2S2321 (205 cM), located 121 kb proximal to the cyclic AMP response element binding protein 1 (CREB1), a ubiquitous nuclear transcription factor [23]. An overall number of 19 chromosomal regions contained linkage peaks that reached genome-wide statistical significance. Six linkage peaks were revealed after an analysis of covariance controlled for the effects of gender and epistatic interaction with the CREB1 locus. Based on a systematic analysis of candidate genes located in the linked chromosomal regions, it is concluded that both gene products deriving from these genes participate in cellular signaling pathways that converge on CREB and allelic variants of downstream target genes of CREB may affect susceptibility to mood disorders. Since CREB is a pivotal regulatory protein in many cell types, additional spatio-temporally specific (protein) factors are likely contribute to the genetic risk in order to specify the depression-associated endophenotypes that constitute a clinically relevant depressive syndrome. The next level of complexity will be reached with the identification of these genetic factors which modify the disease mechanism (as well as treatment response and long-term course of illness) in individual patients with a disorder from the depressive spectrum.

Abkevich and coworkers [24] conducted a genome-wide scan in 1890 individuals from 110 pedigrees with a strong family history of major depression and provided strong evidence for the existence of a sex-specific disposition locus for major depression on chromosome 12q22-12q23.2. Interestingly, a previous linkage analysis for QTLs influencing variation in the personality trait Neuroticism also identified a gender-specific locus on chromosome 12q23.1 [25]. Although the findings of these three linkage analyses require rigorous replication, they confirm previous evidence that one or more genes involved in psychiatric diseases are present on chromosome 12q.

A considerable number of linkage studies have been published for manic-depressive disorder suggesting a number of candidate regions on different chromosomes, including 1q, 4p, 10p, 12q, 13q, 18p, 18q, 21q, 22q and Xq but no bipolar disorder susceptibility gene has been identified as yet (for reviews, see [26, 27]). A recent meta-analysis of all reported genome scans found the strongest evidence for bipolar susceptibility loci on 13q and 22q [28]. The same regions were also implicated in the schizophrenic spectrum disorders, suggesting that certain susceptibility genes may be shared. Additional loci including regions on chromosomes 2p, 4q, 6q, 7q, 8q, 9q, 10q, 14q, 16p, and 17q [29–32] have also been linked to bipolar disorder, but these findings have yet to be replicated by independent studies. However, although some of these chromosomal regions meet strict criteria for significant evidence of linkage, narrowing the linkage regions and identifying candidate genes has proven difficult, and no genes have yet been conclusively demonstrated to affect risk for bipolar disorder. The inconsistencies appear to result

from still widely underestimated genetic heterogeneity, and insufficient statistical power to detect loci with smaller effects.

On the other hand, the clinical (categorical) diagnoses, no matter how carefully assessed, do not reflect neurobiological (dimensional) processes and may therefore not be the appropriate phenotype for genetic analysis. The definition of more homogenous disease phenotypes or clinical subtypes, like the presence of catatonic features or response to anti-bipolar treatment, or functional neuroimaging-derived endophenotypes with less genetic complexity, preferably biologically measurable but not necessarily exclusive for the disease, is required [33]. Chromosomal rearrangements, such as the balanced translocation of chromosomes 1 and 11 which is associated with schizophrenic and affective disorders or other chromosomal aberrations such as the 22q11 microdeletion, may also carry the potential to identify the chromosomal location of a candidate gene (for review, see [34]). Lastly, population isolates may be used to increase the probability of all affected individuals having the same disease alleles.

Because the power of linkage analysis to detect small gene effects is quite limited, at least with realistic cohort sizes, molecular genetic research in depression has primarily relied on association analysis using DNA variants in or near candidate genes with etiological or pathophysiological relevance. Gene variants with a significant impact on the functionality of components of brain neurotransmission, such as the serotonin (5HT) system, are a rational beginning. Based on converging lines of evidence that the 5HT and serotonergic gene expression are involved in a myriad of processes during brain development as well as synaptic plasticity in adulthood, depression-related temperamental predispositions and behavior is likely to be influenced by genetically-driven variability of 5HT function. Consequently, the contribution of genetic variants of the 5HT transporter (5HTT), a protein critically involved in the control of 5HT function, to the risk of mood disorders including depression and bipolar disorder, was explored in several independent population- and family-based studies (for reviews see [35, 36]). Moreover, evidence is accumulating that a polymorphisms in the 5'-flanking transcriptional control region of the 5HTT gene (5HTTLPR) resulting in allelic variation of 5HTT expression and function, is associated with personality traits of negative emotionality including anxiety, depression, and aggressiveness (neuroticism and agreeableness) [37, 38]. The short and long 5HTTLPR variants differentially modulate transcriptional activity of the 5HTT gene promoter, 5HTT protein concentration, 5HT uptake activity in lymphoblastoid cells, mRNA concentrations in the Raphe complex of human postmortem brain, platelet 5HT uptake and content, 5HT system responsiveness elicited by pharmacologic challenge tests, mood changes following tryptophan depletion, and *in vivo* SPECT imaging of human brain 5HTT with the short variant associated with lower 5HTT expression and function.

29.4

Depression-related Traits

A growing body of evidence implicates personality traits such as neuroticism or the anxiety-related cluster in the comorbidity of mood disorders [6, 14, 39]. The dimensional structure of neuroticism comprising fearfulness, depression, negative emotionality, and stress reactivity has been delineated by systematic research. As indexed by the personality scale of neuroticism, general vulnerability is likely to overlap genetically with both anxiety and depression. Separation of depression from depression-related personality disorders in current consensual diagnostic systems therefore enhanced interest in the link between temperament, personality, and mood disorders as well as the impact of this interrelationship on the heterogeneity within diagnostic entities, prediction of long-term course, and treatment response. This concept may predict that when a quantitative trait locus (QTL), such as the 5HTTLPR is found for neuroticism, the same QTL should be associated with symptoms of anxiety and depression [39]. Anxiety and mood disorders are therefore likely to represent the extreme end of variation in negative emotionality. The genetic factor contributing to the extreme ends of dimensions of variation commonly recognized as a disorder may be quantitatively, not qualitatively, different from the rest of the distribution. This possibility has important implications for identifying genes for complex traits related to distinct disorders.

However, the effect sizes for the 5HTTLPR–personality associations indicate that this polymorphism has only a moderate influence on these behavioral predispositions that corresponds to less than 5% of the total variance based on estimates from twin studies using these and related measures which have consistently demonstrated that genetic factors contribute 40–60% of the variance in neuroticism and other related personality traits [38]. The associations represent only a modest share of the genetic contribution to depression- and anxiety-related traits. Additional contributions of comparable size or epistatic interaction have, in fact, been found in studies of other quantitative traits. Thus, the results are consistent with the view that the influence of a single, common polymorphism on continuously distributed traits is likely to be modest, if not minimal.

A modulatory effect of the 5HTTLPR on cortical activity provided the first evidence that genotype–phenotype correlations may be accessible by functional imaging of the brain. Recently, Hariri and associates [40] reported that individuals with one or two copies of the low-activity short 5HTTLPR variant exhibit greater amygdala neuronal activity, as assessed by functional magnetic resonance imaging (fMRI), in response to fearful stimuli compared with individuals homozygous for the high-activity long allele. These findings confirm that genetically-driven variation of serotonergic function contributes to the response of brain regions underlying human emotional behavior and indicate that differential excitability of the amygdala to emotional stimuli may contribute to increased fear and anxiety-related responses.

Variants that change the structure of 5HTT protein are rare and their potential to alter 5HT uptake activity remains to be determined [41–44]. Most of these variants have yet to be explored with respect to a functional effect on transport activity or

association with a behavioral phenotype or disorder. Nevertheless, two non-synonymous single nucleotide polymorphisms (SNPs) that change the coding sequence of the 5HTT were found to segregate in complex serotonergic dysfunction-related phenotypes including obsessive-compulsive disorder (OCD) and other 5HT-spectrum disorders (SSDs) or were associated with severe depression. OCD is characterized by either obsessions or compulsions that cause marked distress and are time-consuming or significantly interfere with an individual's normal routine or functioning. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images that an individual attempts to ignore or suppress, whereas compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession to neutralize or prevent discomfort, worry and anxiety or some dreaded event. OCD often co-occurs with other disorders including depression.

A missense mutation resulting in a conserved Ile425Val substitution in the 5HTT gene was detected in two affected individuals and their family members with OCD and related disorders [45]. Six of seven family members with the variant had OCD or OC personality disorder. In addition, the affected individuals and their immediate family members carrying the Ile425Val variant met diagnostic criteria for other disorders including autism, social phobia, anorexia nervosa, tic disorder, depression, and alcohol abuse/dependence. The evolutionary conserved Ile425Val substitution is located in transmembrane domain 8 (TMD8) and may modify the α -helical secondary structure of the 5HTT protein and consequently alter function. Expression studies of the mutant 5HTT cDNA in human cells demonstrated a gain-of-function via constitutive activation of 5HT transport in a nitric oxide-stimulated pathway resulting in a two-fold increase in 5HT uptake [46]. Taken together, these findings strongly indicate that gain-of-function mutations associated with coding sequence may contribute to the expression of psychopathology related to serotonergic dysfunction in some families. Interestingly, two brothers from one of the families suffering from OCD and autism and carrying the Ile425Val variant also had the long/long 5HTTLPR genotype which was previously found to be associated with or preferentially transmitted in both OCD [47, 48] and autism [49, 50]. Moreover, a conservative Leu255Met substitution located in TMD4 was detected in a patient with delusional depression, who was also found to carry a short/short 5HTTLPR genotype which is implicated in anxiety- and depression-related traits [42]. Possibly, low 5HTT gene expression in interaction with the Leu255Met variant, which is highly conserved among various species, could additively perturb 5HTT function or regulation. These two examples of co-occurrence and possible cooperativity of allelic variation in gene expression and protein structure might represent a “double-hit” with functional consequences in the same gain- and loss-of-function direction for both of these 5HTT gene variations.

Analogous to the 5HTT gene and its allelic variation of expression, a functional single nucleotide polymorphism (SNP, C-1019G) in the transcriptional control region of the gene for the 5HT_{1A} receptor (HTR1A) is associated with anxiety- and depression-related personality traits [51] as well as depression and suicidal ideation. *In vitro* experiments demonstrated that the G variant displays differential binding efficiency of transcriptional regulators (repressors/enhancers) which may lead to

allelic variation of 5HT_{1A} receptor expression and function [52]. Interestingly, the agoraphobic subtype of panic disorder also appears to be associated with HTR1A [53]. These findings further support multiple lines of evidence that implicate the 5HT_{1A} receptor in the pathophysiology of anxiety and depression as well as in the mode of action of anxiolytic and antidepressant drugs. Patients with panic disorder and depression exhibit an attenuation of 5HT_{1A} receptor-mediated hypothermic and neuroendocrine responses, reflecting dysfunction of both pre- and postsynaptic 5HT_{1A} receptors [54, 55]. Likewise, a decrease in ligand binding to 5HT_{1A} receptors as assessed by positron emission tomography has been shown in forebrain areas and in the Raphe of depressed patients [56, 57]. Downregulation and hypo-responsiveness of 5HT_{1A} receptors in patients with major depression are not reversed by antidepressant drug treatment [57–59], thus further supporting the notion that low receptor function is a trait feature and therefore a pathogenetic mechanism of the disease.

29.5

Gene Expression Profiling

Large scale, high throughput, cDNA microarray technology now allows the identification of altered gene expression patterns in human postmortem brain of patients with neuropsychiatric disorders including depression, bipolar disorder, and schizophrenia – an important step in understanding gene function in these complex disorders. Changes in expression of a number of genes have been reported in bipolar disorder. A meta-analysis of studies using microarrays and other techniques has identified modifications in the expression of genes related to neurotransmission, survival of neuronal and glial cells, and signal transduction [60, 61]. Depression, bipolar disorder, and schizophrenia seem to share a number of changes. While bipolar disorder is associated with low expression of several genes and more closely resembles schizophrenia in the overall pattern of changes, depression shows the smallest number of modifications. Intriguingly, decreased glial fibrillary acidic protein (GFAP) levels and numbers of oligodendrocytes were observed in depression, bipolar disorder, and schizophrenia, which suggests that glial dysfunction may be a common cause for all these disorders. These observations match the increasing number of reports that describe glial abnormalities in neuropsychiatric disorders. Since glial cells are central to homeostatic and regulatory processes that affect neuronal development, plasticity, and survival, this concept suggests that glial regulation of nitric oxide, glutamate, dopamine or serotonin neurotransmission, or calcium homeostasis may have special importance for these disorders. Finally, profiling of gene expression patterns and, eventually, proteome maps associated with clinically effective drugs in cell systems and in animal models, represents a complementary approach and may provide new insights into the understanding of drug mechanisms [62–64].

29.6

Functional Genomics and Animal Models

Animal models are fully discussed in Chapter 27. They have become an indispensable tool for studying the biological function of genes that are involved in the pathogenesis of human diseases. They are also essential to the development of novel therapeutic strategies. Quantitative genetic research on animal models consists primarily of inbred strain and selection studies. While comparisons between different inbred strains of mice expose remarkable differences in measures of depression- and anxiety-related behavior, differences within strains can be attributed to environmental influences. Inbred and recombinant inbred strain studies are highly efficient in determining genetic influences for investigating interactions between genotype and environment, and for testing the disposition-stress model.

Mice strains that have been selectively bred to display a phenotype of interest are currently being used to identify genetic loci that contribute to behavioral traits including fearfulness, emotionality, and behavioral despair. However, linkage analyses provide only a rough chromosomal localization, whereas the next step, identifying the relevant genes by positional cloning, remains a challenging task. Since mice and humans share many orthologous genes mapped to synthetic chromosomal regions, it is conceivable that individual genes identified for one or more types of murine fear-related behavior may be developed as animal models for human anxiety. Behavioral parameters can be investigated after chromosomal mapping of polymorphic genes and evaluation of gene function using genetically-engineered mice. Based on the close similarity in the genomes between the two species and the extensive knowledge derived from the completion of the Mouse Genome Project, mouse mutants have become the ideal model. Mice have almost the same genome size and gene number as humans and with the introduction of gene targeting techniques the mouse is the only mammal uniting the top-down and bottom-up genetic approach, from phenotype to gene and from gene to phenotype, respectively.

As an example, targeted inactivation of the 5HTT gene in mice has been changing current views of the relevance of adaptive 5HT uptake function and 5HT homeostasis in the developing human brain as well as the molecular processes underlying anxiety-related traits [65–69], and 5HT-spectrum disorders including depression and bipolar disorder [36]. Despite growing evidence for a potential role of 5HTT in the integration of synaptic connections in the rodent, nonhuman primate, and human brain during critical periods of development, adult life, and old age, knowledge of the molecular mechanisms involved in these fine-tuning processes remain fragmentary [64, 68–71]. Thus, the combination of elaborate genetic and behavioral analyses may lead to the identification of many genes with effects on variation and development of murine depression- and anxiety-related behavior.

The converging lines of evidence for 5HT_{1A} receptor deficiency or dysfunction being involved in mood and anxiety disorders encouraged investigators to genetically manipulate the 5HT_{1A} receptor in mice. As anticipated, mice with a targeted inactivation of the 5HT_{1A} receptor gene display a spontaneous phenotype that is

associated with a gender-modulated and gene/dose-dependent increase in anxiety-related behavior and stress reactivity in several conflict paradigms [72]. Activation of presynaptic 5HT_{1A} receptors provides the brain with an auto-inhibitory feedback system controlling 5HT neurotransmission. Thus, enhanced anxiety- and depression-related behavior most likely represents a consequence of increased terminal 5HT availability resulting from the lack or reduction in presynaptic somatodendritic 5HT_{1A} autoreceptor negative feedback function. This mechanism is also consistent with recent theoretical models of fear and anxiety that are primarily based upon pharmacologically-derived data. The cumulative reduction in serotonergic impulse flow to septohippocampal and other limbic and cortical areas involved in the control of anxiety is believed to explain the anxiolytic effects of ligands with selective affinity for the 5HT_{1A} receptor in some animal models of anxiety- and depression-related behavior.

Recent advances in conditional knockout and knockin (and overexpression) techniques such as the 5HT_{1A} conditional knockout and 5HT_{1A} overexpressing mice are increasingly impacting upon our understanding of the neurobiological and developmental basis of depression- and anxiety-related behavior. Since the 5HT_{1A} receptor is expressed in different brain subsystems, it is of interest to clarify whether pre- or post-synaptic receptors are required to maintain normal expression of anxiety-related behavior in both humans and animal models. With an elegant conditional rescue approach, Gross and coworkers [73] showed that expression of the 5HT_{1A} receptor in the hippocampus and cortex but not in the Raphe nuclei is required to rescue the behavioral phenotype of 5HT_{1A} knockout mice. The findings indicate that deletion of the 5HT_{1A} receptor in mice, specifically in forebrain structures, results in a robust anxiety-related phenotype and that this phenotype in 5HT_{1A} knockout mice is caused by the absence of the receptor during a critical period of postnatal development, whereas inactivation of 5HT_{1A} receptor in adulthood does not affect anxiety. Intriguingly, mice overexpressing the 5HT_{1A} receptor during brain development display attenuation in anxiety-related behavior. Although 5HT_{1A} receptor expression normalizes in adulthood the alterations in behavior and 5HT system function persist [74]. These findings strongly support a central role for 5HT in the early development of neurocircuits mediating emotionality [72]. Although there is converging evidence that the 5HT_{1A} receptor mediates anxiety-related behavior, the neuro-developmental mechanisms that render 5HT_{1A} receptor-deficient mice more anxious, are highly complex and remain to be elucidated in detail.

Finally, anxiety disorders and depression are known to be influenced not only by environmental stressors but also by each individual's genetic background. The mouse model also permits analysis of synthetic mutant phenotypes or polygenic characteristics based on epistatic interaction [75]. However, the majority of neural substrates and circuitries that regulate emotional processes or cause mood disorders remain remarkably elusive. Among the reasons for the lack of progress are several conceptual deficiencies regarding the psychobiology of emotionality and behavioral despair, which make it difficult to develop and validate reliable models of depression. The clinical presentation of mood disorders and the lack of consensus regarding

clinical categories results in further complications for the development of mouse models for depressive disorders. The dilemma that no single paradigm mimics the diagnostic entities or treatment response of mood disorders, may reflect the inadequacy of classification rather than the failure to develop valid mouse models. The understanding of both gene \times gene and gene \times environment interactions will be the key to developing future psychiatric neurosciences based upon functional genomics.

29.7

Gene \times Environment Interaction

Investigations in rats have shown that maternal behavior has long-lasting consequences on anxiety-like behavior of the offspring. Maternal separation for several hours a day during the early postnatal period results in increased anxiety-like behaviors as well as increased stress hormone reactivity in adult animals [76]. Similarly, pups that are raised by mothers that display low licking-and-grooming behavior show higher levels of anxiety-like behavior than pups raised by mothers that display high licking-and-grooming behavior and cross fostering studies show that these influences are primarily environmental [77, 78]. Cross fostering offspring of low licking-and-grooming mothers to high licking-and-grooming mothers is able to impart low anxiety-like behavior to the offspring, whereas the converse does not influence this behavior. Offspring of high licking-and-grooming mothers raised by low licking-and-grooming mothers do not show high anxiety-like behavior, suggesting that specific genes inherited by the high licking-and-grooming offspring protect them from the effects of low licking-and-grooming mothering. Furthermore, Francis et al. [79] have shown that the effect of high licking-and-grooming can be passed from one generation to the next. Females raised by high licking-and-grooming mothers themselves become high licking-and-grooming mothers and go on to produce low-anxiety offspring regardless of whether their biological mother showed low or high licking-and-grooming. This epigenetic inheritance of anxiety-like behavior underscores the power that environmental influences can exert to persistently remodel circuits in the brain during early development.

Studies using mice of defined genetic backgrounds have also begun to shed light on the molecular mechanisms of specific gene \times environment interactions. Anisman et al. [80] found that mice of the low licking-and-grooming Balb/c inbred strain cross-fostered at birth to the high licking-and-grooming C57BL/6 inbred strain display improvements in a hippocampal-dependent memory task. Because the reverse cross-fostering, where C57BL/6 pups are raised by Balb/c mothers, does not alter the behavior of C57BL/6 mice, it appears that the C57BL/6 genetic background protects the pups from the effects of a Balb/c maternal environment. However, by transplanting C57BL/6 embryos into Balb/c foster mothers shortly after conception, Francis et al. [81] were able to show that a combined prenatal and postnatal Balb/c maternal environment is sufficient to confer Balb/c behavior on C57BL/6 offspring, demonstrating that intra- and extra-uterine maternal signals

can synergistically induce long-term plastic changes in anxiety- and depression-related neurocircuits.

Since the genetic basis of present-day temperamental and behavioral traits is already laid out in all mammalian species including mice and may reflect selective forces among our remote ancestors, research efforts have recently been focused on nonhuman primates, especially rhesus macaques. In this primate model environmental influences are probably less complex, can be more easily controlled for, and thus less likely to confound associations between behavior and genes. All forms of emotionality in rhesus monkeys – major categories are anxiety and aggression – appear to be modulated by environmental factors, and marked disruptions to the mother–infant relationship are likely to confer increased risk.

In rhesus monkeys, maternal separation and replacement of the mother by an inanimate surrogate mother during the first months of life results in long-term consequences for the functioning of the central 5HT system, defects in peer interaction and social adaptation, and is associated with increases in anxiety- and depression-related behaviors like rocking and grooming [82, 83]. In bonnet macaques, increasing the unpredictability associated with foraging for food causes mothers to rear offspring that have abnormal stress hormone and anxiety responses in adulthood [84]. These studies suggest that early environmental trauma can directly induce long-term plastic changes in the brain that alter anxiety-related responses in adulthood.

One of the most replicated findings in psychobiology is the observation of lower 5HIAA, the major metabolite of 5HT, in the brain and cerebrospinal fluid (CSF) in impulsive aggression and suicidal behavior. In rhesus monkey brain 5HT turnover, as measured by cisternal CSF 5HIAA concentrations, shows a strong heritable component that is trait-like, with demonstrated stability over the lifespan of an individual [83, 85, 86]. Early experiences have long-term consequences for the function of the central 5HT system, as indicated by robustly altered CSF 5HIAA levels, as well as anxiety, depression, and aggression-related behavior in rhesus monkeys deprived of their mother at birth and reared only with peers. This model of maternal separation was therefore used to study the gene \times environment interaction by testing for associations between central 5HT turnover and polymorphism in the transcriptional control region of the 5HTT gene [87]. The findings suggest that the rh5HTTLPR genotype is predictive of CSF 5HIAA concentrations, but that early experiences make unique contributions to variation in later 5HT system function and thus provide evidence of an environment-dependent association between the 5HTT gene and a direct measure of brain 5HT function. The consequences of deleterious early experiences of maternal separation seem consistent with the notion that the 5HTTLPR may influence the risk for mood disorders.

The interactive effect of the rh5HTTLPR genotype and early rearing environment on social play and aggression was also explored [88]. Infant rhesus monkeys homozygous for the long variant were more likely to engage in rough play than were long/short individuals with a significant interaction between 5HTT genotype and rearing condition. Peer-reared infants carrying the short variant were less likely

to play with peers than those homozygous for the long allele, whereas the rh5HTTLPR genotype had no effect on the incidence of social play among mother-reared monkeys. Socially-dominant mother-reared monkeys were more likely than their peer-reared counterparts to engage in aggression. In contrast, peer-reared but not mother-reared monkeys with the low-activity short allele exhibited more aggressive behaviors than their long/long counterparts. This genotype by rearing interaction for aggressive behavior indicates that peer-reared subjects with the short allele, while unlikely to win in a competitive encounter, are more inclined to persist in aggression once it begins. Moreover, high composite scores for alcohol intake and alcohol-elicited aggression are associated with the low-activity short rh5HTTLPR variant in male rhesus monkeys, a potential model for type II alcoholism [89].

Taken together, these findings provide evidence of an environment-dependent association between allelic variation of 5HTT expression and central 5HT function, and illustrate the possibility that specific genetic factors play a role in 5HT-mediated behavior in primates. Because rhesus monkeys exhibit temperamental and behavioral traits that parallel anxiety, depression, and aggression-related personality dimensions associated in humans with the low-activity 5HTTLPR variant, it may be possible to search for evolutionary continuity in this genetic mechanism for individual differences. Nonhuman primate studies may also be useful in the search to identify environmental factors that either compound the vulnerability conferred by a particular genetic make-up or, conversely, act to improve the behavioral outcome associated with a distinct genetic make-up.

Consequently, it is increasingly accepted that much of the impact of genes on emotionality including anxiety and depression depends on interactions between genes and the environment. Such interactions would lead to the expression of environmental effects only in the presence of a permissive genetic background. Not unexpected, a recent study by Caspi and coworkers [90] robustly confirmed that individuals with one or two short versions of the 5HTTLPR are up to two-fold more likely to become depressed after stressful events such as bereavement, romantic disasters, illnesses, or losing their job. Moreover, childhood maltreatment significantly increased the probability of developing depressive syndromes in later life in individuals with the low-activity short allele of the 5HTTLPR. These results further support the notion that a combination of genetic disposition and specific life events may interact to facilitate the development of mental illness. What went largely unnoticed, though, were the implications for the relevance of studying the genetics of personality. Depression is strongly associated with anxiety- and depression-related traits, the factual personality dimensions that have been linked to allelic variation of the 5HTT. Given the high comorbidity between anxiety and depression and the evidence for their modulation by common genetic factors [91], it is likely that a predisposition to mood disorders will also be determined by environmental influences whose impact on the brain is under genetic control.

Another finding by Caspi et al. [90] that early trauma inflicted by childhood maltreatment interacts with allelic variation of 5HTT function to increase vulnerability to the development of mood disorders, is particularly interesting. A remarkable body of evidence suggests that emotionality and stress reactivity can

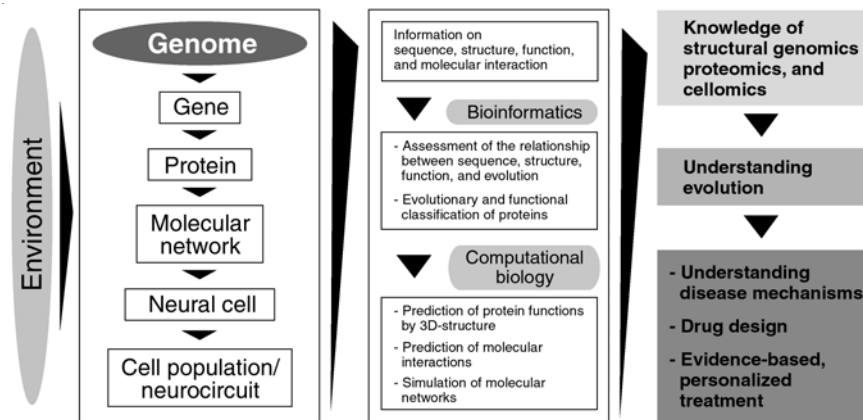


Figure 29.1 Transition from genomics to proteomics and cellomics

be influenced by experiences early in life and it has long been supposed that severe early life trauma may increase the risk for anxiety and affective disorders [92]. For example, adults who had experienced four out of a list of seven severe early traumatic events showed a more than four-fold increased risk for depressive symptoms and about a 12-fold increased risk for attempted suicide [93]. No direct correlation between any specific childhood trauma and a specific adult anxiety or mood disorder could be established however, suggesting that other, possibly genetic, factors determine the precise pathology that is precipitated by the traumatic event. The observation that during early developmental stages individuals are particularly susceptible to adverse environmental influences is confirmed by animal studies that have demonstrated the influential effects of the quality of maternal care on life-long emotional behavior and brain functioning.

29.8 Bioinformatics and Computational Biology

The major challenge for bioinformatics as applied to the elucidation of neuro-circuitries of emotionality and brain pathology associated with mood disorders, will be the shift from the analysis of gene sequence and protein structure to gene and protein function as well as to the understanding of disease mechanisms (Figure 8.1). In order to achieve this goal the application of biological knowledge to the elucidation of functional information will be essential. The sequel to the gene knowledge spiral will therefore require extraction and integration from experimental data, construction of gene networks, and the creation of functional information by feedback from simulation to empirical approaches. The various types of genes involved include those representing structural constituents of neural cells, those that control biochemical reactions within cells, and those that regulate the expression of other genes. All these genes and protein products interact and form a network

in any given neural cell in which the expression of transcription factors controls the expression of other genes. The information gained from these gene networks will facilitate the assessment of sequential changes in gene transcript levels, protein complex formation and interaction of protein complexes, metabolic reactions within the cell, and the effects of regulatory and structural variants of specific genes in relation to the behavioral outcome. Following development of models incorporating this knowledge and simulation of gene \times gene and protein \times protein interactions, it will be possible to predict the consequences of gene variations such as SNPs and polymorphic repeats as well as the efficacy and adverse reactions of therapeutic drugs achieving evidence-based personalized antidepressant and anxiolytic treatment.

29.9 Conclusion

Although monoaminergic dysfunction is likely to occur in depression, etiopathogenetic mechanisms continue to be inadequately understood at the neuronal and molecular level. A complementary approach to genetic studies of depression and related disorders involves investigation of genes and their protein products (i.e. construction of transcriptome and proteome maps) implicated in the brain neurocircuitries of emotionality and behavioral despair in animal models. Based on converging lines of evidence that genetically-driven variability of expression and function of proteins which regulate the function of brain neurotransmitter systems (e.g. receptors, ion channels, transporters, and enzymes), is associated with complex behavioral traits, the emphasis of research is now on the molecular basis of depression- and anxiety-related behaviors in rodents and, increasingly, nonhuman primates as well as emotional and cognitive endophenotypes in healthy individuals and patient populations.

More functionally relevant polymorphisms in genes within a single neurotransmitter system, or in genes which comprise a functional unit in their concerted actions, need to be identified and assessed in both large population- and family-based association studies that carefully minimize stratification artifacts, and the complex interactions of multiple loci also need to be elucidated. It is now generally accepted that even pivotal regulatory proteins of neurotransmission, such as neurotransmitter-modifying enzymes, neurotrophin, receptors, ion channels, transporters, mediators of intracellular signaling, and transcription factors will have only a modest impact which may vary considerably among different patient populations, while noise from non-genetic mechanisms is likely to obstruct identification of relevant genes. Although current methods to elucidate the role of environmental stressors in behavioral and psychiatric genetics are largely indirect and incomplete, the most relevant consequence of gene identification for behavioral traits related to depression may be that it will provide the tools required to systematically clarify the effects of both gene \times gene and gene \times environment interactions and to apply this advanced knowledge to the design of preventive therapeutic strategies in addition to those for manifest disease.

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References

- 1 FARMER, A., HARRIS, T., REDMAN, K., SADLER, S., MAHMOOD, A., MCGUFFIN, P., Cardiff Depression Study: A sib-pair study of life events and familiarity in major depression. *Br. J. Psychiatry* **2000**, *176*, 150–155.
- 2 HARRINGTON, R. C., RUTTER, M., WEISSMAN, M., Psychiatric disorders in the relatives of depressed probands I: comparison of pre-pubertal, adolescent and early adult onset cases. *J. Affect Disord.* **1997**, *42*, 9–22.
- 3 SULLIVAN, P. F., NEALE, M. C., KENDLER, K. S., Genetic epidemiology of major depression: review and meta-analysis. *Am. J. Psychiatry* **2000**, *157*, 1552–1562.
- 4 KOVACS, M., DEVLIN, B., POLLOCK, M., RICHARDS, C., MUKERJI, P., A controlled family history study of childhood-onset depressive disorder. *Arch. Gen. Psychiatry* **1997**, *54*, 613–623.
- 5 MERIKANGAS, K. R., CHAKRAVARTI, A., MOLDIN, S. O., et al., Future of genetics of mood disorders research. *Biol. Psychiatry* **2002**, *52*, 457–477.
- 6 THAPAR, A., MCGUFFIN, P., Anxiety and depressive symptoms in childhood – a genetic study of comorbidity. *J. Child Psychol. Psychiatry* **1997**, *38*, 651–656.
- 7 JONES, I., CRADDOCK, N., Candidate gene studies of bipolar disorder. *Ann. Med.* **2001**, *33*, 248–256.
- 8 KENDLER, K. S., Major depression and the environment: a psychiatric genetic perspective. *Pharmacopsychiatry* **1998**, *31*, 5–9.
- 9 MALHI, G. S., MOORE, J., MCGUFFIN, P., The genetics of major depressive disorder. *Curr. Psychiat. Rep.* **2000**, *2*, 165–169.
- 10 KENDLER, K. S., NEALE, M. C., SULLIVAN, P., COREY, L. A., GARDNER, C. O., PRESCOTT, C. A., A population-based twin study in women of smoking initiation and nicotine dependence. *Psychol. Med.* **1999**, *29*, 299–308.
- 11 LYONS, M. J., EISEN, S. A., GOLDBERG, J., et al., A registry-based twin study of depression in men. *Arch. Gen. Psychiatry* **1998**, *55*, 468–472.
- 12 MCGUFFIN, P., KATZ, R., WATKINS, S., RUTHERFORD, J., A hospital-based twin register of the heritability of DSM-IV unipolar depression. *Arch. Gen. Psychiatry* **1996**, *53*, 129–136.
- 13 SILBERG, J., PICKLES, A., RUTTER, M., et al., The influence of genetic factors and life stress on depression among adolescent girls. *Arch. Gen. Psychiatry* **1999**, *56*, 225–232.
- 14 KENDLER, K. S., WALTERS, E. E., NEALE, M. C., KESSLER, R. C., HEATH, A. C., EAVES, L. J., The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Arch. Gen. Psychiatry* **1995**, *52*, 374–383.
- 15 KENDLER, K. S., KESSLER, R. C., WALTERS, E. E., et al., Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am. J. Psychiatry* **1995**, *152*, 833–842.
- 16 KENDLER, K. S., KARKOWSKI, L. M., PRESCOTT, C. A., Causal relationship between stressful life events and the onset of major depression. *Am. J. Psychiatry* **1999**, *156*, 837–841.
- 17 THAPAR, A., HAROLD, G., MCGUFFIN, P., Life events and depressive symptoms in childhood – shared genes or shared adversity? A research note. *J. Child Psychol. Psychiatry* **1998**, *39*, 1153–1158.
- 18 TAYLOR, L., FARAONE, S. V., TSUANG, M. T., Family, twin, and adoption studies of

- bipolar disease. *Curr. Psychiat. Rep.* **2002**, 4, 130–133.
- 19 CRADDOCK, N., KHODEL, V., VAN EERDEWEGH, P., REICH, T., Mathematical limits of multilocus models: the genetic transmission of bipolar disorder. *Am. J. Hum. Genet.* **1995**, 57, 690–702.
 - 20 NEISWANGER, K., ZUBENKO, G. S., GILES, D. E., FRANK, E., KUPFER, D. J., KAPLAN, B. B., Linkage and association analysis of chromosomal regions containing genes related to neuroendocrine or serotonin function in families with early-onset, recurrent major depression. *Am. J. Med. Genet.* **1998**, 81, 443–449.
 - 21 BALCIUNIENE, J., YUAN, Q. P., ENGSTROM, C., et al., Linkage analysis of candidate loci in families with recurrent major depression. *Mol. Psychiatry* **1998**, 3, 162–168.
 - 22 ZUBENKO, G. S., MAHER, B., HUGHES 3RD, H. B., et al., Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. *Am. J. Med. Genet.* **2003**, 123B, 1–18.
 - 23 ZUBENKO, G. S., HUGHES 3RD, H. B., STIFFLER, J. S., et al., Sequence variations in CREB1 cosegregate with depressive disorders in women. *Mol. Psychiatry* **2003**, 8, 611–618.
 - 24 ABKEVICH, V., CAMP, N. J., HENSEL, C. H., et al., Predisposition locus for major depression at chromosome 12q22-12q23.2. *Am. J. Hum. Genet.* **2003**, 73, 1271–1281.
 - 25 FULLERTON, J., CUBIN, M., TIWARI, H., et al., Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative-trait loci that influence variation in the human personality trait neuroticism. *Am. J. Hum. Genet.* **2003**, 72, 879–890.
 - 26 BARON, M., Manic-depression genes and the new millennium: poised for discovery. *Mol. Psychiatry* **2002**, 7, 342–358.
 - 27 SKLAR, P., Linkage analysis in psychiatric disorders: the emerging picture. *Annu. Rev. Genomics Hum. Genet.* **2002**, 3, 371–413.
 - 28 BADNER, J. A., GERSHON, E. S., Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol. Psychiatry* **2002**, 7, 342–358.
 - 29 DICK, D., FOROUD, T., FLURY, L., et al., Genome-wide linkage analyses of bipolar disorder: a new sample of 250 NIMH genetics initiative pedigrees. *Am. Hum. Gen.* **2003**, 73, 107–114.
 - 30 NURNBERGER JR., J. I., FOROUD, T., Genetics of bipolar affective disorder. *Curr. Psychiat. Rep.* **2000**, 2, 147–157.
 - 31 LIU, J., JUO, S. H., DEWAN, A., et al., Evidence for a putative bipolar disorder locus on 2p13–16 and other potential loci on 4q31, 7q34, 8q13, 9q31, 10q21–24, 13q32, 14q21 and 17q11–12. *Mol. Psychiatry* **2003**, 8, 333–342.
 - 32 BENNETT, P., SEGURADO, R., JONES, I., et al., The Wellcome trust UK–Irish bipolar affective disorder sibling-pair genome screen: first stage report. *Mol. Psychiatry* **2002**, 7, 189–200.
 - 33 LEBOYER, M., BELLIVIER, F., NOSTEN-BERTRAND, M., JOUVENT, R., PAULS, D., MALLET, J., Psychiatric genetics: search for phenotypes. *Trends Neurosci.* **1998**, 21, 102–105.
 - 34 MACINTYRE, D. J., BLACKWOOD, D. H., PORTEOUS, D. J., PICKARD, B. S., MUIR, W. J., Chromosomal abnormalities and mental illness. *Mol. Psychiatry* **2003**, 8, 275–287.
 - 35 LESCH, K. P., Neuroticism and serotonin: a developmental genetic perspective. In PLOMIN, R., DEFRIES, J., CRAIG, I., MCGUFFIN, P. (Eds.), *Behavioral Genetics in the Postgenomic Era*. Washington, DC: American Psychiatric Press, **2002**, 389–423.
 - 36 LESCH, K. P., Serotonin transporter: from genomics and knockouts to behavioral traits and psychiatric disorders. In SULSER, F. (Ed.), *Molecular Genetics of Mental Disorders*. London: Martin Dunitz Publishers, **2001**, 221–267.
 - 37 GREENBERG, B. D., LI, Q., LUCAS, F. R., et al., Association between the serotonin transporter promoter polymorphism and personality traits in a primarily female population sample. *Am. J. Med. Genet.* **2000**, 96, 202–216.
 - 38 LESCH, K. P., BENDEL, D., HEILS, A., et al., Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **1996**, 274, 1527–1531.
 - 39 LESCH, K. P., Gene–environment interaction in generalized anxiety disorder.

- In NUTT, D., RICKELS, R., STEIN, D. (Eds.), *Generalized Anxiety Disorders: Symptomatology, Pathogenesis and Management*. London: Dunitz, **2002**, 71–87.
- 40 HARIRI, A. R., MATTAY, V. S., TESSITORE, A., et al., Serotonin transporter genetic variation and the response of the human amygdala. *Science* **2002**, 297, 400–403.
 - 41 GIATT, C. E., DEYOUNG, J. A., DELGADO, S., et al., Screening a large reference sample to identify very low frequency sequence variants: comparisons between two genes. *Nature Genet.* **2001**, 27, 435–438.
 - 42 DI BELLA, D., CATALANO, M., BALLING, U., SMERALDI, E., LESCH, K. P., Systematic screening for mutations in the coding region of the 5-HTT gene using PCR and DGGE. *Am. J. Med. Genet.* **1996**, 67, 541–545.
 - 43 LESCH, K. P., GROSS, J., WOLOZIN, B. L., MURPHY, D. L., RIEDERER, P., Primary structure of the serotonin transporter in unipolar depression and bipolar disorder. *Biol. Psychiatry* **1995**, 37, 215–223.
 - 44 ALTEMUS, M., MURPHY, D. L., GREENBERG, B., LESCH, K. P., Intact coding region of the serotonin transporter in obsessive-compulsive disorder. *Am. J. Med. Genet.* **1996**, 67, 104–109.
 - 45 OZAKI, N., GOLDMAN, D., KAYE, W. H., GREENBERG, B. D., MURPHY, D. L., Functional missense mutation in the serotonin transporter gene associated with obsessive-compulsive disorder and related neuropsychiatric disorders. *Mol. Psychiatry* **2003**, 8, 933–936.
 - 46 LESCH, K. P., MURPHY, D. L., Molecular genetics of transporters for norepinephrine, dopamine, and serotonin in behavioral traits and complex diseases. In BRÖERS, S., WAGNER, C. A. (Eds.), *Membrane Transport Diseases: Molecular Basis of Inherited Transport Defects*. New York: Kluwer Academic/Plenum, **2003**, 349–364.
 - 47 BENGEL, D., GREENBERG, B., CORA-LOCATELLI, G., et al., Association of the serotonin transporter promoter regulatory region polymorphism and obsessive-compulsive disorder. *Mol. Psychiatry* **1999**, 4, 463–466.
 - 48 MCDUGGLE, C. J., EPPERSON, C. N., PRICE, L. H., GELERNTER, J., Evidence for linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and obsessive compulsive disorder. *Mol. Psychiatry* **1998**, 3, 270–273.
 - 49 KLAUCK, S. M., POUSTKA, F., BENNER, A., LESCH, K. P., POUSTKA, A., Serotonin transporter (5-HTT) gene variants associated with autism? *Hum. Mol. Genet.* **1997**, 6, 2233–2238.
 - 50 YIRMIYA, N., PILOWSKY, T., NEMANOV, L., et al., Evidence for an association with the serotonin transporter promoter region polymorphism and autism. *Am. J. Med. Genet.* **2001**, 105, 381–386.
 - 51 STROBEL, A., GUTKNECHT, L., ROTHE, C., et al., Allelic variation in 5-HT1A receptor expression is associated with anxiety- and depression-related personality traits. *J. Neural Transm.* **2003**, 110, 1445–1453.
 - 52 LEMONDE, S., MORRIS, S. J., BAKISH, D., et al., Abrogated protein–DNA interactions at a C(-1019)G polymorphism in the 5-HT1A receptor gene associated with major depression. *Soc. Neurosci. Meeting* **2000**, 26, 1850.
 - 53 ROTHE, C., GUTKNECHT, L., FREITAG, C. M., et al., Association of a functional 1019C>G 5-HT1A receptor gene polymorphism with panic disorder with agoraphobia. *Int. J. Neuropsychopharmacol.* **2004**, 7, 189–192.
 - 54 LESCH, K. P., MAYER, S., DISSELKAMP-TIETZE, J., et al., 5-HT1A receptor responsivity in unipolar depression. Evaluation of ipsapirone-induced ACTH and cortisol secretion in patients and controls. *Biol. Psychiatry* **1990**, 28, 620–628.
 - 55 LESCH, K. P., WIESMANN, M., HOH, A., et al., 5-HT1A receptor–effector system responsivity in panic disorder. *Psychopharmacology (Berl.)* **1992**, 106, 111–117.
 - 56 DREVETS, W. C., FRANK, E., PRICE, J. C., et al., PET imaging of serotonin 1A receptor binding in depression. *Biol. Psychiatry* **1999**, 46, 1375–1387.
 - 57 SARGENT, P. A., KJAER, K. H., BENCH, C. J., et al., Brain serotonin1A receptor binding measured by positron emission tomography with [¹¹C]WAY-100635: effects of depression and antidepressant treatment. *Arch. Gen. Psychiatry* **2000**, 57, 174–180.
 - 58 LESCH, K. P., DISSELKAMP-TIETZE, J., SCHMIDTKE, A., 5-HT1A receptor function in depression: effect of chronic

- amitriptyline treatment. *J. Neural Transm. Gen. Sect.* **1990**, *80*, 157–161.
- 59 LESCH, K. P., HOH, A., SCHULTE, H. M., OSTERHEIDER, M., MÜLLER, T., Long-term fluoxetine treatment decreases 5-HT_{1A} receptor responsivity in obsessive-compulsive disorder. *Psychopharmacology (Berl.)* **1991**, *105*, 415–420.
 - 60 KNABLE, M. B., TORREY, E. F., WEBSTER, M. J., BARTKO, J. J., Multivariate analysis of prefrontal cortical data from the Stanley Foundation Neuropathology Consortium. *Brain Res. Bull.* **2001**, *55*, 651–659.
 - 61 KNABLE, M. B., BARCI, B. M., BARTKO, J. J., WEBSTER, M. J., TORREY, E. F., Molecular abnormalities in the major psychiatric illnesses: Classification and Regression Tree (CRT) analysis of post-mortem prefrontal markers. *Mol. Psychiatry* **2002**, *7*, 392–404.
 - 62 BOSETTI, F., SEEMANN, R., BELL, J. M., et al., Analysis of gene expression with cDNA microarrays in rat brain after 7 and 42 days of oral lithium administration. *Brain Res. Bull.* **2002**, *57*, 205–209.
 - 63 LESCH, K. P., SCHMITT, A., Antidepressants and gene expression profiling: how to SNARE novel drug targets. *Pharmacogenomics J.* **2002**, *2*, 346–348.
 - 64 LESCH, K. P., Serotonergic gene expression and depression: implications for developing novel antidepressants. *J. Affect Disord.* **2001**, *62*, 57–76.
 - 65 MURPHY, D. L., LI, Q., ENGEL, S., et al., Genetic perspectives on the serotonin transporter. *Brain Res. Bull.* **2001**, *56*, 487–494.
 - 66 HOLMES, A., YANG, R. J., LESCH, K. P., CRAWLEY, J. N., MURPHY, D. L., Mice lacking the serotonin transporter exhibit abnormalities in exploratory locomotion and anxiety-like behavior. *Neuropsychopharmacology* **2003**, *28*, 2077–2088.
 - 67 BENGEL, D., MURPHY, D. L., ANDREWS, A. M., et al., Altered brain serotonin homeostasis and locomotor insensitivity to 3, 4-methylenedioxymethamphetamine (“Ecstasy”) in serotonin transporter-deficient mice. *Mol. Pharmacol.* **1998**, *53*, 649–655.
 - 68 PERSICO, A. M., REVAY, R. S., MÖSSNER, R., et al., Barrel pattern formation in somatosensory cortical layer IV requires serotonin uptake by thalamocortical endings, while vesicular monoamine release is necessary for development of supragranular layers. *J. Neurosci.* **2001**, *21*, 6862–6873.
 - 69 SALICHON, N., GASPARD, P., UPTON, A. L., et al., Excessive activation of serotonin (5-HT) 1B receptors disrupts the formation of sensory maps in monoamine oxidase a and 5-HT transporter knock-out mice. *J. Neurosci.* **2001**, *21*, 884–896.
 - 70 PERSICO, A. M., BALDI, A., DELL’ACQUA, M. L., et al., Reduced programmed cell death in brains of serotonin transporter knockout mice. *Neuroreport* **2003**, *14*, 341–344.
 - 71 GASPARD, P., CASES, O., MAROTEAUX, L., The developmental role of serotonin: news from mouse molecular genetics. *Nature Rev. Neurosci.* **2003**, *4*, 1002–1012.
 - 72 LESCH, K. P., ZENG, Y., REIF, A., GUTKNECHT, L., Anxiety-related traits in mice with modified genes of the serotonergic pathway. *Eur. J. Pharmacol.* **2003**, *480*, 185–204.
 - 73 GROSS, C., ZHUANG, X., STARK, K., et al., Serotonin_{1A} receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* **2002**, *416*, 396–400.
 - 74 THEURING, F., Reduced anxiety-related behaviour in transgenic mice over-expressing serotonin 1A receptors. *Pharmacopsychiatry* **2003**, *36*, 267–268.
 - 75 MURPHY, D. L., UHL, G., HOLMES, A., et al., Experimental gene interaction studies with SERT mutant mice as models for human polygenic and epistatic traits and disorders. *Genes Brain Behav.* **2003**, *2*, 350–364.
 - 76 KALINICHEV, M., EASTERLING, K. W., HOLTZMAN, S. G., Early neonatal experience of Long-Evans rats results in long-lasting changes in reactivity to a novel environment and morphine-induced sensitization and tolerance. *Neuropsychopharmacology* **2002**, *27*, 518–533.
 - 77 CALDJI, C., TANNENBAUM, B., SHARMA, S., FRANCIS, D., PLOTSKY, P. M., MEANEY, M. J., Maternal care during infancy regulates the development of neural systems mediating the expression of

- fearfulness in the rat. *Proc. Natl. Acad. Sci. USA* **1998**, 95, 5335–5340.
- 78 LIU, D., DIORIO, J., DAY, J. C., FRANCIS, D. D., MEANEY, M. J., Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neurosci.* **2000**, 3, 799–806.
 - 79 FRANCIS, D., DIORIO, J., LIU, D., MEANEY, M. J., Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* **1999**, 286, 1155–1158.
 - 80 ANISMAN, H., ZAHARIA, M. D., MEANEY, M. J., MERALI, Z., Do early-life events permanently alter behavioral and hormonal responses to stressors? *Int. J. Dev. Neurosci.* **1998**, 16, 149–164.
 - 81 FRANCIS, D. D., SZEGDA, K., CAMPBELL, G., MARTIN, W. D., INSEL, T. R., Epigenetic sources of behavioral differences in mice. *Nature Neurosci.* **2003**, 6, 445–446.
 - 82 HARLOW, H. F., DODSWORTH, R. O., HARLOW, M. K., Total social isolation in monkeys. *Proc. Natl. Acad. Sci. USA* **1965**, 54, 90–97.
 - 83 HIGLEY, J. D., SUOMI, S. J., LINNOILA, M., CSF monoamine metabolite concentrations vary according to age, rearing, and sex, and are influenced by the stressor of social separation in rhesus monkeys. *Psychopharmacology* **1991**, 103, 551–556.
 - 84 ROSENBLUM, L. A., FORGER, C., NOLAND, S., TROST, R. C., COPLAN, J. D., Response of adolescent bonnet macaques to an acute fear stimulus as a function of early rearing conditions. *Dev. Psychobiol.* **2001**, 39, 40–45.
 - 85 HIGLEY, J. D., THOMPSON, W. W., CHAMPOUX, M., et al., Paternal and maternal genetic and environmental contributions to cerebrospinal fluid monoamine metabolites in rhesus monkeys (*Macaca mulatta*). *Arch. Gen. Psychiatry* **1993**, 50, 615–623.
 - 86 KRAEMER, G. W., EBERT, M. H., SCHMIDT, D. E., MCKINNEY, W. T., A longitudinal study of the effect of different social rearing conditions on cerebrospinal fluid norepinephrine and biogenic amine metabolites in rhesus monkeys. *Neuropsychopharmacology* **1989**, 2, 175–189.
 - 87 BENNETT, A. J., LESCH, K. P., HEILS, A., et al., Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol. Psychiatry* **2002**, 7, 118–122.
 - 88 BARR, C. S., NEWMAN, T. K., BECKER, M. L., et al., The low activity variant of the serotonin transporter gene promoter is associated with decreased social play and increased aggression in rhesus macaques. *Behav. Brain Res.* **2003**, 2, 336–340.
 - 89 BARR, C. S., NEWMAN, T. K., BECKER, M. L., et al., Serotonin transporter gene variation is associated with alcohol sensitivity in rhesus macaques exposed to early-life stress. *Alcohol Clin. Exp. Res.* **2003**, 27, 812–817.
 - 90 CASPI, A., SUGDEN, K., MOFFITT, T. E., et al., Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **2003**, 301, 386–389.
 - 91 KENDLER, K. S., Major depression and generalised anxiety disorder, Same genes, (partly) different environments – revisited. *Br. J. Psychiatry Suppl.* **1996**, 68–75.
 - 92 HEIM, C., NEMEROFF, C. B., The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol. Psychiatry* **2001**, 49, 1023–1039.
 - 93 FELITTI, V. J., ANDA, R. F., NORDENBERG, D., et al., Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am. J. Prev. Med.* **1998**, 14, 245–258.

30

Genetic Approaches to Depression: Linkage Studies

Francis M. Mondimore and James B. Potash

Abstract

Genetic linkage studies provide a means of localizing disease genes to chromosomal regions without any prior knowledge of the underlying pathophysiologic processes and have been used extensively in the study of the genetic basis of illnesses known to be heritable. Linkage studies of depression were initiated in the 1970s and 1980s, with unremarkable results. In the 1990s there were virtually no such studies, although many linkage studies of bipolar disorder were carried out which included family members with depression in the phenotype (illness) definition. In 2003 the results of the first three genome-wide linkage scans of depression were reported. Two of these studies focused on cases of depression with recurrence and early onset of illness, as this subset of cases has a stronger familial component. All three of these studies reported statistically significant linkage findings, though the regions implicated by each (on chromosomes 2q, 12q, and 15q) differed across the studies. These three regions may each contain genes conferring susceptibility to major depression, although replication will be necessary before firm conclusions can be drawn. Further elucidation of the genetic basis of depression will come from linkage studies that employ: larger family samples, more specific clinical subtypes to potentially enhance genetic homogeneity, biological markers as phenotypes (endophenotypes), denser DNA marker maps, and statistical methods that allow for modeling of gene–gene interactions.

30.1**Introduction**

Experiments using linkage methods can be thought of as prospecting expeditions into the genome, identifying promising areas on chromosomes where genes that cause or confer increased risk for disease, are likely to be located. They identify chromosomal areas for further genetic mining, pointing the way for additional studies that use other techniques (such as *association studies*, discussed in the

Chapter 31) to pinpoint which of the many genes in a linkage region is the one of etiologic relevance.

The distinctive advantage of linkage studies is their ability to detect genetic signals without any prior knowledge of the pathophysiology of the disease being investigated. This has made them tremendously useful in identifying areas of interest within the genome and focusing further investigative efforts into psychiatric disorders, illnesses whose molecular pathophysiology remains uncertain.

Linkage studies derive this power by taking advantage of the fact that crossovers between chromosomes occur during the formation of germ cells. A mathematical relationship exists between the *likelihood* of a crossover occurring between any two points on the DNA molecule and the *distance* between those two points. This relationship makes it possible to determine the location of genetic signals among and along the chromosomes. By using established DNA landmarks as markers, the proximity of putative risk-conferring genes to markers, and thus their location on the genome, can be established.

This chapter will first give a brief review of basic cellular genetics and a straightforward overview of some of the mathematical methods used in linkage studies, followed by a discussion of the strategies used to design linkage studies and finally, a discussion of linkage studies in affective disorders, with attention to how these strategies have been employed.

30.2

Meiosis and Mechanisms of Genetic Diversity

Meiosis is the specialized form of cell division that results in the formation of the germ cells: oocytes in females and spermatozoa in males. Meiosis differs from ordinary cell division (*mitosis*) in that the end-products, the germ cells, have only half the number of chromosomes present in the other cells in the body (oocytes and spermatozoa are said to be *haploid* cells, as opposed to *diploid* somatic cells.) In human diploid (somatic) cells there are 46 chromosomes, 22 pairs of non-sex chromosomes (*autosomes*) and two sex chromosomes: two X chromosomes in women and one X and one Y in men.

Early in meiosis, each of the 46 chromosomes pairs up with its partner (the *homologous* chromosome) along a plane within the dividing cell and microfilaments form to pull one of each chromosomal pair towards one or the other of the two newly-forming cells. Which member of the pair ends up in which new cell is a random event and this randomization is an important mechanism by which genetic diversity in germ cells is generated. Since there are 23 chromosome pairs, there are 2^{23} or about 8.4×10^6 possible outcomes of this randomization process.

Another diversity-generating mechanism is *recombination*. This also occurs during an early phase of meiosis, at the point when chromosomes have paired up in the center of the soon-to-be dividing cell. At this point, the DNA in each chromosome has been duplicated, so that each chromosome is actually *bivalent*, that is, composed of two *chromatids*. As the homologous chromosomes pair up, they are in close

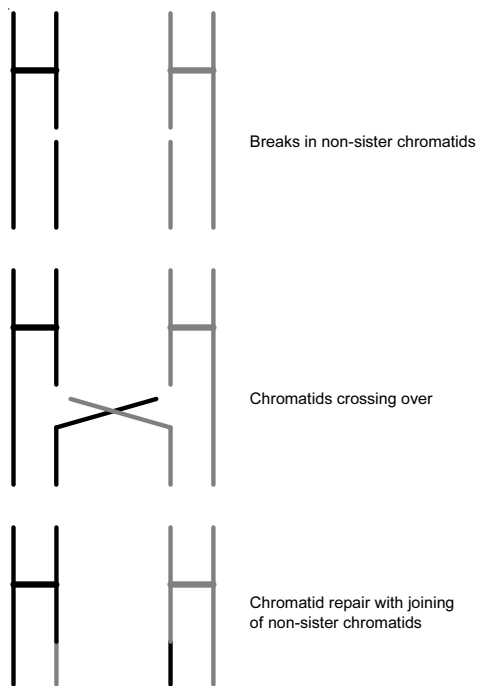


Figure 30.1 Schematic illustration of crossovers between chromatids showing alignment of bivalent homologous chromosomes during meiosis (top), crossing over of non-sister chromatids (middle) and DNA repair (bottom) that results in recombination of alleles.

approximation to each other and exchanges of DNA can occur among the chromatids of each chromosomal pair. These *crossovers* involve physical breaks in the DNA molecules in each chromatid followed by a repair of the DNA strands between the opposite members of the pair (Figure 30.1). Multiple crossovers (*chiasma*) occurring in a pair of chromatids are possible, indeed are common. Recombinations through crossovers are normal, probably even necessary events during meiosis, possibly responsible in some way for the proper pairing of homologous chromosomes during cell division. Recombination events are common during meiosis, with an average of 49 crossovers per cell occurring in human male meiosis and about double that in females [1].

The random distribution of homologous chromosomes during meiosis, together with the recombination events that occur among chromatids enable an individual to produce a nearly unlimited number of genetically different gametes.

30.3

Recombination Fractions and Genetic Distance

Individuals can be thought of as having inherited one of each homologous chromosome from each parent. Thus, a male whose sex chromosome pair consists of one X and one Y chromosome can be thought of as having inherited the X

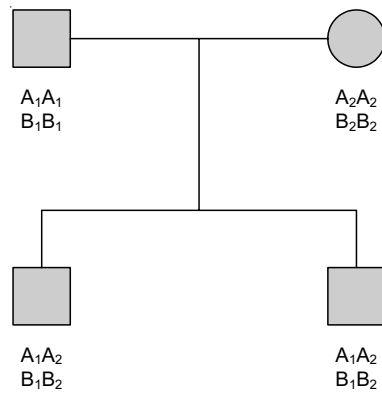


Figure 30.2 Homozygous parents producing all heterozygous offspring (no recombinants).

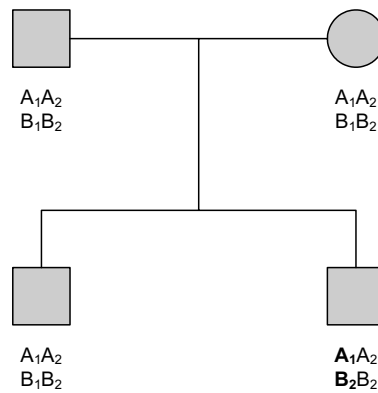


Figure 30.3 Heterozygous parents producing one fully heterozygous offspring (left) and one offspring who is heterozygous at allele A but homozygous at allele B (right). This can only have occurred if a recombination between A and B occurred during parental meiosis.

chromosome from his mother and the Y chromosome from his father. The same is true for the other 22 homologous pairs. In the first example above, two parents are homozygous (have the same form or *allele* of a particular gene or DNA marker) for two markers within hypothetical genes, A and B, that are located on the same chromosome (thus said to be *syntenic* genes). Each offspring will inherit one A_1B_1 chromosome and one A_2B_2 and will be heterozygous for each marker (Figure 30.2).

In the next example, each parent is heterozygous at each location. Inspection of Figure 30.3 shows however, that one of the offspring is heterozygous at gene A but homozygous at gene B.

This can only be possible if a crossover or recombination event occurred during meiosis in one of the parents, a crossover that must have occurred at a point on the chromosome that lies between the two genes (Figure 30.4).

The further apart two genes are on the chromosome, the more likely it is that a crossover event will occur to separate them, and conversely, the closer two loci (locations of specific DNA sequences) are on the chromosome, the less likely that they will be separated. In this example, if the loci of genes A and B were very close to each other, it would be unlikely that they will be separated by a crossover event – such an event would need to occur precisely along a very short length of the DNA molecule for a recombination to occur. As the physical distance between genes decreases, the probability of them being transmitted together increases: this relationship is the basis of genetic linkage studies.

The *recombination fraction* in the offspring, the fraction of offspring in whom allele identification (called *genotyping*) indicates that recombination of alleles has occurred, will be a measure of the *genetic distance* between two loci. This distance is

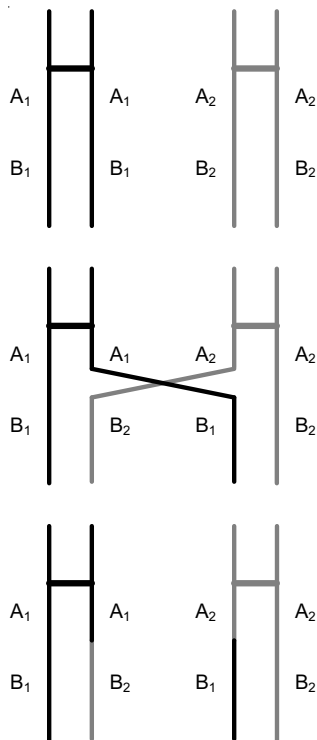


Figure 30.4 Schematic of the crossover during parental meiosis that resulted in the recombinant offspring in Figure 30.3. Alleles A and B are separated when a crossover occurs between them on non-sister chromatids (middle). After crossover and DNA repair (bottom), each chromosome has one recombinant and one non-recombinant chromatid. As meiosis progresses and each chromatid is distributed to a gamete, four different combinations of alleles A and B will result (A_1B_1 , A_1B_2 , A_2B_1 , and A_2B_2).

measured in centimorgans (cM), defined as the distance between two loci that show a 1% recombination fraction (the term honors Thomas Hunt Morgan, the pioneering geneticist who proposed the linkage method for estimating genetic distances). Although genetic distance along the DNA molecule is not the same as physical distance, a rough approximation can be made, with $1 \text{ cM} \approx 1 \text{ megabase (Mb)}$, a length of one million (10^6) nucleotide (base) pairs of DNA.

Several factors often limit linkage studies in humans. In order to determine the recombination fraction in offspring, the genotypes of the parents must also be known, necessitating recruitment of several generations of family members who must be available and willing to give the blood sample needed for genotyping. Also, parents must be heterozygous at the alleles of interest; crossover events involving two copies of the same allele will be undetectable (such matings are called *uninformative* for the purposes of linkage studies). Several strategies are used to circumvent these limitations: statistical methods can be used to reconstruct missing parental data and to estimate the probabilities of these estimations being correct. These strategies can increase the power of a linkage study but also introduce the potential for error. Also, the greater availability of an increased number of highly variable DNA markers now makes parental marker homozygosity less of an obstacle.

30.4

Linking Phenotypic Traits

In 1910, Morgan published a paper describing the heredity of eye color in fruit flies; he had observed that two genetically transmitted observable traits (*phenotypes*) in *Drosophila*, eye color and sex, were always transmitted together to offspring. He concluded that a gene for eye color was located on the same chromosome as the gene(s) responsible for sex determination, the now familiar *X-linked* inheritance pattern. This was the first description of two *linked* traits. In this case, the loci for eye color and sex determination are linked by virtue of both being located on the X chromosome in the fruit fly.

In the 1930s and 1940s, studies appeared which estimated the linkage interval between hemophilia and color blindness on the X chromosome in humans. In the 1950s, a subtype of hemophilia (hemophilia B or Christmas disease) was described and analysis of previous work on color blindness and hemophilia showed that this variant was much more loosely linked to color blindness than classic hemophilia (hemophilia A). More recent work has shown that the locus for hemophilia A is much closer to that for color blindness than is the locus for hemophilia B.

The scarcity of observable genetically-mediated traits in humans made early linkage studies of human diseases exceedingly difficult. In addition to a few observable genetic traits such as color blindness, measurable traits such as blood group antigens, human leukocyte antigens (HLA markers) and enzymatic variations allowed for the development of rudimentary linkage maps for human genetic diseases, but it would be several decades before linkage studies in humans were made practical by the development of new methods in molecular biology.

Starting in the 1960s, advancements in the ability to sequence and manipulate DNA molecules resulted in the development of a much wider variety of DNA markers, greatly enhancing the capacity to perform linkage studies. The discovery and isolation of restriction enzymes in 1968 led to the development of markers called Restriction Fragment Length Polymorphisms (RFLPs). Restriction enzymes are specialized molecules that cut the DNA molecule at precise points determined by a particular sequence of nucleotides. Individual variations in DNA sequence mean that the fragments of DNA that remain after treatment with restriction enzymes will also vary from individual to individual, providing the opportunity to classify individuals according to the presence or absence of particular cleavage sites in their DNA.

Variable number tandem repeat polymorphisms (VNTRs or, alternatively: *simple sequence tandem repeat polymorphisms*, SSTRPs) consist of repeated sequences of base pairs in non-coding DNA (so-called “junk DNA”), portions of DNA that do not code for genes and have no known biological function, that makes up 97% of the human genome. VNTRs that consist of only a few nucleotides repeated in tandem (frequently referred to as *microsatellites*) are the DNA markers currently most commonly used in linkage studies. Microsatellite markers occur frequently, vary significantly among individuals and can be easily identified in the laboratory and tracked in pedigrees. These attributes make them nearly ideal markers for

use in linkage studies. Linkage studies typically use approximately 400 markers to achieve an average resolution of 10 cM. Even more precise genetic maps are being developed using *single nucleotide polymorphisms* (SNPs), which consist of a single nucleotide substitution in the DNA molecule. SNPs occur even more frequently in the genome, raising the possibility of even greater resolution for linkage studies.

Other molecular techniques can map DNA sequences to their physical location on chromosomes, enabling the physical location of markers to be determined and the translation of linkage data maps into physical maps of chromosomes.

30.5 Linkage Analysis

Even genetic loci that are located on different chromosomes will have at most a 50% chance of being separated during gametogenesis and thus give a recombination fraction of 0.5; this can be thought of as the maximum possible recombination fraction for two genetic loci. Loci that are on the same chromosome and located close to one another will be less likely to be separated from one another and will therefore have a recombination fraction significantly less than 0.5. The statistic used to define “significantly less” is the LOD score, initially described in 1955 by Newton Morton.

The first step in calculating a LOD score involves computing the likelihood that the inheritance pattern observed in a particular pedigree (or set of pedigrees) results from a particular amount of linkage between the genetic marker and the phenotype being investigated (expressed as the recombination fraction: Θ , the Greek letter theta). Put another way, the likelihood that a particular pedigree will result if the marker locus and the phenotype-conferring locus are a certain genetic distance apart is determined. Likelihoods are calculated for a range of values of Θ and the highest number will identify the most likely genetic distance between the marker and the risk-conferring gene. Many factors can go into these likelihood calculations, including not only genotype and pedigree data, but also estimates of the frequency of the various alleles of the marker of interest in the general population and the putative inheritance pattern of the disease. This includes the familiar dominant/recessive dichotomy as well as the likelihood that an individual inheriting a risk-conferring gene will actually develop the illness (known as the *penetrance*). Manipulating this large array of data has only become possible with the development of modern computers and powerful software programs that use complex algorithms to perform the required calculations.

The ratio between each of these likelihoods and the likelihood that the observed data would result if there were no linkage (i.e. if the recombination fraction were equal to 0.5) is then calculated and this number is the *odds* of linkage. The *logarithm* of this *odds* ratio is the *LOD score*. A table of LOD scores is generated for a range of Θ values; the highest of them will identify amount of linkage or genetic distance between the two loci that is best supported by the pedigree data. Positive LOD

Table 30.1 LOD scores for linkage of Alzheimer disease to DNA markers on chromosome 14

DNA marker	<i>Recombination fraction</i>						
	0.001	0.05	0.10	0.15	0.20	0.30	0.40
TCDR	-10.34	-4.52	-2.84	-1.86	-1.21	-0.44	-0.09
D14S47	-5.29	-0.87	-0.01	-0.35	0.35	0.39	0.15
D14S52	2.02	4.59	4.56	4.19	3.64	2.25	0.08
D14S52	8.91	8.40	7.67	6.79	5.79	3.55	1.33
D14S53	4.24	7.12	6.88	6.19	5.28	3.10	0.99
D14S55	-1.32	0.43	0.66	0.70	0.64	0.43	0.19

From [45].

scores provide evidence for linkage and negative LOD scores provide evidence against linkage (see Table 30.1).

In the decades since the LOD score method of assessing linkage data was first developed, there has been much discussion regarding the proper interpretation of LOD scores. For a linkage study assessing linkage between a disease and one DNA marker for an illness showing simple Mendelian inheritance, a LOD score of 3.0 corresponds to the familiar $p = 0.5$, or a 5% chance that the results are a result of error. As modern molecular and computing methods developed that permit linkage analysis using hundreds of DNA markers (*genome scan* studies) and several different models of inheritance, it became apparent that this significance threshold was inadequate.

In 1995, Lander and Kruglyak proposed new thresholds for significance levels of LOD scores that have been widely accepted in psychiatric genetics [2]. These thresholds have been devised to take into account the issue of multiple testing and they vary somewhat depending on the type of analysis being carried out. For studies in which illness inheritance patterns are specified (called *parametric analyses*) a LOD score of 1.9 is considered to be “suggestive” of linkage and a score of 3.3 is considered to represent “significant” linkage.

As noted above, this approach requires that the mode of inheritance of the disease of interest be specified and that genotype and phenotype data be obtained for as many members of affected families as possible. An alternative approach that does not require that the mode of inheritance be specified for the calculation of the LOD score is *affected relative pair analysis*. One variant of this approach involves using pairs of siblings that are affected by the illness of interest, called *affected sib pair* (ASP) analysis and was first described by the pioneering medical geneticist Lionel Penrose in 1953 [3]. This approach is based on the knowledge that siblings who are both affected by a condition of interest will share the risk-conferring alleles (as well as neighboring or *linked* markers) more often than would be otherwise expected and thus does not require that the trait’s inheritance pattern be known (making it a *non-parametric analysis*). The extent to which sibs who are both affected by the condition of interest share marker alleles is determined by genotyping and then complex software algorithms are used to calculate non-parametric LOD scores. For this approach, the Lander and Kruglyak thresholds are LOD scores of 2.2 for

“suggestive” of linkage and 3.6 for significant linkage. Though potentially more robust, ASP studies have decreased power compared to parametric LOD score methods making larger sample sizes necessary for ASP analysis.

A more recent approach to testing for the statistical significance of linkage findings employs simulation. In this technique, a computer simulation program *randomly* assigns the alleles of interest to family members in the study pedigrees and then randomly sorts through the family. The procedure is repeated several thousand times with LOD scores calculated for each trial. The frequency with which a given LOD score would arise by chance alone in the study families is thus determined, giving an empirical *p*-value for LOD scores within the study.

30.6

Phenotype Definition in Linkage Studies for Depressive Disorders

The greatest strength of linkage studies is their ability to identify chromosomal locations of risk-conferring genes in the absence of knowledge about the pathophysiology of the disease process being investigated. Furthermore, affected relative or sibling pair analysis allows linkage studies to be carried out in the absence of any knowledge about the mechanism(s) of inheritance of the illness of interest. As might be expected then, linkage studies using these techniques have dominated efforts to elucidate the genetics of depressive disorders, the neurochemical basis of which is largely unknown and the inheritance of which is complex and heterogeneous.

Linkage studies are however, dependent on the investigators' ability to clearly identify individuals who have the trait of interest, in this case: individuals affected with depressive illness. Defining who should be considered affected with depression, however, has not been entirely straightforward.

It has been suggested, for example, that some cases of major depression represent sporadic rather than familial illnesses, that is, some episodes of illness are more related to environmental factors than genetic mechanisms. This is a not uncommon finding in common illnesses with complex relationships between environmental and genetic factors. For example, although some cases of breast cancer clearly are highly familial, many others are not. However, if these *phenocopies* are classified as familial cases in linkage studies, the ability to detect linkage can be seriously impaired.

One study attempted to address this issue by comparing family information in twins who were concordant versus discordant for major depression requiring hospitalization. Andrew and colleagues suggested that major depression in a twin whose co-twin did *not* suffer from the illness might be more likely to represent a phenocopy, in which case the families of discordant pairs would be expected to have fewer affected members than families of concordant twins. However, they found no differences in lifetime prevalence or age-corrected lifetime risk of developing depression between discordant and concordant pairs and concluded that “where all probands have received hospital treatment, there is homogeneity with respect to a genetic contribution to major depression” [4].

The researchers of the NIH Collaborative Program on the Psychobiology of Depression compared clinical characteristics of the illnesses of affected family members of affectively ill probands to those of affectively ill subjects who were identified from a control group and thus more likely to represent possible phenocopies [5]. They found that individuals from the control group had some differentiating features (they were less likely to be hospitalized or incapacitated) but concluded “we do not have the perfect ability to separate autonomous disease on the basis of clinical characteristics.”

Studying families in which there are many affected individuals is one obvious way of selecting study subjects in which the heritability of illness is higher than in the general population. Two other features of major depression have been robustly associated with increased familial risk, recurrent episodes and an early age at onset [6, 7]. Most data suggest that familial risk is greater when the proband's age of onset is below 40 years and greater still when it is below 30 or 20 years. Lyons et al. reported that in 3372 male veteran twin pairs, heritability of major depression was 0.47 when the age at onset was earlier than 30 years, and 0.10 when it was after 30 years [8] and Bland et al., in a study of 763 first-degree relatives of 75 probands with major depression, found that relatives of probands with an early age at onset and recurrent depression had a 17.4% risk of depression while relatives of probands with single-episode depression and a late age at onset had a 3.4% risk [9].

Another difficulty in assigning phenotype status in depression is the unclear relationship between unipolar depressive disorders and bipolar disorder. The Kraepelinian conceptualization of “manic-depressive illness” included all recurrent severe disorders of mood: those characterized by depression and mania, but also those characterized by depression alone [10]. In the 1950s, Karl Kleist proposed a nosological division of mood disorders into unipolar and bipolar types and Karl Leonhard's 1959 classification of psychoses made a clear distinction between bipolar illness and recurrent unipolar depression [11]. Carlo Perris reported family findings in a 1966 monograph suggesting that unipolar and bipolar illness were genetically separate, concluding “the heredity is different between the two groups” [12]. However, almost simultaneously, Winokur et al. reported from their study of manic probands that there is an excess of unipolar depressive illness in the families of individuals with bipolar illness [13]. This has been confirmed in several studies including a family study of over 500 unipolar and bipolar probands that was completed several decades later. This study found a higher incidence of unipolar depressive illness in the families of bipolar probands, but no excess of bipolar disorder in the families of unipolar probands¹⁾ [14, 15]. Because of these findings, many genetic studies of bipolar disorder include individuals with unipolar depressive illness, classifying them as affected family members for the purpose of linkage analysis. In 1974, Mendlewicz and Fleiss concluded from this body of data that “within a family unit identified by a bipolar proband, bipolar illness and unipolar illness are genetically related and express the same genotype” [16]. The degree to which this is true continues to be debated [17].

1) Not all similar studies have obtained these results. Other investigators have found an increase of bipolar relatives in the families of unipolar probands (see, for example [18]).

The finding that persons with manic episodes are not overrepresented in the families of unipolar probands suggests, however, that at least some risk-conferring genes for unipolar illness do not predispose to bipolar disorder, that is, some forms of unipolar depressive illness breed true and have a separate genetic basis that may be amenable to genetic analysis.

30.7

Early Linkage Studies in Depression and Depressive Spectrum Disease

Early linkage studies of depressive illness were hampered by the paucity of genetic traits available to use as genetic markers. The 1974 paper by Mendlewicz and Fleiss investigating linkage of affective disorder to markers on the X chromosome illustrates the difficulties involved [16]. This paper reports on 54 families assembled over nearly a decade that had members affected with bipolar or unipolar affective disorder as well as either color blindness (an X-linked trait) or the presence of an X-linked blood antigen (the Xg glycoprotein). Because of missing data of various types, precise recombination fractions could be determined in less than half of the pedigrees and statistical methods were needed to estimate probabilities for recombination fractions for the others. The authors tested an X-linked dominant model in these families and concluded that although their data supported a dominant X-linked gene involved in the transmission of bipolar disorder, there was no evidence of linkage to the X chromosome for unipolar depressive illness. By 1980, several dozen genetic markers showing allelic variation had been identified, including blood group antigens, HLA antigens, immunoglobulin and other serum proteins. Weitcamp and colleagues performed linkage studies using 35 different markers, but could detect no evidence of linkage of unipolar depression to any of them. They concluded that they had therefore “excluded the postulated gene (for major depression) from 6% of the autosomal genome” [19].

Researchers at the Washington University School of Medicine in St. Louis working under the leadership of George Winokur had meanwhile proposed, based on family studies, that there were two genetic subtypes of depressive illness: “pure depressive illness”, characterized by later onset of symptoms and equal risk in men and women, and “depression spectrum disease”, characterized by early onset of affective illness in women and substance abuse or antisocial personality disorder in men [20]. Using blood group antigens and enzymatic and protein markers, Tanna, Winokur and colleagues performed linkage studies using the sib-pair method and although they could not demonstrate genetic linkage to any of their markers in the case of pure depressive illness [21], they found possible weak linkage of depression spectrum disease to two markers: alpha-haptoglobin (HP) and a component of complement called C3 [22]. At the time, it was suspected that these markers were on two different chromosomes (a fact that was subsequently confirmed with the HP gene located on chromosome 16 and C3 on chromosome 19), making these findings interesting, but arguing against the simple dominant model of inheritance for the disorder that Winokur had proposed. A later analysis of this data using more robust statistical

methods did not confirm the C3 linkage, but again suggested possible linkage of depressive spectrum disease to the HP locus [23]. These same investigators reported on new linkage studies in 1989, this time finding weak evidence of linkage to several markers for pure depressive disease [24]. They did not, however, replicate their earlier findings of linkage of depression spectrum disorder to HP or C3 and instead found evidence of weak linkage to yet another location, the orosomucoid protein marker on chromosome 9 [25]. Other teams were also either unable to replicate the various linkage findings for depression or obtained conflicting results with evidence of linkage to other markers [26–28]. Through the 1980s, genetic studies of depressive disorders appeared to have largely stalled and enthusiasm for the concept of depression spectrum disorder as a possible phenotypic expression of an underlying gene for depressive illness waned in light of additional family studies that did not support the model [4].

Despite these disappointments, interest in linkage studies in depressive illness was sustained by twin and family studies that continued to indicate that genetic mechanisms were important in the development of unipolar depression [29, 30] and was then reinvigorated by the development of molecular techniques that tremendously increased the number of available genetic markers and also greatly decreased the time and cost of conducting linkage studies.

30.8

Genetic Studies of Complex Diseases

Early studies of the genetics of depression usually assumed that the inheritance of affective disorder was fairly simple, that straightforward Mendelian mechanisms operated in the transmission of risk genes and that only a few genes would be found to underlie the development of depressive illness. It is now clear that this is almost certainly not the case. The evidence for this comes from *segregation analysis* studies, in which the pedigrees of affected families are analyzed for the “goodness of fit” of various models of inheritance. These models will include illness prevalence, penetrance estimates, allele frequencies, age-of-onset data and other factors as well as putative inheritance mechanisms. As with LOD score analysis, these analytic methods have become possible only with the development of sophisticated statistical techniques and faster, more powerful computers able to process large amounts of data. Affective disorder appears to be what has come to be called a *genetically complex* disease. The development of affective disorder in individuals, like that of most other common diseases, appears to be determined by interacting genetic and environmental influences, with the genetic influences in all likelihood caused by several, perhaps many genes that may interact with one another (a genetic phenomenon known as *epitasis*).

Genetic mechanisms appear to affect susceptibility to affective disorder rather than causing it more or less directly as is seen for example, in sickle cell disease or Huntington's disease. The leading current hypothesis is that, as with type II diabetes mellitus or hypertension, genetic vulnerability to depressive disorders is probably

acted upon by environmental factors (such as psychological trauma, personal loss, or substance abuse) that trigger the onset of illness. The amount of variation in disease occurrence that is explained by genetic as opposed to environmental factors is known as *heritability* which has been estimated at 37% for major depression across six studies [6]. In contrast the heritability of bipolar disorder has been estimated to be around 80% [17, 31, 32]. Obviously, lower heritability for an illness predicts that underlying genetic factors will be more difficult to elucidate.

Another useful way of estimating the strength of genetic contribution to illness uses the concept of *sibling relative risk*. This figure, typically designated by λ_s , compares the rate of illness in siblings of ill probands to the rate of illness in the general population and is 2 to 3 in major depression, and about 10 in bipolar disorder. By comparison, the relative risk²⁾ to siblings in a single-gene disease such as phenylketonuria is 2500.

Additionally, different genetic mechanisms may operate to confer vulnerability to illness development in depressive disorders, with different genes being responsible for conferring risk to affective disorder in different individuals, an additional complicating factor known as *genetic heterogeneity*.

The chances of success in elucidating the genetic factors that confer risk to complex diseases can be increased if individuals and families can be identified where there is less genetic heterogeneity of the illness and in whom heritability for the illness is higher.

One strategy to reduce genetic heterogeneity for a complex disease is to study a population that is more genetically homogeneous because of geographical or cultural factors that have affected the gene pool in that population. Centuries of geographical isolation have resulted in *genetic isolates*, populations in which the individuals are more genetically alike because of comparative inbreeding in the population. The populations of Iceland and Sardinia are two examples of such isolates. Although not geographically isolated, the Old Order Amish and Ashkenazi Jews are two populations that have tended to marry within their own community and thus are also more genetically homogeneous. Cases of complex diseases that occur in a more genetically homogeneous population may be more likely to share common genetic mechanisms. That is, even when illness development can be affected by many different risk-conferring genes, it may be more likely that only a few are operating to confer risk in genetically more similar affected individuals. To date, this strategy has not been exploited to any large degree in linkage studies of depressive disorder.

2) Relative risk is also known as *recurrence risk*. In the context of discussions of genetic illness, “recurrence risk” does not refer to the risk of a recurrence of illness in an affected individual, but rather the risk of the illness recurring in a family and affecting a relative of the proband.

30.9

Linkage Studies of Major Depressive Disorder

In 2002, a genetics research group at the University of Pittsburgh reported the first study of DNA markers across the genome in subjects with recurrent early onset depression. Although not a linkage study, but rather one testing for linkage disequilibrium³⁾, it identified a marker on chromosome 2 (D2S2944) that appeared to be associated with recurrent early onset depression in women but not men [33]. These investigators then went on to perform a linkage analysis in 81 families ascertained through probands with recurrent early onset major depression. They used the affected relative pair method and genotyped six additional DNA markers in the same vicinity as marker D2S2944. Using a very broad illness definition, this analysis resulted in strong LOD scores (> 6), providing evidence of linkage in a portion of chromosome 2. A group headed by Nurnberger had previously reported possible linkage to a nearby marker, D2S1371, using genome-wide sibling pair linkage analysis which specified comorbid major depression and alcoholism as the affected phenotype [35]. Because of an explosion of information about specific genes, especially their locations in relation to known markers and thanks to availability of comprehensive public databases such as the University of California Santa Cruz's Genome Browser, known genes of interest in a chromosomal region can be identified in a few moments. For example, the region 2q34⁴⁾ near marker D2S2944 is known to contain a gene called CREB1 that codes for a cAMP-responsive element-binding protein [36]. This protein appears to be important for many aspects of neuronal functioning and levels of CREB have been found to be abnormally low in persons with major depression and in the brain tissue of suicide victims and have been found to be altered by exposure of rat neurons to antidepressants and lithium (reviewed in [37]).

After chromosomal regions of interest are identified using linkage techniques, genes with possibly relevant functions in the pathophysiology of the illness under investigation (*candidate genes*), such as CREB1 in the case of depressive disorders, can be selected and additional studies, such as association studies (to be discussed in Chapter 31) can be performed in an attempt to associate particular allelic variations with illness states. In the case of this area of chromosome 2, CREB1 is being intensively studied by the Pittsburgh group.

In 2003, the results of the first three genome-wide linkage scans of depression were reported (see Table 30.2). The first of these was from the Pittsburgh group.

3) This technique is a kind of association study (see Chapter 31) and compares either the prevalence of specific alleles in affected versus unaffected individuals, or the transmission versus the non-transmission of alleles from parents to affected subjects [34].

4) Nomenclature for chromosomal locations is set by the Standing Committee on Human Cytogenetic Nomenclature based on terminology originally developed at a 1971 meeting of the committee in Paris. The short arm of each chromosome is labeled *p* (for "petit") and the long arm *q* (for "queue"). Numbers are added after one of these letters to specify more precise locations relative to morphological landmarks such as chromosomal bands. Thus, 2q34 (pronounced "two q three four") refers to a location on the long arm of chromosome 2 marked by a band visualized by staining with Giemsa, a DNA-binding dye.

Table 30.2 Linkage studies in major depression

<i>Study</i>	<i>Linkage method</i>	<i>Proband phenotype</i>	<i>Main findings</i>
Zubenko et al. [36]	ARP	Recurrent MDD with onset before the age of 26 years	Peak LOD score at 2q33-34 in female relative pairs with "any mood disorder"
Abkevich et al. [39]	ARP	MDD, only families with four or more affected members analyzed	Peak LOD score at 12q22-23.2 in male relative pairs with recurrent major depression or bipolar disorder
Holmans et al. [40]	ARP	Recurrent MDD with onset before the age of 31 years with at least one sibling with MDD and onset before the age of 41 years	Peak LOD score at 15q25.3-26.2 in "all affecteds" analysis

ARP, affected relative pair analysis; MDD, major depressive disorder.

This study assessed linkage using 392 DNA markers spaced evenly throughout the genome in the same 81 families mentioned earlier. The families contained between 86 and 432 affected relative pairs depending on the stringency of the phenotype definition. The strongest findings in primary analyses were on chromosome 11p15 (LOD = 4.2), 5q21-23 (LOD = 3.74), and 1p35-36 (LOD = 3.60). Two additional regions, 4q13-21 and Xq13-21 appeared interesting when only female sex was considered. The investigators also tested for epistasis and found that five more chromosomal regions, on chromosomes 10, 11q, and 19, appeared to be linked when only families with linkage to chromosome 2q were considered. This suggests the possibility that genes in these regions might interact with a 2q gene to enhance susceptibility to depression [38].

Abkevich and colleagues reported on a linkage study they performed in Mormon families in Utah which found significant linkage on chromosome 12q [39]. In this study, only families with a minimum of four affected relatives were included and in addition to analyzing the pedigrees including all affected members, analyses were also carried out separately on males and females. Also, individuals with only a single episode of major depression were considered affected, as were individuals with bipolar disorder (who made up almost 15% of the individuals with affective disorder in these families). This study illustrates a number of study strategies designed to facilitate finding linkage signals. The families were large and severely affected: the average pedigree had 17 studied individuals, of whom an average of 10 was affected. Mormon families are larger than the American average and the selection of this population resulted in large pedigrees capable of generating a large amount of genetic data. Also, many Mormons abstain from alcohol and do not use illegal drugs; this means there would probably be a lower incidence of substance use in these families, resulting in fewer individuals with substance-induced mood disorders (i.e. possible phenocopies). The linkage signal from these

families was only present when analysis was limited to families with at least four affected males, suggesting the presence of a risk-conferring gene on chromosome 12q that predisposes to unipolar and, less frequently, to bipolar disorder, primarily in males.

The GenRED project (Genetics of Recurrent Early-onset Depression) is a multi-center collaborative project on the genetics of depressive illness [7]. This project has collected 680 families that include 971 affected sibling pairs for genetic analysis, a sample that is large enough to have power to detect linkage even for a susceptibility gene of modest effect. Families have been recruited through probands with recurrent major depressive disorder who experienced their first episode prior to the age of 31 years. An affected relative pair analysis of about half of the sample resulted in a significant linkage signal on chromosome 15q [40]. Additional signals were detected on chromosomes 6, 8, and 17 when gender was used as a covariate and on 8 and 1 when age of onset was factored into the analysis.

The results of the first three major linkage studies in depression can be viewed as encouraging insofar as they report significant linkage findings. However, the strongest regions reported differ in each, making it difficult to draw firm conclusions about the importance of the chromosomal regions implicated by them.

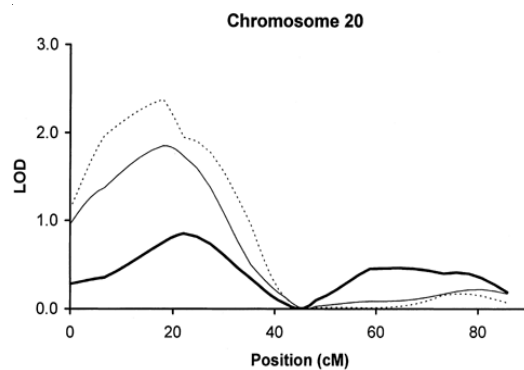


Figure 30.5 Multipoint nonparametric linkage results for chromosome 20 from [55].

The three lines trace the LOD score for various distances along the chromosome with each line indicating the results obtained from a different phenotypic model:

- Model I: BP I, schizoaffective disorder
- - - Model II: BP I, schizoaffective disorder, BP II
- Model III: BP I, schizoaffective disorder, BP II, recurrent unipolar depression

Note that model II, which adds BP II to the phenotype definition, results in higher LOD scores than is seen in the model that includes only subjects who have had manic symptoms as affected. Model III, which also adds recurrent depressions, results in even higher scores.

30.10

Linkage Studies of Bipolar and Unipolar Depression

Many more studies using linkage analysis have been completed for bipolar disorder than for unipolar depression. Many of these studies include several alternative affection status models in calculating LOD scores and often take the strategy of starting with an analysis using a narrow phenotypic definition and performing additional analyses using a broader phenotypic model that includes subjects with depressive disorders. The “narrow” phenotypic model usually includes only subjects who have mania as part of their illness: bipolar I and schizoaffective disorder. Some researchers add subjects with bipolar II to this “narrow” definition; others include bipolar II subjects in the “broad” model. Most “broad” phenotypic definitions include patients with recurrent major depression and a few studies have added in subjects with single-episode major depression, or subjects with other depressive symptoms [41] in alternative models. Several studies have achieved suggestive results for

Table 30.3 Linkage studies of bipolar disorder including recurrent early onset depression

<i>Study</i>	<i>Phenotype model</i>	<i>Linkage method</i>	<i>Implicated region(s)</i>
Straub et al. [46]	Bipolar I, II; schizoaffective disorder; recurrent major depression	ARP	21q22
Stine et al. [47]	Bipolar I, II; schizoaffective disorder; recurrent major depression; higher linkage scores for paternal transmission	ASP	18q21
Detera-Wadleigh et al. [48]	Bipolar I, II; schizoaffective disorder; recurrent major depression	ASP	21q22
Berrettini et al. [49]	Bipolar I, II; schizoaffective disorder; recurrent major depression	ARP, ASP	18p11
Ewald et al. [50]	Bipolar I, I; schizoaffective disorder and recurrent major depression	PL, ARP	4q16
Aita et al. [51]	Bipolar I, II; schizoaffective disorder; recurrent major depression	ARP	21q22
Detera-Wadleigh et al. [52]	Bipolar I, II; schizoaffective disorder and recurrent major depression	ASP	13q32, 18p11.2, 22q11-q13
Morissette et al. [41]	Bipolar I, II; schizoaffective disorder and recurrent major depression	PL, ARP, ASP	12q23-q24
Cichon et al. [53]	Bipolar I, II; schizoaffective disorder and recurrent major depression	PL	10q25-q26
Kelsoe et al. [54]	Bipolar I, II; schizoaffective disorder; recurrent major depression	ASP	22q12
Willour et al. [55]	Bipolar I, II; schizoaffective disorder; recurrent major depression	ARP	20p12
Dick et al. [56]	Bipolar I, II; schizoaffective disorder; recurrent major depression	ARP	2p, 3q, 6q, 8q, 17q

ASP, affected sib pair analysis; ARP, affected relative pair analysis; PL, parametric LOD score analysis. **Bold print** indicates possible areas of linkage found in multiple independent studies.

particular chromosomal areas only when these broader models are specified (see Figure 30.5). A selection of linkage studies that recruited probands with bipolar disorder and that included depressive illness in the model generating the most suggestive linkage results are summarized in Table 30.3.

A meta-analysis of genome scan studies in bipolar disorder attempted to identify chromosomal regions with significant support for linkage by combining data from 18 genome scan studies and dividing the markers used in the studies among 120 “bins” that were then ranked according to highest LOD scores or lowest *p*-values with results adjusted for sample size [42]. In this analysis, no region achieved genome-wide significance by simulation-based criteria and furthermore, using “broad” models that included subjects with unipolar depression did not result in more significant results than those obtained for narrower models. In fact, more significant *p*-values were obtained for very narrow models of bipolar disorder (BP I with or without schizoaffective disorder) than for models that included BP II and depressed subjects. The authors suggested that analyzing larger numbers of families using narrow bipolar phenotype models may be more productive than using broader models. The relationship between unipolar illnesses seen in families with bipolar disorder and in other families where there is no apparent bipolar diathesis remains speculative. Whether the same or different genes contribute to the heritability of depressive illness in these two types of families remains an open question that will only be answered when the risk genes in both are identified.

30.11

Conclusions

Although familial patterns of depressive illnesses have been noted for over 100 years, a precise description of their genetic mechanisms continues to remain an elusive goal. As emphasized in this chapter, the unique advantage of genetic linkage studies is that they do not require any knowledge of the pathophysiology of the illness being investigated. By identifying chromosomal regions of interest where risk genes may reside, linkage studies pave the way for further investigations such as fine-mapping studies to further define the region, and candidate gene studies, which can pin down the disease gene itself. As the entire DNA sequence of the human genome is progressively refined, as more genes are identified, as more sequence variants (SNPs) are catalogued, and as the expression of genes in areas of the brain becomes easier to detect and measure through more efficient molecular techniques, it will become progressively easier to investigate the implications of linkage findings. As neuroscience elucidates the function of the products of these genes, a verifiable model of the pathophysiology of depression should become possible.

Linkage studies of depressive illnesses have accumulated slowly relative to similar studies in schizophrenia and bipolar disorder, largely because the lower heritability of depressive disorders led to the belief that linkage would be more difficult to find. Nevertheless, at the time of this writing, the first three genome scans in depression have been completed and more are on the way.

Several developments in the field of linkage studies have the potential to accelerate progress in investigations of the genetics of depressive illnesses. First, larger samples will provide more power to detect genes of modest effect. For example, the complete GENRED sample consists of some 971 sibling pairs, surpassing the number gathered for any previous study of depressive illness. The Depression Network Project based in England aims to collect a sample of comparable size.

Molecular and statistical developments are also advancing rapidly. As denser genotyping becomes available, it will be possible to perform linkage analyses that include more DNA markers that are more tightly spaced, enhancing the power to detect linkage. More sophisticated computational approaches to test for marker–marker interaction that are being developed will allow for better power to detect interacting genes.

Approaches that emphasize clinical insights into the depressive phenotype may prove useful as well. Phenotypic subtyping has already included recurrent illness, early onset, and sex as co-variants in analyses and other variables such as comorbid dysthymia, chronicity of depressive symptoms, comorbid substance dependence, and comorbid panic disorder may prove useful phenotypic subcategories of depressive illness.

Endophenotypes may help to parse genetic heterogeneity. Endophenotypes are measurable phenotypic traits or markers that represent the effect of underlying risk genes carried by individuals with genetic vulnerability to developing illness but who may or may not have illness symptoms themselves. Endophenotypes can be thought of as intermediates between risk genes and illness expression, or perhaps, as proxies for illness genes. Abnormal eye movements have been described in patients with schizophrenia and also in their non-ill relatives and are thought to represent just such a proxy measure of risk genes for schizophrenia [43]. It has been suggested that investigations into variations in mood regulation, neuroendocrine function, sleep regulation, and stress responsivity in patients with depressive illness and their relatives may identify endophenotypes for depressive disorders that will facilitate genetic research [44].

References

- 1 MORTON, N. E., LINDSTEN, J., ISELIUS, L., YEE, S., Data and theory for a revised chiasma map of man. *Hum. Genet.* **1982**, *62*, 266–270.
- 2 LANDER, E., KRUGLYAK, L., Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nature Genet.* **1995**, *11*, 241–247.
- 3 PENROSE, L. S., The general purpose sib-pair linkage test. *Ann. Eugen.* **1953**, *18*, 120–124.
- 4 ANDREW, M., MCGUFFIN, P., KATZ, R., Genetic and non-genetic subtypes of major depressive disorder. *Br. J. Psychiatry* **1998**, *173*, 523–526.
- 5 WINOKUR, G., CORYELL, W., ENDICOTT, J., AKISKAL, H., KELLER, M., MASER, J. D., et al., Familial depression versus depression identified in a control group: are they the same? *Psychol. Med.* **1995**, *25*, 797–806.
- 6 SULLIVAN, P. F., NEALE, M. C., KENDLER, K. S., Genetic epidemiology of major depression: review and meta-analysis. *Am. J. Psychiatry* **2000**, *157*, 1552–1562.
- 7 LEVINSON, D. F., ZUBENKO, G. S., CROWE, R. R., DePAULO, R. J., SCHEFTNER, W. S.,

- WEISSMAN, M. M., et al., Genetics of recurrent early-onset depression (GenRED): Design and preliminary clinical characteristics of a repository sample for genetic linkage studies. *Am. J. Med. Genet.* **2003**, *119B* (1), 118–130.
- 8 LYONS, M. J., EISEN, S. A., GOLDBERG, J., TRUE, W., LIN, N., MEYER, J. M., et al., A registry-based twin study of depression in men. *Arch. Gen. Psychiatry* **1998**, *55*, 468–472.
 - 9 BLAND, R. C., NEWMAN, S. C., ORN, H., Recurrent and nonrecurrent depression. A family study. *Arch. Gen. Psychiatry* **1986**, *43*, 1085–1089.
 - 10 KRAEPELIN, E., *Manic-depressive Insanity and Paranoia*. Trans. BARCLAY, R. M., ROBERTSON, G. M. (Eds.) (1921 reprint). New York: Arno Press, **1976**.
 - 11 LEONHARD, K., *Aufteilung der endogenen Psychosen* (2nd ed.). Berlin: Akademie Verlag, **1959**.
 - 12 PERRIS, C., A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. *Acta Psychiatr. Scand.* **1966**, *42* (Suppl. 194).
 - 13 WINOKUR, G., CLAYTON, P., REICH, T., *Manic Depressive Illness*. Saint Louis: The C. V. Mosby Company, **1969**.
 - 14 ANDREASEN, N. C., RICE, J., ENDICOTT, J., CORYELL, W., GROVE, W. M., REICH, T., Familial rates of affective disorder. A report from the National Institute of Mental Health Collaborative Study. *Arch. Gen. Psychiatry* **1987**, *44*, 461–469.
 - 15 WINOKUR, G., CORYELL, W., KELLER, M., ENDICOTT, J., LEON, A., A family study of manic-depressive (bipolar I) disease. Is it a distinct illness separable from primary unipolar depression? *Arch. Gen. Psychiatry* **1995**, *52*, 367–373.
 - 16 MENDLEWICZ, J., FLEISS, J. L., Linkage studies with X-chromosome markers in bipolar (manic-depressive) and unipolar (depressive) illnesses. *Biol. Psychiatry* **1974**, *9*, 261–294.
 - 17 MCGUFFIN, P., RIJSDIJK, F., ANDREW, M., SHAM, P., KATZ, R., CARDNO, A., The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch. Gen. Psychiatry* **2003**, *60*, 497.
 - 18 TSUANG, M. T., WINOKUR, G., CROWE, R. R., Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. *Br. J. Psychiatry* **1980**, *137*, 497–504.
 - 19 WEITKAMP, L. R., PARDUE, L. H., HUNTZINGER, R. S., Genetic marker studies in a family with unipolar depression. *Arch. Gen. Psychiatry* **1980**, *37*, 1187–1192.
 - 20 WINOKUR, G., CADORET, R., DORZAB, J., BAKER, M., Depressive disease: a genetic study. *Arch. Gen. Psychiatry* **1971**, *24*, 135–144.
 - 21 TANNA, V. L., WINOKUR, G., ELSTON, R. C., GO, R. C., A linkage study of pure depressive disease: the use of the sib-pair method. *Biol. Psychiatry* **1976**, *11*, 767–771.
 - 22 TANNA, V. L., WINOKUR, G., ELSTON, R. C., GO, R. C., A linkage study of depression spectrum disease: the use of the sib-pair method. *Neuropsychobiology* **1976**, *2*, 52–62.
 - 23 TANNA, V. L., GO, R. C., WINOKUR, G., ELSTON, R. C., Possible linkage between alpha-haptoglobin (Hp) and depression spectrum disease. *Neuropsychobiology* **1979**, *5*, 102–113.
 - 24 TANNA, V. L., WILSON, A. F., WINOKUR, G., ELSTON, R. C., Linkage analysis of pure depressive disease. *J. Psychiatr. Res.* **1989**, *23*, 99–107.
 - 25 WILSON, A. F., TANNA, V. L., WINOKUR, G., ELSTON, R. C., HILL, E. M., Linkage analysis of depression spectrum disease. *Biol. Psychiatry* **1989**, *26*, 163–175.
 - 26 CROWE, R. R., NAMBOODIRI, K. K., ASHBY, H. B., ELSTON, R. C., Segregation and linkage analysis of a large kindred of unipolar depression. *Neuropsychobiology* **1981**, *7*, 20–25.
 - 27 HILL, E. M., WILSON, A. F., ELSTON, R. C., WINOKUR, G., Evidence for possible linkage between genetic markers and affective disorders. *Biol. Psychiatry* **1988**, *24*, 903–917.
 - 28 COX, N., REICH, T., RICE, J., ELSTON, R., SCHOBBER, J., KEATS, B., Segregation and linkage analyses of bipolar and major depressive illnesses in multigenerational pedigrees. *J. Psychiatr. Res.* **1989**, *23*, 109–123.
 - 29 MCGUFFIN, P., KATZ, R., WATKINS, S., RUTHERFORD, J., A hospital-based twin

- register of the heritability of DSM-IV unipolar depression. *Arch. Gen. Psychiatry* **1996**, 53, 129–136.
- 30 KENDLER, K. S., GARDNER, C. O., PRESCOTT, C. A., Clinical characteristics of major depression that predict risk of depression in relatives. *Arch. Gen. Psychiatry* **1999**, 56, 322.
 - 31 BERTENSEN, A., HARVALD, B., HAUGE, M., A Danish twin study of manic-depressive disorders. *Br. J. Psychiatry* **1977**, 130, 330–351.
 - 32 TORGENSEN, S., Genetic factors in moderately severe and mild affective disorders. *Arch. Gen. Psychiatry* **1986**, 43, 222–226.
 - 33 ZUBENKO, G. S., HUGHES, H. B., STIFFLER, J. S., ZUBENKO, W. N., KAPLAN, B. B., Genome survey for susceptibility loci for recurrent, early-onset major depression: results at 10cM resolution. *Am. J. Med. Genet.* **2002**, 114, 413–422.
 - 34 SPIELMAN, R. S., MCGINNIS, R. E., EWENS, W. J., Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am. J. Hum. Genet.* **1993**, 52, 506–516.
 - 35 NURNBERGER JR., J. I., FOROUD, T., FLURY, L., SU, J., MEYER, E. T., HU, K., et al., Evidence for a locus on chromosome 1 that influences vulnerability to alcoholism and affective disorder. *Am. J. Psychiatry* **2001**, 158, 718–724.
 - 36 ZUBENKO, G. S., HUGHES III, H. B., MAHER, B. S., STIFFLER, J. S., ZUBENKO, W. N., MARAZITA, M. L., Genetic linkage of region containing the CREB1 gene to depressive disorders in women from families with recurrent, early-onset, major depression. *Am. J. Med. Genet.* **2002**, 114, 980–987.
 - 37 SULSER, F., The role of CREB and other transcription factors in the pharmacotherapy and etiology of depression. *Ann. Med.* **2002**, 34, 348–356.
 - 38 ZUBENKO, G. S., MAHER, B., HUGHES III, H. B., ZUBENKO, W. N., STIFFLER, J. S., KAPLAN, B. B., et al., Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. *Am. J. Med. Genet.* **2003**, 123B, 1–18.
 - 39 ABKEVICH, V., CAMP, N. J., HENSEL, C. H., NEFF, C. D., RUSSELL, D. L., HUGHES, D. C., et al., Predisposition locus for major depression at chromosome 12q22-12q23.2. *Am. J. Hum. Genet.* **2003**, 73, 1271–1281.
 - 40 HOLMANS, P., ZUBENKO, G. S., CROWE, R. R., DEPAULO JR., J. R., SCHEFTNER, W., WEISSMAN, M. M., et al., Genome scan of recurrent early-onset major depression. *Am. J. Hum. Genet.* **2004**, 14, 1154–1167.
 - 41 MORISSETTE, J., VILLENEUVE, A., BORDELEAU, L., ROCHETTE, D., LABERGE, C., GAGNE, B., et al., Genome-wide search for linkage of bipolar affective disorders in a very large pedigree derived from a homogeneous population in quebec points to a locus of major effect on chromosome 12q23-q24. *Am. J. Med. Genet.* **1999**, 88, 567–587.
 - 42 SEGURADO, R., DETERA-WADLEIGH, S. D., LEVINSON, D. F., LEWIS, C. M., GILL, M., NURNBERGER JR., J. I., et al., Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. *Am. J. Hum. Genet.* **2003**, 73, 49–62.
 - 43 CALKINS, M. E., IACONO, W. G., CURTIS, C. E., Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives. *Int. J. Psychophysiology* **2003**, 49, 139–146.
 - 44 MERIKANGAS, K. R., CHAKRAVARTI, A., MOLDIN, S. O., ARAJ, H., BIANGERO, J., BURMEISTER, M., et al., Future of genetics of mood disorders research. *Biol. Psychiatry* **2002**, 52, 457–477.
 - 45 SCHELLENBERG, G. D., BIRD, T. D., WIJSMAN, E. M., ORR, H. T., ANDERSON, L., NEMES, E., et al., Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14. *Science* **1992**, 258, 668–671.
 - 46 STRAUB, R. E., LEHNER, T., LUO, Y., LOTH, J. E., SHAO, W., SHARPE, L., et al., A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nature Genet.* **1994**, 8, 291–296.
 - 47 STINE, O. C., XU, J., KOSKELA, R., MCMAHON, F. J., GSCHWEND, M., FRIDDLE, C., et al., Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *Am. J. Hum. Genet.* **1995**, 57, 1384–1394.

- 48 DETERA-WADLEIGH, S. D., BADNER, J. A., GOLDIN, L. R., BERRETTINI, W. H., SANDERS, A. R., ROLLINS, D. Y., et al., Affected-sib-pair analyses reveal support of prior evidence for a susceptibility locus for bipolar disorder, on 21q. *Am. J. Hum. Genet.* **1996**, *58*, 1279–1285.
- 49 BERRETTINI, W. H., FERRARO, T. N., GOLDIN, L. R., DETERA-WADLEIGH, S. D., CHOI, H., MUNIEC, D., et al., A linkage study of bipolar illness. *Arch. Gen. Psychiatry* **1997**, *54*, 27–35.
- 50 EWALD, H., DEGN, B., MORS, O., KRUSE, T. A., Support for the possible locus on chromosome 4p16 for bipolar affective disorder. *Mol. Psychiatry* **1998**, *3*, 442–448.
- 51 AITA, V. M., LIU, J., KNOWLES, J. A., TERWILLIGER, J. D., BALTAZAR, R., GRUNN, A., et al., A comprehensive linkage analysis of chromosome 21q22 supports prior evidence for a putative bipolar affective disorder locus. *Am. J. Hum. Genet.* **1999**, *64*, 210–217.
- 52 DETERA-WADLEIGH, S. D., BADNER, J. A., BERRETTINI, W. H., YOSHIKAWA, T., GOLDIN, L. R., TURNER, G., et al., A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. *PNAS* **1999**, *96*, 5604–5609.
- 53 CICHON, S., SCHMIDT-WOLF, G., SCHUMACHER, J., MULLER, D. J., HURTER, M., SCHULZE, T. G., et al., A possible susceptibility locus for bipolar affective disorder in chromosomal region 10q25–q26. *Mol. Psychiatry* **2001**, *6*, 342–349.
- 54 KELSOE, J. R., SPENCE, M. A., LOETSCHER, E., FOGUET, M., SADOVNICK, A. D., REMICK, R. A., et al., A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. *PNAS* **2001**, *98*, 585–590.
- 55 WILLOUR, V. L., ZANDI, P. P., HUO, Y., DIGGS, T. L., CHELLIS, J. L., MACKINNON, D. F., et al., Genome scan of the fifty-six bipolar pedigrees from the NIMH genetics initiative replication sample: chromosomes 4, 7, 9, 18, 19, 20, and 21. *Am. J. Med. Genet.* **2003**, *121B* (1), 21–27.
- 56 DICK, D. M., FOROUD, T., FLURY, L., BOWMAN, E. S., MILLER, M. J., RAU, N. L., et al., Genome-wide linkage analyses of bipolar disorder: a new sample of 250 pedigrees from the National Institute of Mental Health Genetics Initiative. *Am. J. Hum. Genet.* **2003**, *73*, 107–114.

Recommended reading

- FARAONE, S. V., TSUANG, M. T., TSUANG, D. W., *Genetics of Mental Disorder: A Guide for Students, Clinicians and Researchers*. New York: The Guilford Press, **1999**.
An excellent introduction to psychiatric genetics.
- HAINES, J. L., PERICAK-VANCE, M. A. (Eds.), *Approaches to Gene Mapping in Complex Human Diseases*. New York: Wiley-Liss, **1998**.
A more advanced text focusing on research design and execution.
- STRACHAN, T., READ, A. P., *Human Molecular Genetics*, 2nd ed. New York: John Wiley & Sons, Inc., **1999**.
A well-written and comprehensive resource for understanding all things genetic, from basic cell biology to gene therapy.

31

Genetic Approaches to Depression: Association Studies*Kopal Tandon and Katherine J. Aitchison***Abstract**

Genetic association studies provide a powerful mechanism with which to identify susceptibility genes for depression. Most of the association studies conducted in depression to date have concentrated on candidate genes from the monoamine system, including monoamine receptors, transporters and enzymes that are involved in the synthesis and breakdown of monoamines. However, despite the significant *a priori* evidence to suggest the involvement of the genes encoding these proteins in the etiology of depression, the results from association studies have been inconsistent. The reasons for this include lack of power in studies due to factors such as small sample sizes, use of phenotypes in depression which are not associated with optimal measures of heritability, and inadequately screened controls. Susceptibility genes may increase our susceptibility to depression through their interaction with the environment, and association studies are now beginning to examine gene–environment correlations and interactions. Linkage scans in the depression are now beginning to be published, and association studies investigating genes in the hot-spots identified by the linkage scans will have the potential for identifying new depression genes.

31.1**Introduction**

The study of the genetic epidemiology of depression through adoption, family and twin studies has revealed that there is a clear genetic contribution to depression [1], and the focus has now turned to finding the genes that are involved in the susceptibility to the disorder. The molecular tools available for hunting these genes include linkage analysis and allelic association, and this chapter will focus on allelic association studies. Early studies looked at the association between depression and blood groups, which were easily identified polymorphisms present in the general population [2–6]. Now, with the completion of the initial draft of the human genome

sequence and the accessibility of databases of polymorphisms present in the sequence, the door for future association studies in neuropsychiatric disorders including depression has been thrown open. However, these early studies provided an early indication of the difficulties that future association studies in depression would face, with failure of replication of initial positive findings and contradictory results in different ethnic populations. Nevertheless, some positive findings have been replicated and investigators are using increasingly sophisticated techniques in the search for the 'blue' genes.

31.2

Allelic Association

A disease is said to be associated with an allele at a particular locus when the allele is present in subjects with the disease at a frequency greater than that expected by chance. This association between the allele and the disease does not necessarily imply a causative relationship, due to the phenomenon of linkage disequilibrium, and false positive associations can also result from population stratification. Linkage disequilibrium (LD) occurs when two markers are linked on the same chromosome, such that they are unlikely to be separated by recombination during meiosis and tend to be inherited together even over subsequent generations. The degree of LD does gradually decay over time, and is also affected by factors relating to the population in which it is occurring, e.g. the size and the degree of outbreeding of the population, and the mutational and recombinational history of the two markers within that particular population. There has been shown to be great variability in the level of LD, ranging from being almost complete to almost absent, for loci separated by the same distance [7]. Population stratification results from the presence of subgroups which vary both in the frequency of a disease as well as the frequency of a particular allele, so that the frequency of both may be higher in particular subgroups compared to others. This will result in a "spurious" association between the disease and the allele. It is also possible for population stratification to mask a real association.

Allelic association studies are normally case-control studies in design, and genotype or allele frequencies are compared between individuals with the disease and unaffected control subjects from the same population. The significance of an association is determined using the chi-squared test, and some studies also use the odds ratio to measure the size of an association between a particular polymorphism and the disorder. The presence of confounding factors (e.g. sex or ethnicity) can be overcome through the use of either linear regression, controlling for the confounding factor, or stratified analysis. It is particularly interesting to examine the effects of a candidate gene on the two genders separately as there is evidence from both quantitative genetic studies as well as association studies that genes may be having differential effects, depending on gender, on the susceptibility to depression [8, 9]. Association can be determined by examining the overall difference in the frequency of an allele between the cases and controls, or by comparing the cases

and controls for the frequency of the different genotypes (e.g. homozygous for wild type allele, heterozygous wild type allele or homozygous for mutant allele at a locus with two alleles).

If two or more markers within a gene are genotyped for association with a disease, haplotype analysis can be performed. This is useful if there are a number of polymorphisms present at various positions in the gene of interest and it is not clear, which, if any, of the polymorphisms genotyped, is causative. Assuming that the causative polymorphism is not itself included, the disease may be more significantly associated with a particular haplotype (a set of alleles at two or more adjacent loci) than with a single high risk allele at any of the loci genotyped. Haplotype analysis depends on the presence of LD between the specific alleles of a haplotype, and if a particular haplotype is strongly associated with a disease, it suggests that this haplotype is descended from an ancestral chromosome on which the causative mutation had occurred and that each of the high risk alleles within this haplotype are still flanked by a variable-length segment of that ancestral chromosome [10]. Haplotypes can be inferred using statistical techniques [11], or alternatively may be accurately constructed if sufficient family data is available.

One method for overcoming the problems posed by population stratification is to carefully choose cases and controls so that they come from as similar a population as possible, and to exclude individuals of mixed or uncertain ethnic origin. However, in modern multi-ethnic societies, this is not always feasible without the loss of valuable subjects and the population substructure may also be not so apparent. The most popular method used to overcome this is to perform a family-based association study using a case-parent trio (affected case and both parents). The genotypes at the locus of interest in the affected case and the parents are compared to determine which alleles are transmitted to the case and which are not. The results can be analysed using the haplotype-based haplotype relative risk method [12] or the transmission-disequilibrium test [13].

Allelic association studies have in the main been used to examine candidate genes that are hypothesized to be involved in the etiology of the disorder, although this does have the restriction that it depends on our current understanding of the pathophysiology of the disorder. With depression, the candidate genes selected have on the whole been from the pathways involved in monoamine neurotransmission. Allelic association, however, can also be used to complement linkage analysis studies, by further examining chromosomal hot-spots which have been identified by linkage analysis as being likely to contain a susceptibility gene.

31.3

Diagnostic Issues

Diagnostic validity, or the extent to which a diagnosis captures a cohort of cases with a disorder of relatively homogenous underlying pathophysiology, is of importance in the success of molecular genetic studies. For a complex disorder such as depression, where twin studies show that there is complex interplay of

environmental and genetic factors in the etiology [1], where clinical experience informs us that there is a wide variation in presentation, and where multiple genes of small effect are likely to be involved [14], this poses particular problems. However, there are certain subtypes of depression that are associated with increased measures of heritability, for example recurrent depression [1], and focusing on these subtypes may prove more fruitful in the search for susceptibility genes. Other investigators have focused on the particular symptoms within subjects diagnosed with depression (e.g. paranoid ideation) [15] or possible endophenotypes for the disorder (e.g. alterations in auditory evoked potentials) [16]. The relationship between depression and underlying genetic factors may not be direct, and it may be that the genes involved in the etiology of depression influence a more basic trait, that then makes individuals susceptible to depression (e.g. harm avoidance and neuroticism). These personality traits have been shown to share genetic vulnerability with depression [8, 17, 18]. Given the variable age of onset and fluctuating course of depression, when defining cases and controls, a lifelong perspective should be taken rather than current presentation. Cases and controls should also be matched for age, so that they have passed through a comparable period of risk for development of the disorder. For a quantitative trait, such as neuroticism, it is likely that there are multiple genes involved and that these genes, or quantitative trait loci (QTLs), may act additively or interchangeably [19]. It has also been argued that selecting individuals at the extremes of a trait may increase the power of association studies to find QTLs acting to determine that trait across its range [20]. This depends on the assumption that the QTLs contributing to the extremes of a trait are the same as those that are acting across the normal distribution.

31.4

Association Studies Examining the Monoamine System

The monoamine hypothesis of depression, developed in the 1960s, was the first major theory pertaining to the etiology of depression. The antidepressants available at the time, monoamine oxidase inhibitors and tricyclic antidepressants, were known to increase transmission of serotonin, noradrenaline and dopamine, and further evidence in support for the theory was provided by drugs that depleted stores of these neurotransmitters inducing symptoms of depression [21]. However, it was noted that there was a delay in the action of antidepressants despite an immediate increase in the monoamine levels and this led to the further refinement of the hypothesis. It was proposed that there was an abnormality in the function of the monoamine neurotransmitter receptors rather than in the levels of the neurotransmitters *per se*. Association studies in depression have not only used monoamine receptors as candidate genes, but have also focused on genes involved in the synthesis and degradation of monoamines, neurotransmitter transporters, as well as the G-proteins that are coupled to the monoamine receptors.

31.5

The Serotonin Transporter and Association Studies with Depression

There are several important candidate genes that are present in the serotonin system that have been used in association studies in depression (see Figure 31.1). Most of the published association studies examining the genetic etiology of depression, as well as the personality traits neuroticism and harm avoidance, have focused on the role of the serotonin transporter. This certainly makes a good candidate gene, being the primary site of action of the commonly used serotonin selective reuptake inhibitors, as well as a site of action for tricyclic antidepressants and venlafaxine. It is a transmembrane protein that mediates presynaptic reuptake of serotonin, and therefore acts to terminate serotonin transmission. Post-mortem studies of brains of depressed patients and subjects that have committed suicide show that there are decreased levels of the serotonin transporter present [22]. The gene maps to chromosome 17q11.1-12 and there are two main polymorphisms that have been studied in depression. The promoter region for the serotonin gene has a 44-base pair insertion/deletion polymorphism within a series of repeats [23]. When the deletion is present, i.e. the short form of the gene, the transcriptional efficiency of the promoter is reduced and this results in decreased expression of the transporter

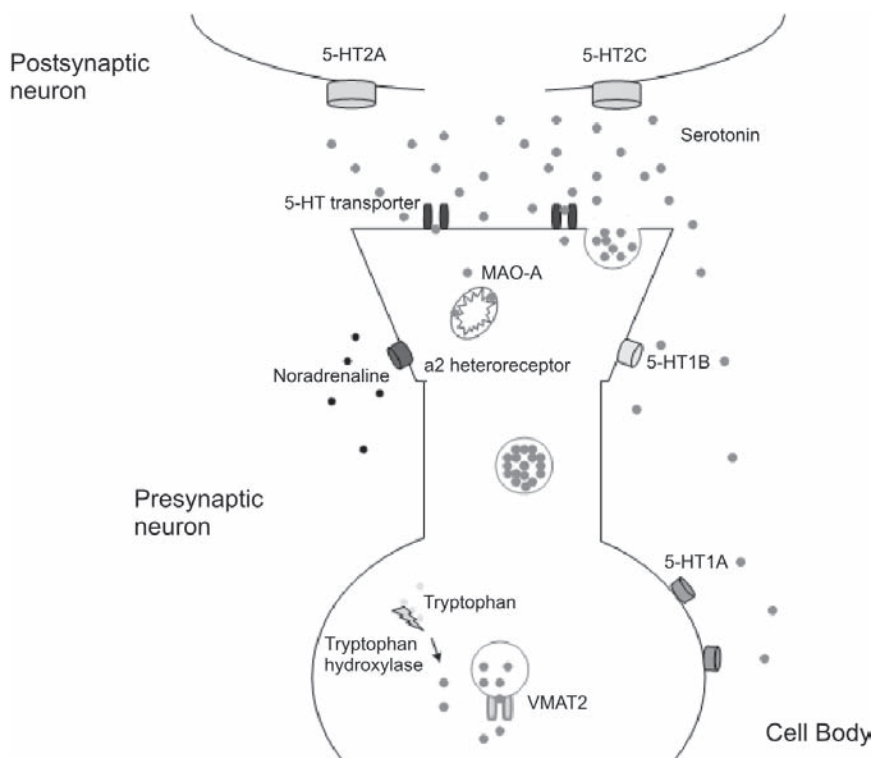


Figure 31.1 Schematic diagram showing pre- and postsynaptic serotonergic neurons

as well as decreased 5-HT (serotonin) uptake in lymphoblasts [24]. Neuroimaging studies in human subjects also demonstrated that individuals with at least one short allele of the transporter polymorphism show greater amygdala activity when exposed to fearful stimuli compared to those homozygous for the long allele [25]. As the serotonin promoter polymorphism is functional, it raises the possibility that, when a positive association is found with it, the polymorphism may be, at least in part, causative.

A variable number tandem repeat (VNTR) polymorphism has also been described in intron 2 of the serotonin transporter. The allele for nine repeats of a 16/17-base pair segment has been found to be rare, while the 10 or 12 repeat alleles are more common [26]. There is some evidence that the VNTR may have functional significance as it has been shown to have transcription regulation properties, and the 12-repeat allele has been shown to have greater enhancer ability compared to the 10-repeat allele in differentiating embryonic stem cells [27]. Sequence differences in the repeat elements themselves may also have an effect on the enhancer activity [28]. Significant linkage disequilibrium has been reported between it and the promoter insertion/deletion polymorphism [29]; however, the extent of this is contentious [30].

The initial positive association with the serotonin transporter in depression was made by Ogilvie et al. in 1996 [31]. They found an association between the nine-repeat VNTR allele and depression in a small sample of 39 Scottish patients diagnosed with depression according to the Schedule for Affective Disorders – Lifetime version (SADS-L) and 122 anonymous blood donors and 71 volunteers screened for psychiatric illness (see Table 31.1). Genotypes containing the nine-repeat allele were significantly increased in frequency in patients with depression ($\chi^2 = 10.05$, $P < 0.004$) and the risk of depression with the presence of the nine-repeat allele was 6.95 (95% confidence interval (CI) 1.8–27.2). This finding was confirmed by extension of the above sample to include 119 subjects with depression (diagnosed using the SADS-L) and 346 controls, 103 of whom were screened for psychiatric illness [32]. Again there was a significant difference found in the allelic frequencies between the control group and the depressed group ($\chi^2 = 10.51$, 2df, $P = 0.005$) and the odds ratio of the risk of unipolar disorder given a single nine-repeat allele was 4.44 (95% CI, 1.65–11.95). We also found an association between the nine-repeat allele and depression in a small sample of patients with recurrent depression of moderate severity (K. Aitchison, unpublished data). However, when this sample was extended to include further patients with less severe forms of depression, the association was lost, although a significant difference in the frequency of the 12-allele repeat in bipolar patients compared to controls was found [33]. Other subsequent association studies with the exon 2 VNTR in depressed Caucasian and Japanese subjects were also negative [30, 34–36]. The subsequent contradictory findings could be in part due to methodological differences. The initial positive findings had used a diagnostic instrument to diagnose depression, and had also screened a proportion of their controls in a systematic manner for a personal history of psychiatric illness. The differing results in the Japanese subjects may also be due to population stratification effects, and all studies involved small sample

sizes, so false negative results cannot be excluded. Furlong et al. [30] undertook a meta-analysis of published findings in Caucasian subjects; this sample included 229 patients with depression and 772 controls. They found that there was no significant association with the VNTR. However, the overall number of patients included in the meta-analysis was small, and it can still be argued that the role of the exon 2 VNTR in depression remains unresolved. A study published subsequent to the meta-analysis, in the Han Chinese with 33 patients with depression and 362 controls, found an association between depression and the 12-repeat allele ($P = 0.0107$) [37]. However, they only located the 12-allele repeat in their small sample of depressed subjects. This may be a false positive result, or the difference in results may be due to population stratification effects.

The initial study of the serotonin promoter polymorphism in depression was by Collier et al. in 155 Caucasian patients with depression and 584 controls of whom 104 had been screened for a personal history of psychiatric illness [38]. The subjects were recruited from three European areas. They were unable to find an association between the serotonin promoter polymorphism and depression. Most of the subsequent studies of the role of the serotonin transporter in depression have also been negative (see Table 31.2). Furlong et al. [30], in their meta-analysis of 275 depressed Caucasian patients and 739 controls, found that the short allele of the polymorphism was associated with depression ($\chi^2 = 4.10$, $df = 1$, $P = 0.042$, $OR = 1.23$ (95% CI, 1.01–1.52). The small OR suggests that the effects of having the short allele are small in terms of risk of depression.

Studies of the role of the promoter polymorphism have also been studied in seasonal affective disorder (SAD), and with an initial positive finding in Caucasian patients with SAD (72 with unipolar depression and 25 with bipolar affective disorder), and 71 controls with low seasonality scores, as measured by the Global Seasonality Score instrument [39]. The investigators found an association with SAD and genotypes containing the short allele (i.e. homozygous or heterozygous for the s allele, $\chi^2 = 7.13$, $P < 0.01$). However, this association was not replicated by others [40–42]. In their meta-analysis of Caucasian subjects, 464 with seasonal affective disorder and 414 controls, Johansson et al. also failed to find an association [42]. The researchers note that there were significant differences in the distribution of genotypes in the control subjects in the initial positive study compared to controls in their study [39], and that this may explain the differences in results. It is also interesting to note that an association between subtypes of depression and the promoter polymorphism was found in seasonal affective disorder patients in one of the studies [41]. Patients with the melancholic depression were significantly more likely to be homozygous for the long allele ($P = 0.0012$), while patients with atypical depression were more likely to have the short allele ($P = 0.007$).

Gutierrez et al. failed to find an association with the exon 2 VNTR of the promoter polymorphism in their study of 74 Spanish Caucasian patients with melancholia and 84 controls who had been screened for personal and family history of depression [43]. However, they did find an association between melancholic depression and a haplotype containing the 10-repeat allele on the exon 2 VNTR and the short allele of the promoter polymorphism ($\chi^2 = 7.298$, $P < 0.0069$).

Table 31.1 Case-controlled studies of depression: serotonin system, serotonin transporter, exon 2 VNTR

Study	Diagnostic instrument used	Ethnicity of subjects	Number of patients	Number of controls	Significant associations found
Ogilvie et al. [31]	SADS-L	Scottish	39	199 (77 screened using the SADS-L)	Association with genotypes containing the 9-repeat allele: $\chi^2 = 10.05$, $P < 0.004$, OR = 6.95 (95% CI: 1.8–27.2)
Battersby et al. [32]	SADS-L	Scottish	119	346, 103 screened for personal psychiatric history	Association with genotypes containing the 9-repeat allele: $\chi^2 = 10.23$, 1df, $P = 0.001$, OR = 4.44 (95% CI: 1.65–11.95)
Liu et al. [37]		Han Chinese	33	362	Association with the 12-repeat allele ($P = 0.0107$)
Collier et al. [33]		Caucasian	86	187	No association found*
Stober et al. [34]	SADS-L	Caucasian	49	218	No significant association
Furlong et al. [30]	SADS-L	Caucasian	125	174	No significant association
Kunugi et al. [35]		Japanese	42	137	No significant association
Kunugi et al. [36]		Japanese	49	212	No significant association

* There was a significant difference in the frequency of the 12-allele repeat in patients with bipolar affective disorder compared to the controls.

Table 31.2 Case-controlled studies of depression: serotonin system, serotonin transporter, promoter VNTR

Study	Diagnostic instrument used	Ethnicity of subjects	Number of patients	Number of controls	Significant associations found
Collier et al. [38]		Caucasian	155	584, 104 screened for personal history of psychiatric illness	No association found*
Furlong et al. [30]	SADS-L	Caucasian	125	174	No association found
Frisch et al. [127]	SADS-L or SCID	Jewish (mainly Ashkenazi)	102	172 screened for personal history of psychiatric illness	No association found
Kunugi et al. [36]		Japanese	49	212	No association found
Ohara et al. [170]	SADS	Japanese	46	92	No association found
Minov et al. [171]		German	173	121 screened for personal history of psychiatric illness	No association found
Johansson et al. [134]	All cases had SAD†	Caucasian	116 (+ 3 with BPAD)	115 screened for personal history of psychiatric illness	No association found with seasonal affective disorder;‡
Rosenthal et al. [39]	All cases had SAD	Mainly Caucasian	72 (+ 25 with BPAD)	71, all with low seasonality scores	Association with at least one s allele: $\chi^2 = 7.13$, $P < 0.01$
Johansson et al. [42]	All cases had SAD	Caucasian	82	82 screened for personal and family history of psychiatric illness	No significant association found
Willleit et al. [41]	All cases had SAD	Caucasian	99 (+ 39 with BPAD)	146 screened for personal psychiatric history, all with low seasonality scores	ll genotype associated with melancholic depression ($P = 0.0012$), and the s allele with atypical depression ($P = 0.007$)
Serretti et al. [172]		Italian descent	667	457	No significant association
Gutierrez et al. [43]		Not detailed	74	84 ethnically matched, and screened for personal and family history of psychiatric illness	No significant association

* An association was found with the short allele in a combined group of patients with affective disorder, which included 305 patients with bipolar affective disorder.

† Seasonal affective disorder.

‡ Did find an association with seasonality scores, as measured by the Global seasonality score (GBS) in 226 subjects recruited due to unusually high or low seasonality scores.

§ Also genotyped the exon 2 VNTR, and found a significant association between a depression and a haplotype consisting of the short promoter allele and the 10-repeat allele of the exon 2 VNTR ($\chi^2 = 7.298$, $P < 0.0069$).

31.6

Serotonin Transporter and Association Studies with Personality Traits

The original study finding an association between neuroticism and harm avoidance and the serotonin transporter promoter polymorphism was by Lesch et al. [24]. In their study of 505 individuals consisting predominantly of male siblings, other family members and volunteers, individuals with at least one short promoter had higher neuroticism scores (measured using the Neuroticism Extraversion Openness–Personality Inventory–Revised (NEO-PI-R™) than individuals homozygous for the long allele ($P = 0.002$). Weighted regression equations were used to estimate Tridimensional Personality Questionnaire (TPQ) scores from the NEO-PI-R™ data, and those genotypes containing the short allele were significantly associated with harm avoidance ($P = 0.004$ for a within pedigree test, $P = 0.0119$ for across pedigrees test). This finding was replicated predominantly in female siblings; in a mainly female population, the genotypes with at least one short allele were associated with neuroticism ($P = 0.006$), with those homozygous for the long allele having lower neuroticism scores than those with at least one short allele [44]. There was no association with the estimated TPQ harm avoidance scores. This predominantly female sample was combined with the previous predominantly male sample [24], to give 125 sib-pairs discordant for a serotonin promoter polymorphism genotypic group (either homozygous for the long allele or at least one short allele). Siblings with at least one short promoter allele were found to score significantly higher on neuroticism scores than their siblings homozygous for the long allele ($P = 0.012$) [44]. The association between the serotonin transporter promoter polymorphism and neuroticism has also been replicated by others. A trend for association between the short allele and higher scores for NEO-PI-R™ neuroticism ($P = 0.06$, after correcting for sex, age, and ethnic group as covariates), and a significant association with TPQ harm avoidance ($P = 0.03$) was found in a sample of 148 Israeli volunteers consisting of 74 same sex siblings [45]. Du et al. found a positive association between the Neuroticism Extraversion Openness–Five-Factor Inventory (NEO-FFI™) neuroticism scores and the short allele of the promoter but only in male patients ($P = 0.018$) [9]. Ricketts et al. showed a significant association between the short allele of the serotonin promoter polymorphism and harm avoidance in their sample of elderly depressed patients and elderly controls, with no significant interaction between diagnosis and genotype [46]. Subjects homozygous for the long allele had significantly lower mean harm avoidance scores than the heterozygous subjects ($P < 0.04$) and subjects homozygous for the short allele ($P < 0.003$), the results indicating a gene–dose effect of the short allele on this personality dimension. Katsuragi et al. found an association between the promoter polymorphism genotype and TPQ harm avoidance scores in a sample of 101 Japanese volunteers ($F = 5.24$, $P = 0.007$) [47]. However, the authors note that there was a statistically significant difference in the genotypic frequencies in their sample compared to those in the original Lesch report [24], and their data was not consistent with a dominant effect of the s-allele, although their results did suggest that the short allele was the “at risk” allele.

Unfortunately, to similar serotonin promoter studies in depression, there have also been negative association studies, as well as findings suggesting that the short promoter allele is the protective and not the “at risk” allele. Brummett et al. found a positive association between neuroticism (measured using the NEO-PI-R™) and the serotonin promoter polymorphism, but their results suggested that the short allele was protective and only affected neuroticism scores in the males in their study of 103 elderly American depressed patients (97 Caucasian) and 99 elderly controls (87 Caucasian), who had been screened for a lifetime diagnosis of depression [48]. They found that those with at least one short promoter allele had significantly lower neuroticism scores, although their *P* value was marginal ($P = 0.043$). The females did not differ in their neuroticism score according to their genotype, and the association in males was found not to vary by clinical group. Similar gender-specific effects were found by Gelertner et al. whose study found that the presence of at least one short allele was associated with higher harm avoidance scores in males, but lower scores in females [49]. However, they did not undertake further stratified analysis by ethnic background in their study of 221 European Americans and 101 African Americans. There was no association with NEO-FFI™ neuroticism scores and the promoter polymorphism in their study. Samochowiec et al., in a study of Polish volunteers, failed to find an association between the serotonin promoter polymorphism and overall Cloninger’s temperament and character inventory (TCI) harm avoidance score, but did find that heterozygous individuals and individuals homozygous for the short allele scored significantly lower in the Harm Avoidance 1 (HA1) subdimension (anticipatory worry and pessimism versus uninhibited optimism) in comparison with individuals without the deletion ($P = 0.021$) [50]. This *P* value, however, was not corrected for multiple testing.

Deary et al. failed to find an association between the serotonin transporter promoter polymorphism or the exon 2 VNTR and neuroticism [51]. In their study of 901 Scottish individuals, who were asked to complete the NEO-FFI™, genotyping was performed on 100 high and 104 low neuroticism scorers, but no differences were found between these two groups in either the allelic or genotypic frequencies of the 5-HTTLPR or the exon 2 VNTR. Using a similar approach, Ball et al. also failed to find a positive association between the two serotonin transporter polymorphisms and a combined self- and peer-rated neuroticism score, assessed using a modified version of NEO-FFI™ [29]. Over 2000 German twins were asked to complete the self-report version, and give the peer-report version to two people who knew them very well and the results of the self- and peer-rated questionnaires were combined. The promoter polymorphism and the VNTR were genotyped in 52 individuals with high neuroticism scores and 54 individuals with low scores (from the top and bottom 5% of the distribution). Only one member of each twin pair was included. There have also been other studies which have failed to find association between the serotonin promoter transporter and neuroticism and harm avoidance [52–57].

From these studies, it is clear that the role of the serotonin transporter polymorphism in the development of the personality traits neuroticism and harm avoidance is far from clear. Nor is it clear if this effect occurs equally in both genders. While

most of the positive association findings suggest the at risk allele is the short allele of the serotonin transporter, there are some findings which indicate that the opposite is true [48–50] but these associations were coupled to small P values or complicated by possible population stratification effects. Burmeister et al. presented the results of a meta-analysis of association studies between the serotonin transporter and neuroticism at the World Congress in Psychiatric Genetics 2003 [58]. They obtained the raw data on neuroticism and harm avoidance scores (measured using various scales) from 23 studies looking at 5629 subjects, and found only weak evidence for association for between the anxiety-related traits. ($P = 0.087$). However, if they only included the studies which only measured NEO neuroticism, then there was a highly significant association between the serotonin promoter short allele and neuroticism ($P = 0.000016$). There did not appear to be any sex-specific effects. Their results suggest that the reasons for non-replication of the original Lesch findings are small sample sizes, and heterogeneity as a result of the use of different scales.

31.7

Serotonin Transporter and Endophenotypes of Depression

Given the complexity of depression, researchers have tried to find an endophenotype that may be accompanied by an increased susceptibility to depression. A genetic endophenotype is associated with the illness, is state independent (i.e. it occurs in individuals whether or not they are in an episode of illness), is heritable, and is found more frequently in unaffected family members than in the general population [59]. The genes acting in an endophenotype should be a subset of those acting in the disorder. Neuroticism and harm avoidance may be considered as endophenotypes. Alterations occurring in auditory evoked potentials are considered endophenotypes for various psychiatric disorders, including schizophrenia. Chen et al. looked for association between the serotonin promoter polymorphism and auditory evoked potentials in 127 depressed Chinese patients [16]; they examined the N1 and P2 components of the auditory evoked potential which is generated in the primary auditory cortex, which is densely innervated by serotonergic neurons. By performing stratified analysis on the women, they found that the P2 latency was significantly lower for individuals homozygous for the short allele compared to the other two genotypic groups ($P = 0.004$). This assumes a recessive effect for the short allele. It would be interesting to determine if this association between the P2 latency and the homozygous short genotype is also present in controls and high-risk subjects (i.e. in relatives of patients with depression).

Response to acute tryptophan depletion (TD) has also been studied as an endophenotype for depression. The depressive response to the TD test has also been shown to be predictor of relapse in depression in unmedicated patients [60]. Neumeister et al. studied the association between tryptophan depletion and the serotonin transporter promoter polymorphism in 24 healthy women without a family history of depression and 21 healthy women with a family history of depression [61]. There was no association between the extent of tryptophan depletion

and the serotonin promoter genotype, nor an effect of family history on the extent of depletion. Those individuals homozygous for the short serotonin promoter allele had the greatest increase in depressive symptoms with TD, and the short-short genotype was associated with an increased risk of developing depressive symptoms during TD irrespective of family history ($P < 0.001$, with FH, and $P = 0.007$ without FH). Individuals homozygous for the long promoter allele did not develop depressive symptoms, irrespective of family history. Individuals with the heterozygous genotype showed a significant increase in depressive symptoms irrespective of family history. However, the extent of these depressive symptoms significantly varied depending on whether there was a family history of depression. Those without a family history had a moderate increase in depressive symptoms, and but those with a family history of depression showed the same depressive effects of TD as seen in the subjects homozygous for the short allele. These results suggest that the effect of the short allele is additive, i.e. it does not appear, in this behavioural paradigm, to conform to a dominant effect of the short allele. It also shows, as would be predicted in a polygenic condition such as depression, that the effects of the short allele are additive to the family history or to the genetic background in which it occurs.

However, it is not clear how the relationship between the promoter polymorphism and response to TD in subjects without depression corresponds to the relationship in those who have experienced depression. Conflicting results were obtained in an association study of the promoter polymorphism in patients in remission from depression [62], where there was a significant association between increase in depressive symptoms and the homozygous long allele genotype in 37 Caucasians, with a main effect of time ($F = 5.422$, $df = 3$, 39 , $P = 0.003$). One reason for the difference in response may be due to 22 patients in this study being medicated at the time of the study, with 19 patients on SSRIs. The homozygous long allele genotype has been associated with a favorable response to SSRIs [63], and individuals with this genotype on SSRI medication may be particularly vulnerable to worsening depressive symptoms with tryptophan depletion.

31.8 Serotonin 2A Receptor

Treatment with antidepressants results in downregulation of brain serotonin 2A receptors (5-HT_{2A}), and alterations in the number of 5-HT_{2A} receptors is seen in post-mortem studies of patients with depression [64, 65]. A silent T102C polymorphism located in exon 1 has been identified [66]. There is evidence from a post-mortem study that the C allele is associated with lower levels of expression in the temporal cortex of normal heterozygous individuals compared to the T allele (ratio of allele C to allele T 0.8, $P < 0.0001$) [67]. Total levels of 5-HT_{2A} receptor mRNA and protein in normal individuals with the C/C genotype were also found to be lower than in individuals with the T/T genotype. However, there are also contradictory results which suggest that there is no effect of imprinting at this gene [68]. A promoter polymorphism 1438G/A has also been identified, which is

Table 31.3 Case-controlled studies of depression: serotonin system, serotonin 2A receptor

<i>Study</i>	<i>Polymorphism</i>	<i>Diagnostic instrument used</i>	<i>Ethnicity of subjects</i>	<i>Number of patients</i>	<i>Number of controls</i>	<i>Significant associations found</i>
Frisch et al. [127]	T102C	SADS-L or SCID	Jewish (mainly Ashkenazi)	102	172 screened for personal history of psychiatric illness	No significant association
Minov et al. [171]	His452Tyr and T102C		German	173	121 screened for personal history of psychiatric illness	No significant association
Johansson et al. [40]	-1438 G/A and 45His/Tyr	All patients with SAD	Caucasian	82	83 screened for personal and family history of psychiatric illness	No significant association found
Enoch et al. [73]	-1438G/A	SCID, all patients with SAD	Caucasian	67	69 screened for personal psychiatric history	A allele associated with SAD $\chi^2 = 6.69$, $P < 0.01$
Du et al. [74]	T102C		Caucasian	120	131	Association with CC genotype: $\chi^2 = 9.0$, $df = 1$, $P = 0.003$ OD 2.4 (95% CI: 1.3–4.3)
Arias et al. [76]	T102C	SCID	Spanish	159	162	No association found*
Bondy et al. [173]	T102C		Caucasian	84	125 screened for personal and family history of psychiatric illness	No association found
Tsai et al. [174]	T102C		Chinese	79	96 screened for personal and family history of psychiatric illness	No association found
Zhang et al. [75]	T102C	'Depressive disorders'†	Japanese	71	150 screened for personal history of psychiatric illness	Association with the T allele: $\chi^2 = 4.03$, $df = 1$, $P = 0.0446$ ‡
Ozaki et al. [72]	T102C, T516C, Ala1340Val, His1354Tyr	SAD	Caucasian	50	112, 62 screened for personal history of psychiatric illness	No association found
Oswald et al. [175]	T102C	SCID or SCAN	Details not given	142	142, ethnically matched and screened for personal history of psychiatric illness	No association found

* Significant association found between the c allele and a seasonal pattern.

† Included dysthymia and depressive disorders NOS.

‡ T allele also associated with depression compared to 31 patients with bipolar affective disorder.

in complete LD with the T102C polymorphism; the 1438G/A polymorphism does not appear to result in differential functional effects [69].

A His452Tyr polymorphism in the 5-HT_{2A} receptor gene has been identified [70], which appears to have functional effects [71]. In a study of 5HT-induced calcium response in platelets, the polymorphism had functional effects on the pattern of calcium mobilization from internal calcium stores, with the Tyr allele being associated with a lower peak in the amount of intracellular calcium ion released, but a longer half-life in the amount of calcium present post-stimulation [71]. Other polymorphisms that have been identified include a silent T516C SNP and a Ala1354Val substitution [72], although the functional effects of these two have not been studied.

As Table 31.3 shows, there have been a few positive findings of association with depression and the 5-HT_{2A} receptor gene. One study found an association between the A allele of the -1438G/A promoter polymorphism and SAD ($\chi^2 = 6.69$, $P < 0.01$) [73]. This finding was not replicated by others [76], and contradictory results have also been published: Du et al. found an association with depression and the CC genotype of the T102C polymorphism in their sample of Caucasian depressed patients [74], and Zhang et al. found an association with the T allele in their Japanese patients with depressive disorders [75]. Arias et al. genotyped 159 patients with major depression together with 164 healthy controls of Spanish origin for the T102C polymorphism [76], and although there was no association with depression, the genotype distributions significantly differed between patients with a seasonal pattern to their episodes and those without ($P = 0.004$). A seasonal pattern was 7.57 times more frequent in 102C allele carriers than in individuals homozygous for the 102T allele ($\chi^2 = 9.45$, $df = 1$, $P = 0.002$; OR = 7.57 (95% CI: 1.65–48.08).

31.9

Serotonin 2C Receptor

The serotonin 2C (5-HT_{2C}) receptor is involved in regulation of appetite [77], and fenfluramine-induced prolactin release (mediated by the 5-HT_{2C} receptor) has been shown to be blunted in depressed patients [78]. The 5-HT_{2C} receptor gene has been mapped to chromosome Xq24, and a Cys23Ser substitution in the first hydrophobic region of the 5-HT_{2C} receptor has been identified [79]. A reduced hypophagic response to m-chloro-phenylpiperazine in subjects with the Ser23 allele has been found, suggesting that there may be a functional consequence of carrying this allele [80]. Lerer et al. examined the Cys23Ser polymorphism in 513 patients with recurrent major depression and 901 normal controls drawn from 10 different European population groups [81]. There was significant variation in the frequency of the Ser23 allele among the 10 population groups included in the sample. Logistic regression analysis demonstrated that over and above this inter-population variability, there was a significant excess of genotypes containing the Ser23 allele in patients with depression compared to normal controls ($P = 0.006$). Results of studies on the serotonin 2C receptor, as well as other candidate genes from the serotonin system, are given in Table 31.4.

Table 31.4 Case-controlled studies of depression: serotonin system

Study	Gene	Poly-morphism	Diagnostic instrument used	Ethnicity of subjects	Number of patients	Number of controls	Significant associations found
Frisch et al. [127]	5-HT2C receptor	Cys23Ser	SCID or SADS-L	Jewish (mainly Ashkenazi)	102	172 screened for personal history of psychiatric illness	No significant association
Johansson et al. [40]	5-HT2C receptor	Cys23Ser	All patients with SAD	Caucasian	82	82 screened for personal and family history of psychiatric illness	No significant association
Lerer et al. [81]	5-HT2C receptor	Cys23Ser	SADS-L or SCAN	10 European population groups	513	901 screened for personal and family history of psychiatric illness	Associated with genotypes containing the Ser23 allele $\chi^2 = 7.45$, $df = 1$, $P = 0.006$
Frisch et al. [127]	Tryptophan hydroxylase	Bfa1	SCID or SADS-L	Jewish (mainly Ashkenazi)	102	172 screened for personal history of psychiatric illness	No significant association
Johansson et al. [40]	Tryptophan hydroxylase	218A/C	All patients with SAD	Caucasian	82	82 screened for personal and family history of psychiatric illness	No significant association
Tan et al. [90]	Tryptophan hydroxylase	A218C, G-1067A and T-347G		Chinese Singaporean	91	139 screened for personal history of psychiatric illness	Significant differences in genotypic distribution for the A218C polymorphism: $\chi^2 = 6.915$, $df = 2$, $P = 0.032$
Tsai et al. [91]	Tryptophan hydroxylase	A218C		Chinese	68	200 screened for personal history of psychiatric illness	Significant differences in genotypic distribution ($P = 0.018$), OR depression with 218A/A homozygote was 2.26 (95% CI: 1.20–4.27)

Table 31.4 (continued)

Study	Gene	Poly-morphism	Diagnostic instrument used	Ethnicity of subjects	Number of patients	Number of controls	Significant associations found
Kunugi et al. [176]	Tryptophan hydroxylase	A218C, A779C		Japanese	73	208	No association found
Du et al. [92]	Tryptophan hydroxylase	A218C		Caucasian	135	196 screened for personal and family history of psychiatric illness	No association found
Arias et al. [86]	5-HT1A receptor	C-1019G, Ile28Val, Asp272Gly, Pro16Leu	SCID	Spanish	249	170	No association found
Lemondé et al. [85]	5-HT1A receptor	C-1019G		Mostly Caucasian	129	134 screened for personal history of psychiatric illness	Association with the G allele ($P = 0.006$)
Hong et al. [106]	5-HT6 receptor	C267T		Chinese	77	147 screened for personal history of psychiatric illness	No association found
Huang et al. [105]	5-HT1B	G861C	SCID	Mainly Caucasian	208	96 screened for personal history of psychiatric illness	No association found*
Fehr et al. [104]	5-HT1B	G861C		German	108	74 screened for personal history of psychiatric illness	No association found
Birkett et al. [107]	5-HT5A	-19G/C; 12A/T	SADS-L or SCAN	Caucasian	75	187 screened for personal history of psychiatric illness	Association found; need to check

* Found an association with the C allele when patients with a definite history of depression ($N = 208$) were compared to patients with no history of depression ($N = 183$).

31.10

Serotonin 1A Receptor

The serotonin 1A (5-HT_{1A}) receptor is an autoreceptor located on the cell bodies and dendrites of the serotonin neurons of the dorsal raphe nucleus, and stimulation of these receptors in the midbrain has been shown in animal studies to result in decreased firing of these neurons and decreased release of serotonin in the prefrontal cortex [82]. Long-term treatment with antidepressants desensitizes the receptor leading to enhanced serotonin release [83]. The 5-HT_{1A} receptor gene (*HTR1A*) is located at 5q11.2-q13 [84], and several non-synonymous SNPs have been identified, Gly22Ser, Ile28Val, Asp272Gly and Pro16Leu. There is also a promoter polymorphism –1019C/G, which may influence promoter activity [85]. Arias et al. failed to find an association between the promoter SNP and depression in a Spanish sample [86]. The frequency of heterozygosity at the Ile28Val, Asp272Gly and Pro16Leu polymorphisms was too small to consider statistical analysis. Serreti et al. also found only one patient in their study sample (84 patients with unipolar depression and bipolar patients) who showed heterozygosity at the Ile28Val polymorphism [87]. However, Lemonde et al. found a significant association between depression and the promoter G allele in their sample of 129 patients with depression and 134 controls screened for psychiatric illness ($P = 0.006$) [85]. The gene for the serotonin 1A receptor does still make a good candidate gene, and association studies will need to be carried out using larger sample sizes.

31.11

Tryptophan Hydroxylase

Tryptophan hydroxylase is the rate-limiting enzyme in the biosynthesis of serotonin. The gene is located at 11p15.3-p14. Two intron 7 polymorphisms have been identified, A218C and C779CA and the C779A polymorphism has been associated with lower CSF 5-hydroxyindoleacetic acid (5-HIAA) levels [88]. Low CSF levels of 5-HIAA, indicating low 5-HT turnover has been found in depressed patients [89]. There have been two positive studies of association with the A218C polymorphism, but the results were contradictory. This may be due to population stratification effects as one study was performed in subjects from Singapore, and the other in Chinese subjects, or it could be due to false positive results [90, 91]. Tan et al. found an association between the A218C polymorphism and depression in their subjects from Singapore [90]. The genotype homozygous for the C allele was found to be more frequent in the depressed patients. They found no association with depression and two promoter SNPs that they also genotyped, –1067A/G and –347T/G. However, Tsai et al. found that the 218A allele was more frequent in their Chinese patients with depression, and those homozygous for the 218A allele had an odds ratio of 2.26 (95% CI: 1.20–4.27) for the disorder compared to carriers of the 218C allele [91]. Du et al. [92] found no association between the A218C polymorphism and depression in their Caucasian sample, although subanalysis found that patients

with a 218A/A genotype had a significantly higher somatic anxiety scores compared to other genotypes. These studies need to be repeated in larger samples.

31.12

Monoamine Oxidase Type A

Monoamine oxidase type A (MAO-A) is a mitochondrial enzyme that is involved in the degradation of several different biological amines including noradrenaline, dopamine and serotonin. MAO inhibitors are used in the treatment of patients with depression. There is also some evidence that, in women with endogenous depression, the activity of the enzyme is positively correlated to the severity of depression [93]. The gene encoding MAO-A is located on chromosome Xp11.23-p11.4 and several polymorphisms in the MAO-A gene have been identified. A dinucleotide repeat, MAOA-CA, in intron 2 [94], two silent Restriction Fragment Length Polymorphisms (RFLPs; a T941G and C1460T), which have been associated with differences in MAOA activity [95], and a A1609G in exon 15, which results in an amino-acid substitution (lysine to arginine) with higher MAOA levels associated with the G allele have been identified [96]. A VTNR repeat located in the promoter region, 1.2 kb upstream of the transcription start codon ATG, and affecting MAOA transcription has also been identified [97, 98]. The polymorphism consists of a rare 2- and 3-, 3.5-, 4- and 5-repeat alleles of a 30-bp section. The 3-repeat allele has been associated with significantly lower activity compared to the longer alleles in neuroblastoma cells [99], which is consistent with the finding that the longer alleles were associated with approximately threefold greater activity in cultured fibroblasts from males compared to the short alleles [98]. For examining association, most studies have grouped together the 3.5-repeat alleles and longer due to their higher activity.

In a study of 146 German patients with depression (104 of whom had recurrent depression) and a control group of 101 individuals with a negative life history for affective disorders, a significantly increased frequency of genotypes containing only long alleles (high activity alleles) of the MAO-A promoter VNTR in female patients with recurrent major depression was found in comparison with age- and sex-matched controls [100]. However, other studies have failed to find an association with the gene (see Table 31.3).

Jorm et al. failed to find an association between the promoter VNTR and neuroticism, as well as depressive symptoms in a general population of 850 Caucasians [101]. However, they analyzed their results slightly differently from the others, as the 2.5- and 3.5-repeat alleles were classified as short alleles and grouped together whereas the 4-, 4.5- and 5.5-alleles were classified as long alleles and grouped together. Other investigators included the 3.5-allele in the high activity long allele group.

31.13

Other Serotonin Receptors

Another candidate gene that has been studied in the serotonin system is the serotonin 1B (5-HT_{1B}) receptor, which is another autoreceptor located on serotonin neurons, and is involved in the regulation of serotonin release [102]. Several polymorphisms have been detected, including a G861C polymorphism that has been found to have a functional effect, with the C allele being associated with a lower maximal binding capacity (B_{\max} binding) to the receptor in post-mortem samples [103]. Fehr et al. failed to find an association with the G861C polymorphism and depression in their sample of 108 patients with depression and 74 controls [104]. Huang et al. looked for association with this polymorphism and various diagnoses, including depression, in a sample of 490 patients, mainly Caucasian, and 96 controls [105], but failed to find an association with depression when their sample of 208 patients with depression was compared to the controls. However, they found a significant difference in the genotypic distribution and the allelic frequencies between those patients with a definite history of depression ($N = 208$) and those without such a history ($N = 183$), with the C allele being the “at risk” allele ($\chi^2 = 6.83$, $df = 2$, $P = 0.033$ for differences in genotypic distribution, and $\chi^2 = 5.81$, $df = 1$, $P = 0.016$ for differences in allelic frequencies). The C allele had a significant dose effect for risk of depression as assessed by the Armitage linearity tendency test ($\chi^2 = 6.80$, $df = 1$, $P = 0.009$). The serotonin 6 receptor and the serotonin 5A receptor have also been studied [106, 107]. Hong et al. failed to find an association between depression and the C267T polymorphism of the serotonin 6 receptor in their Chinese population, although their sample size of depressed patients was small ($N = 77$) [106]. Birkett et al. found an association between depression and two polymorphisms (–19G/C; 12A/T) in the serotonin 5A receptor in a sample of 75 patients with depression and 187 controls [107].

31.14

The Noradrenaline and Dopamine System

There is good evidence for the role of noradrenaline in depression. Elevated levels of noradrenaline have been found in the CSF of a patients with depression compared to controls [108], and reduced levels of the noradrenaline transporter (NAT) have also been found in the locus coeruleus of depressed patients [109]. Antidepressants also directly target the noradrenaline system: tertiary TCAs bind to the NAT to enhance noradrenaline (NA) transmission; monoamine oxidase inhibitors prevent breakdown of the NA, and the newer antidepressants also act on the NAT (venlafaxine and reboxetine). The gene for the noradrenaline transporter (*SLC6A2*) is located at chromosome 16q12.2. There are a number of polymorphisms that have been identified [110], but the functional significance of these polymorphisms is yet to be determined. Zill et al. failed to find an association between the noradrenaline transporter promoter polymorphisms –182T/C and a silent G1287A

in exon 9 and depression in their Caucasian population [111]. Owen et al. also failed to find an association between the G1287A and the Thr99Ile polymorphism and depression [112], and Samochowiec et al. failed to find an association with the polymorphism and TCI harm avoidance in their Polish sample ($N = 127$) [50]. Table 31.5 gives results from association studies conducted using candidate genes from the noradrenaline and dopamine system.

31.15

Alpha 2A Adrenergic Receptor

The alpha 2A adrenoceptor is an autoreceptor found on noradrenergic neurons, and is involved in the regulation of noradrenaline release in the cortex [113], and there is evidence for upregulation of the receptor in depression [114]. Ohara et al. failed to find an association between the alpha 2A adrenergic receptor gene, *ADDRA2A*, polymorphism at position -1291C/G [115] and depression in a sample of 114 healthy controls and 103 mood disorder patients, 70 of whom had depressive disorder diagnosed using the Schedule for Affective Disorders and Schizophrenia (SADS) [116].

31.16

Dopamine Beta-hydroxylase

Given the dopamine hypothesis of schizophrenia, it has been suggested that increased dopaminergic activity may play a primary role in psychotic depression. Dopamine beta-hydroxylase (D β H) catalyzes the key step in the biosynthesis of the neurotransmitter noradrenaline from dopamine, and low D β H has been hypothesized to be a risk factor in the etiology of psychotic depression [117]. The gene for the protein is located at chromosome 9q34 [118], and several polymorphisms have been identified, including a G/A at cDNA position 444 in exon 2, which has been associated with differences in plasma levels of the enzyme [119]. Wood et al. genotyped 164 Caucasian patients who suffered from depressive episodes according to the Structured Clinical Interview for DSM-IV (SCID; including patients with bipolar affective disorder II) and examined the association of this polymorphism with paranoid ideation, interpersonal sensitivity, and psychoticism on the Hopkins Symptom Checklist [15]. Patients who possessed the A allele were significantly more likely to have higher scores for interpersonal sensitivity and paranoia than patients without the A allele ($\chi^2 = 5.68$, $P = 0.004$, and $\chi^2 = 3.08$, $P = 0.048$, respectively), suggesting that this allele may predispose patients to paranoia in major depression.

Table 31.5 Case-controlled studies of depression: noradrenaline and dopamine system

Study	Gene	Poly-morphism	Diagnostic instrument used	Ethnicity of subjects	Number of patients	Number of controls	Significant associations found
Frisch et al. [127]	COMT	Met158val	SCID or SADS-L	Jewish (mainly Ashkenazi)	102	172 screened for personal history of psychiatric illness	No significant association
Ohara et al. [132]	COMT	Met158val	Depressive disorders*	Japanese	75	135	Association with genotypes containing the Met allele: $\chi^2 = 5.72$, $df = 1$, $P = 0.012$, OR 2.19 (95% CI: 1.19–4.03) No association found
Kunugi et al. [133]	COMT	Met158val		Caucasian	62	121	No association found
Schulze et al. [100]	MAO-A	Promoter VNTR	SADS-L	German	146	101 screened for personal history of psychiatric illness	Association seen in women with recurrent depression ($N = 73$) with 3-repeat homozygous genotype: $\chi^2 = 4.767$, $P = 0.029$ No association found
Kunugi et al. [176]	MAO-A	Promoter VNTR		Japanese	98	258	No association found
Syagailo et al. [178]	MAO-A	Promoter VNTR		Caucasian	74	229	No association found
Sasaki et al. [179]	MAO-A	T941G		Japanese	43	169	No association found
Tadic et al. [180]	MAO-A	T941G	Mini international neuro-psychiatric interview	Caucasian	108	276 screened for personal history of psychiatric illness	No association found
Zill et al. [111]	Nor-adrenaline transporter	T-182C, G1287A		German	193	136 screened for personal history of psychiatric illness	No association found
Owen et al. [112]	Nor-adrenaline transporter	G1287A, Thr991le		Caucasian	105	74 screened for personal and family history of psychiatric illness†	No association found

Table 31.5 (continued)

Study	Gene	Poly-morphism	Diagnostic instrument used	Ethnicity of subjects	Number of patients	Number of controls	Significant associations found
Ohara et al. [116]	Alpha 2A receptor	C-1291G	SADS	Japanese	70	114 screened for a personal history of psychiatric illness	No association found
Dikeos et al. [123]	D3 receptor	Bal 1		Greek	36	38	Association with the Gly allele: $\chi^2 = 6.037$, $df = 1$, $P = 0.014$, OR 2.32 (95% CI: 1.18–4.57)
Manki et al. [124]	D3 receptor	Bal 1		Japanese	49	100	No association found
Manki et al. [124]	D4 receptor	Exon 3 VNTR		Japanese	49	100	Association with 5-repeat allele: $\chi^2 = 4.18$, $df = 1$, $P = 0.041$
Frisch et al. [127]	D4 receptor	Exon 3 VNTR	SCID or SADS-L	Jewish (mainly Ashkenazi)	102	172 screened for personal history of psychiatric illness	No significant association
Oruc et al. [126]	D4 receptor	Exon 3 VNTR	SADS-L	Croatian	41	71 screened for personal and family history of psychiatric illness	No association found
Oruc et al. [126]	Tyrosine hydroxylase	Intron 1 tetranucleotide repeat	SADS-L	Croatian	41	71 screened for personal and family history of psychiatric illness	No association found
Furlong et al. [127]	Tyrosine hydroxylase	Intron 1 tetranucleotide repeat	SADS-L	Caucasian	126	246	No association found
Furlong et al. [127]	Tyrosine hydroxylase	PstI	SADS-L	Caucasian	133	246	Association with the uncut allele: $\chi^2 = 4.621$, $df = 1$, $P < 0.05$
Frisch et al. [127]	DAT 1 (transporter)	3'UTR VNTR	SCID or SADS-L	Jewish (mainly Ashkenazi)	102	172 screened for personal history of psychiatric illness	No significant association

* Including the diagnosis of dysthymia and depression NOS.

† Sixty case and control genotypes for the Thr99Ile polymorphism.

31.17

Dopamine Receptors

Dopamine 3 (D3) receptor levels are found to be elevated in the amygdala of patients with depression, which is thought to be consistent with a reduction in mesolimbic dopamine in depression [120]. The gene for the D3 receptor is localized to 3q13.3 [121]. The Bal 1 polymorphism (a Ser9Gly substitution) is present in exon 1 [122]. Dikeos et al. genotyped 36 depression and 38 ethnically-matched controls for the Bal 1 polymorphism, and found that the Gly allele was more frequent amongst the patients ($\chi^2 = 6.037$, $df = 1$, $P = 0.014$, OR = 2.32, 95% CI: 1.18–4.5), and patients with depression were more likely to have a genotype containing this allele ($\chi^2 = 4.91$, $df = 1$, $P = 0.027$, OR = 3.00, 95% CI: 1.12–8.05) [123]. However, Manki et al. failed to find an association between the D3 receptor Bal 1 polymorphism and depression in a small Japanese sample of depressed patients, $N = 49$, and 100 controls [124], and Henderson et al. failed to find an association with neuroticism or depression symptoms in their community sample of 2327 Caucasian subjects [125].

Manki et al. also looked for an association between depression and polymorphisms in the D2 receptor (ser311cys), D4 receptor (48bp VNTR in exon 3), and the DAT1 (3'UTR 40-bp VNTR) and found an association between the gene for the D4 receptor, *DRD4*, and depression in their sample [124]. There were statistically significant differences in the allelic frequencies, and the 4-repeat allele was significantly lower in the depressed patients ($\chi^2 = 6.49$, $df = 1$, $P = 0.011$), while the 5-repeat allele was significantly more common in the depressed patients ($\chi^2 = 4.18$, $df = 1$, $P = 0.041$). This association between the D4 receptor VNTR and depression was not replicated by Oruc et al. in their Croatian sample [126], or by Frisch et al. in their mainly Ashkenazi Jewish sample [127].

31.18

Tyrosine Hydroxylase

This is the rate-limiting enzyme in the synthesis of noradrenaline and dopamine. It is located on 11q15.5, and has a tetranucleotide repeat within intron 1 [128], which has been shown to regulate transcription in cell lines [129]. Oruc et al. failed to find an association between the tetranucleotide repeat and depression in their small Croatian sample [126]. Furlong et al. also failed to find an association with this polymorphism in their Caucasian sample [130]. They performed a meta-analysis of results from their own and three other studies, and also failed to find an association with the polymorphism in the combined sample of 204 patients and 359 controls. However, they did find an association between another tyrosine hydroxylase polymorphism *PstI* and depression, with the uncut allele being associated with depression in their sample of 133 Caucasian patients and 246 controls.

31.19**Catechol-O-Methyltransferase**

Catechol-O-methyltransferase (COMT) is involved in the inactivation of adrenaline, noradrenaline and dopamine. A G472A polymorphism in the first position of codon 158 of the COMT gene results in a functional valine (high activity) to methionine (low activity) transition associated with a three- to fourfold difference in thermolability [131]. Ohara et al. in their study of Japanese subjects, found an association between genotypes containing the low activity allele and depression ($\chi^2 = 5.71$, $df = 1$, $P = 0.012$. OR = 2.19, 95% CI: 1.19–4.03) [132]. However, this result was not replicated in a Caucasian and mainly Ashkenazi Jewish sample [36, 130]. Henderson et al. failed to find an association between the COMT Met/Val polymorphism and neuroticism in their large Caucasian sample of over 800 individuals [125].

31.20**Other Candidate Genes**

More recently, investigators have begun to look outside the monoamine system for candidate genes for depression, including genes involved in the control of circadian rhythm (e.g. Circadian Locomotor Output Cycles Kaput (CLOCK), Normal PAS Domain Protein 2 (NPAS2)) [134, 135], metabolic pathways (e.g. neuronal nitric oxide synthase, angiotensin converting enzyme, corticotropin-releasing hormone receptor-2) [136–140], as well as receptors for other neurotransmitters (e.g. cholinergic 2 receptor, nicotinic receptor, GABA-A receptor α -1 subunit) [141–144] and genes involved in regulating the immune response (e.g. Cytotoxic T lymphocyte antigen-4) [145]. Most of these studies have been negative. Where a positive association has been found, the finding has not been replicated in subsequent studies.

Arinami et al. found an association between the 287-bp insertion/deletion polymorphism present in the intron 16 of the angiotensin converting enzyme (ACE) gene and Japanese patients with affective disorder ($N = 65$) compared to controls ($N = 579$) [146]. The gene is a relatively good candidate gene as ACE catalyzes the degradation of substance P, which is involved in the regulation of mood and substance P antagonists are currently undergoing clinical trials for the treatment of depression [147]. The insertion/deletion polymorphism has been found to be associated with levels of substance P in post-mortem tissue [146]. However, subsequent association studies conducted using this polymorphism were negative [137–139].

One finding that has been replicated is that of Bjelland et al., who found an association between the T/T genotype of the methylenetetrahydrofolate reductase C677T polymorphism (OR, 1.69; 95% CI: 1.09–2.62) and depression [148]. The gene is involved in folate metabolism, and folate deficiency has been implicated in depression. The C677T polymorphism is associated with reduced enzyme activity [149]. An association between the homozygous TT genotype and depression was

also found in a small sample of depressed Japanese patients, $N = 32$ ($P = 0.005$) [150]. However, this finding was not replicated in a subsequent Japanese sample [151].

Three interesting candidate genes are those encoding for the G Protein $\beta 3$ -subunit, Brain Derived Neurotrophic factor, BDNF, and cAMP-responsive element-binding protein (CREB). G proteins are involved in signal transduction following binding of a neurotransmitter at its transmembrane receptor. The proteins consist of three subunits (α -, β - and γ -subunits), and following binding of the transmitter to its receptor, the subunits separate into $G\alpha$ and $G\beta\gamma$ units, that then initiate a signaling cascade which results in cellular responses. The functional effects of the $G\beta\gamma$ unit have been reviewed by Clapham and Neer [152]. The gene for the G protein $\beta 3$ -subunit is present on 12pter-12p.3 [153], and a C825T polymorphism in exon 10 has been identified [154]. The presence of a T-allele leads to variant splicing and the splice variant of the protein has been shown to have functional consequences [154]. This polymorphism has also been shown to influence the response to antidepressants [155]. Zill et al. found an association between the T allele and depression in their sample of 78 patients with depression and 111 controls (genotype, $\chi^2 = 9.571$, $df = 2$, $P = 0.008$; alleles, $P = 0.004$, OR = 1.87, 95% CI: 1.23–2.84; Fisher's exact test, two sided) [156]. However, they failed to find an association with another of the polymorphisms in the same gene (T131C) [157]. Willeit et al. also found an association between the genotypes containing the 825T allele and seasonal affective disorder (SAD) in their sample of 172 patients with SAD (128 of whom had recurrent depression) and 143 controls ($\chi^2 = 10.303$, $P = 0.001$, OR = 2.085, 95% CI: 1.13–3.05) [158]. However, Kunugi et al. failed to replicate the association between depression and the C825T polymorphism in their Japanese sample [159].

BDNF is upregulated by antidepressant treatment, and is a neurotrophic factor that has both long-term neurotrophic and protective effects, as well acute effects on excitatory transmission [160]. Two of the polymorphisms present in the gene include a Val66Met polymorphism and a dinucleotide repeat (GT) polymorphism located in the promoter region (–1040 bp). The Met allele of the Val66Met polymorphism has been implicated in abnormal hippocampal activation during a memory task in a study of the hippocampus [161]. The Val allele and a haplotype consisting of the Val allele and the 3-repeat allele of the dinucleotide repeat has been associated with bipolar affective disorder in a mainly Caucasian population [162]. However, a recently published study using a Chinese sample of patients with either depression ($N = 84$) or bipolar affective disorder ($N = 108$) and 392 controls was not able to replicate the association between the Val66Met polymorphism and bipolar affective disorder, and was unable to find an association with depression [163]. However, the numbers involved in this study were small, and the ethnic group being studied was different. The gene makes a promising candidate and warrants further study.

The *CREB1* gene is located on chromosome 2q33-34, a region to which linkage was found in a study of 81 families ascertained through probands with recurrent early-onset depression [164]; this linkage was present only in the affected female relative pairs. CREB is involved in cell survival and plasticity, and its expression is

upregulated by chronic treatment with antidepressants [165]. Association studies on CREB will add further evidence to the involvement of this gene in depression, and they will also allow confirmation of whether the gene has differential effects in men and women.

31.21

The Future of Association Studies in Depression

From quantitative genetics, and the modeling of twin data, it is clear that the contribution of a person's unique individual environment to the risk of depression is significant [1]. This was not something new to psychiatrists, as the role of life events in the depression had been clearly established previously by epidemiologists, and was also obvious to psychiatrists via the clinical setting. Capsi et al., in their seminal paper, have perhaps heralded the way for future association studies by looking for gene–environment interactions in the risk of depression [166]. They studied 847 Caucasian members from the Dunedin Multidisciplinary Health and Development Study, a birth cohort of 1037 children which was followed prospectively. They looked at the interaction between the serotonin transporter promoter polymorphism and life-events between the ages of 21 and 26 years and the risk of depression in the preceding year at the age of 26 years. There was no association between the number of life events and the promoter polymorphism, nor was there a significant association between the polymorphism and depression. However, there was an interaction between the promoter genotype and life events in the probability of depression at the age of 26 years ($P = 0.056$, $P = 0.02$ in those who did not have a prior history of depression before the age of 21 years). There also was evidence for a similar interaction for self-reported depressive symptoms and informant reports of depression, as well as for suicide ideation or attempts. In all cases, there appeared to be a dose–response relationship, with those homozygous for the short allele being most vulnerable to the adverse effects of life events, and those homozygous for the long allele being the least vulnerable. Genes other than the serotonin-transporter could have played a role in the susceptibility to adverse life events, but the authors cite evidence against a gene–gene interaction as the lack of an interaction between the genotype and life events between the ages of 18 and 21 years in predicting depression at the age of 26 years.

It has also become clear that by genotyping a single polymorphism, it is far from possible to capture most of the variation that is present in the gene [167]. Until we are aware of the functional effects of most polymorphisms, the role of the gene in the etiology of depression can only be comprehensively be studied if sufficient polymorphisms across the gene are examined in a sample large enough to detect small effect sizes. As an example, let us assume that a causative, functional polymorphism for depression is present in a gene with a frequency of 50% in the general population, and that the polymorphism has a dominant effect, with those carrying the polymorphism having a relative risk of depression of 1.5. If the polymorphism is itself not genotyped, but is in strong linkage disequilibrium with

a marker that is genotyped, then 1000 cases of depression and 1000 controls screened for a life-time diagnosis of depression, will be required to detect an association at the 0.05 significance level and with a power of 80% [168]. Through collaborative research, these large samples have been collected, and information regarding life events preceding depressive episodes will also become available.

31.22

Conclusion

Complex traits such as depression pose particular problems in the identification of susceptibility genes, and the findings from association studies conducted to date have been contradictory. This has led investigators to use increasingly sophisticated techniques in their search, collecting large samples of patients with carefully selected phenotypes of depression and systematically screened controls, and also gathering information about life events to assess gene–environment interactions. While in the past, we have been somewhat constrained in the choice of candidate genes by our current understanding of the etiology of depression, the last few years has seen the publication of genome-wide linkage scans for depression and neuroticism. There has been replication in their identification of hot-spots containing susceptibility genes, and the screening of these regions using linkage disequilibrium will provide an exciting opportunity to identify genes for depression and expand our current understanding of the disorder. This may lead to the identification of novel biochemical pathways involved in the etiology of the disorder, as well as to a better understanding of environmental risk factors in those who are genetically susceptible to depression. The challenges then will be in the ethical and social issues surrounding testing for the presence of susceptibility genes [169], and in the utilization of our new found knowledge to produce tangible health improvements for future patients.

References

- 1 SULLIVAN, P. F., NEALE, M. C., KENDLER, K. S., Genetic epidemiology of major depression: review and meta-analysis. *Am. J. Psychiatry* **2000**, *157*, 1552–1562.
- 2 TURNER, W. J., Blood types and affective disorders. *Am. J. Psychiatry* **1977**, *134*, 1053–1054.
- 3 SHAPIRO, R. W., RAFAELSEN, O. J., RYDER, L. P., SVEJGAARD, A., SORENSEN, H., ABO blood groups in unipolar and bipolar manic-depressive patients. *Am. J. Psychiatry* **1977**, *134*, 197–200.
- 4 BECKMAN, L., CEDERGREN, B., PERRIS, C., STRANDMAN, E., Blood groups and affective disorders. *Hum. Hered.* **1978**, *28*, 48–55.
- 5 RINIERIS, P. M., STEFANIS, C. N., LYKOURAS, E. P., VARSOU, E. K., Affective disorders and ABO blood types. *Acta Psychiatr. Scand.* **1979**, *60*, 272–278.
- 6 TAKAZAWA, N., KIMURA, T., NANKO, S., Blood groups and affective disorders. *Jpn. J. Psychiatry Neurol.* **1988**, *42*, 753–758.
- 7 ABECASIS, G. R., NOGUCHI, E., HEINZMANN, A., TRAHERNE, J. A., BHATTACHARYA, S., LEAVES, N. I., ANDERSON, G. G., ZHANG, Y., LENCH, N. J., CAREY, A., CARDON, L. R., MOFFATT,

- M. F., COOKSON, W. O. C., Extent and distribution of linkage disequilibrium in three genomic regions. *Am. J. Hum. Genet.* **2001**, *68*, 191–198.
- 8 FANOUS, A., GARDNER, C. O., PRESCOTT, C. A., CANCRO, R., KENDLER, K. S., Neuroticism, major depression and gender: a population-based twin study. *Psychol. Med.* **2002**, *32*, 719–728.
 - 9 DU, L., BAKISH, D., HRDINA, P. D., Gender differences in association between serotonin transporter gene polymorphism and personality traits. *Psychiatr. Genet.* **2000**, *10*, 159–164.
 - 10 SHAM, P., MCGUFFIN, P., Linkage and association. In MCGUFFIN, P., OWEN, M., GOTTESMAN, I. I. (Eds.), *Psychiatric Genetics Genomics*, 1st ed. Oxford University Press, **2002**, 55–73.
 - 11 ZHAO, H., ZHANG, S., MERIKANGAS, K. R., TRIKLER, M., WILDENAUER, D. B., SUN, F., KIDD, K. K., Transmission/disequilibrium tests using multiple tightly linked markers. *Am. J. Hum. Genet.* **2000**, *67*, 936–946.
 - 12 TERWILLIGER, J., OTT, J., A haplotype-based “haplotype relative risk” approach to detecting allelic associations. *Hum. Hered.* **1992**, *42*, 337–346.
 - 13 SPIELMAN, R. S., MCGINNIS, R. E., EWENS, W. J., Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am. J. Hum. Genet.* **1993**, *52*, 506–516.
 - 14 RISCH, N., Linkage strategies for genetically complex traits *Am. J. Med. Genet.* **1990**, *46*, 222–228.
 - 15 WOOD, J. G., JOYCE, P. R., MILLER, A. L., MULDER, R. T., KENNEDY, M. A., A polymorphism in the dopamine beta-hydroxylase gene is associated with “paranoid ideation” in patients with major depression. *Biol. Psychiatry* **2002**, *51*, 365–369.
 - 16 CHEN, T. J., YU, Y. W., CHEN, M. C., TSAI, S. J., HONG, C. J., Association analysis for serotonin transporter promoter polymorphism and auditory evoked potentials for major depression. *Neuropsychobiology* **2002**, *46*, 57–60.
 - 17 KENDLER, K. S., NEALE, M. C., KESSLER, R. C., HEATH, A. C., EAVES, L. J., A longitudinal twin study of personality and major depression in women. *Arch. Gen. Psychiatry* **1993**, *50*, 853–862.
 - 18 ONO, Y., ANDO, J., ONODA, N., YOSHIMURA, K., MOMOSE, T., HIRANO, M., KANBA, S., Dimensions of temperament as vulnerability factors in depression. *Mol. Psychiatry* **2002**, *7*, 948–953.
 - 19 PLOMIN, R., OWEN, M. J., MCGUFFIN, P., The genetic basis of complex human behaviors. *Science* **1994**, *264*, 1733–1739.
 - 20 HSU, F. C., LIANG, K. Y., BEATY, T. H., BARNES, K. C., Unified sampling approach for multipoint linkage disequilibrium mapping of qualitative and quantitative traits. *Genet. Epidemiol.* **2002**, *22*, 298–312.
 - 21 SCHILDKRAUT, J. J., The catecholamine hypothesis of affective disorder: a review of the supporting evidence. *Am. J. Psychiatry* **1965**, *122*, 509–522.
 - 22 LEAKE, A., FAIRBURN, A. F., MCKEITH, I. G., FERRIER, I. N., Studies on the serotonin uptake binding site in major depressive disorder and control post-mortem brain: neurochemical and clinical correlates. *Psychiatry Res.* **1991**, *39*, 155–165.
 - 23 HEILS, A., TEUFEL, A., PETRI, S., STOBER, G., RIEDERER, P., BENDEL, D., LESCH, K. P., Allelic variation of human serotonin transporter gene expression. *J. Neurochem.* **1996**, *66*, 2621–2624.
 - 24 LESCH, K. P., BENDEL, D., HEILS, A., SABOL, S. Z., GREENBERG, B. D., PETRI, S., BENJAMIN, J., MULLER, C. R., HAMER, D. H., MURPHY, D. L., Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **1996**, *274*, 1527–1531.
 - 25 HARIRI, A. R., MATTAY, V. S., TESSITORE, A., KOLACHANA, B., FERA, F., GOLDMAN, D., EGAN, M. F., WEINBERGER, D. R., Serotonin transporter genetic variation and the response of the human amygdala. *Science* **2002**, *297*, 400–403.
 - 26 LESCH, K. P., BALLING, U., GROSS, J., STRAUSS, K., WOLOSIN, B. L., MURPHY, D. L., RIEDERER, P., Organisation of human serotonin transporter gene. *J. Neural Transmission Gen. Sect.* **1994**, *95*, 157–164.
 - 27 FISKESTRAND, C. E., LOVEJOY, E. A., QUINN, J. P., An intronic polymorphic

- domain often associated with susceptibility to affective disorders has allele dependent differential enhancer activity in embryonic stem cells. *FEBS Lett.* **1999**, 458, 171–174.
- 28 LOVEJOY, E. A., SCOTT, A. C., FISKESTRAND, C. E., BUBB, V. J., QUINN, J. P., The serotonin transporter intronic VNTR enhancer correlated with a predisposition to affective disorders has distinct regulatory elements within the domain based on the primary DNA sequence of the repeat unit. *Eur. J. Neurosci.* **2003**, 17, 417–420.
 - 29 BALL, D., HILL, L., FREEMAN, B., ELEY, T. C., STRELAU, J., RIEMANN, R., SPINATH, F. M., ANGLEITNER, A., PLOMIN, R., The serotonin transporter gene and peer-related neuroticism. *Neuroreport* **1997**, 8, 1301–1304.
 - 30 FURLONG, R. A., HO, L., WALSH, C., RUBINSZTEIN, J. S., JAIN, S., PAYKEL, E. S., EASTON, D. F., RUBINSZTEIN, D. C., Analysis and meta-analysis of two serotonin transporter gene polymorphisms in bipolar and unipolar affective disorders. *Am. J. Med. Genet.* **1998**, 81, 58–63.
 - 31 OGILVIE, A. D., BATTERSBY, S., BUBB, V. J., FINK, G., HARMAR, A. J., GOODWIM, G. M., SMITH, C. A., Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet* **1996**, 347, 731–733.
 - 32 BATTERSBY, S., OGILVIE, A. D., SMITH, C. A., BLACKWOOD, D. H., MUIR, W. J., QUINN, J. P., FINK, G., GOODWIN, G. M., HARMAR, A. J., Structure of a variable number tandem repeat of the serotonin transporter gene and association with affective disorder. *Psychiatr. Genet.* **1996**, 6, 177–181.
 - 33 COLLIER, D. A., ARRANZ, M. J., SHAM, P., BATTERSBY, S., VALLADA, H., GILL, P., AITCHISON, K. J., SODHI, M., LI, T., ROBERTS, G. W., SMITH, B., MORTON, J., MURRAY, R. M., SMITH, D., KIROV, G., The serotonin transporter is a potential susceptibility factor for bipolar affective disorder. *Neuroreport* **1996**, 7, 1675–1679.
 - 34 STOBER, G., HEILS, A., LESCH, K. P., Serotonin transporter gene polymorphism and affective disorder. *Lancet* **1996**, 347, 1340–1341.
 - 35 KUNUGI, H., TATSUMI, M., SAKAI, T., HATTORI, M., NANKO, S., Serotonin transporter gene polymorphism and affective disorder. *Lancet* **1996**, 347, 40.
 - 36 KUNUGI, H., HATTORI, M., KATO, T., TATSUMI, M., SAKAI, T., SASAKI, T., HIROSE, T., NANKO, S., Serotonin transporter gene polymorphisms: ethnic difference and possible association with bipolar affective disorder. *Mol. Psychiatry* **1997**, 2, 457–462.
 - 37 LIU, W., GU, N., FENG, G., LI, S., BAI, S., ZHANG, J., SHEN, T., XUE, H., BREEN, G., ST CLAIR, D., HE, L., Tentative association of the serotonin transporter with schizophrenia and unipolar depression but not with bipolar disorder in Han Chinese. *Pharmacogenetics* **1999**, 9, 491–495.
 - 38 COLLIER, D. A., STOBER, G., LI, T., HEILS, A., CATALANO, M., DI BELLA, D., ARRANZ, M. J., MURRAY, R. M., VALLADA, H. P., BENDEL, D., MULLER, C. R., ROBERTS, G. W., SMERALDI, E., KIROV, G., SHAM, P., LESCH, K. P., A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol. Psychiatry* **1996**, 1, 453–460.
 - 39 ROSENTHAL, N. E., MAZZANTI, C. M., BARNETT, R. L., HARDIN, T. A., TURNER, E. H., LAM, G. K., OZAKI, N., GOLDMAN, D., Role of serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. *Mol. Psychiatry* **1998**, 3, 175–177.
 - 40 JOHANSSON, C., SMEDH, C., PARTONEN, T., PEKKARINEN, P., PAUNIO, T., EKHOLM, J., PELTONEN, L., LICHTERMANN, D., PALMGREN, J., ADOLFSSON, R., SCHALLING, M., Seasonal affective disorder and serotonin-related polymorphisms. *Neurobiol. Dis.* **2001**, 8, 351–357.
 - 41 WILLEIT, M., PRASCHAK-RIEDER, N., NEUMEISTER, A., ZILL, P., LEISCH, F., STASTNY, J., HILGER, E., THIERRY, N., KONSTANTINIDIS, A., WINKLER, D., FUCHS, K., SIEGHART, W., ASCHAUER, H., ACKENHEIL, M., BONDY, B., KASPER, S., A polymorphism (5-HTTLPR) in the serotonin transporter promoter gene is associated with DSM-IV depression subtypes in seasonal affective disorder. *Mol. Psychiatry* **2003**, 8, 942–946.

- 42 JOHANSSON, C., WILLEIT, M., LEVITAN, R., PARTONEN, T., SMEDH, C., DEL FAVERO, J., BEL KACEM, S., PRASCHAK-RIEDER, N., NEUMEISTER, A., MASELLI, M., BASILE, V., ZILL, P., BONDY, B., PAUNIO, T., KASPER, S., VAN BROECKHOVEN, C., NILSSON, L. G., LAM, R., SCHALLING, M., ADOLFSSON, R., The serotonin transporter promoter repeat length polymorphism, seasonal affective disorder and seasonality. *Psychol. Med.* **2003**, 33, 785–792.
- 43 GUTIERREZ, B., PINTOR, L., GASTO, C., ROSA, A., BERTRANPETIT, J., VIETA, E., FANANAS, L., Variability in the serotonin transporter gene and increased risk for major depression with melancholia. *Hum. Genet.* **1998**, 103, 319–322.
- 44 GREENBERG, B. D., LI, Q., LUCAS, F. R., HU, S., SIROTA, L. A., BENJAMIN, J., LESCH, K. P., HAMER, D., MURPHY, D. L., Association between the serotonin transporter promoter polymorphism and personality traits in a primarily female population sample. *Am. J. Med. Genet.* **2000**, 96, 202–216.
- 45 OSHER, Y., HAMER, D., BENJAMIN, J., Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israeli sibling pairs. *Mol. Psychiatry* **2000**, 5, 216–219.
- 46 RICKETTS, M. H., HAMER, R. M., SAGE, J. I., MANOWITZ, P., FENG, F., MENZA, M. A., Association of a serotonin transporter gene promoter polymorphism with harm avoidance behaviour in an elderly population. *Psychiatr. Genet.* **1998**, 8, 41–44.
- 47 KATSURAGI, S., KUNUGI, H., SANO, A., TSUTSUMI, T., ISOGAWA, K., NANKO, S., AKIYOSHI, J., Association between serotonin transporter gene polymorphism and anxiety-related traits. *Biol. Psychiatry* **1999**, 45, 368–370.
- 48 BRUMMETT, B. H., SIEGLER, I. C., MCQUOID, D. R., SVENSON, I. K., MARCHUK, D. A., STEFFENS, D. C., Associations among the NEO Personality Inventory, Revised and the serotonin transporter gene-linked polymorphic region in elders: effects of depression and gender. *Psychiatr. Genet.* **2003**, 13, 13–18.
- 49 GELERTNER, J., KRANZLER, H., COCCARO, E. F., SIEVER, L. J., NEW, A. S., Serotonin transporter protein gene polymorphism and personality measures in African American and European American subjects. *Am. J. Psychiatry* **1998**, 155, 1332–1338.
- 50 SAMOCHOWIEC, J., RYBAKOWSKI, F., CZERSKI, P., ZAKRZEWSKA, M., STEPIEN, G., PELKA-WYSIECKA, J., HORODNICKI, J., RYBAKOWSKI, J. K., HAUSER, J., Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationship to temperamental dimensions measured by the Temperament and Character Inventory in healthy volunteers. *Neuropsychobiology* **2001**, 43, 248–253.
- 51 DEARY, I. J., BATTERSBY, S., WHITEMAN, M. C., CONNOR, J. M., FOWKES, F. G., HARMAR, A., Neuroticism and polymorphisms in the serotonin transporter gene. *Psychol. Med.* **1999**, 29, 735–739.
- 52 JORM, A. F., HENDERSON, A. S., JACOMB, P. A., CHRISTENSEN, H., KORTEN, A. E., RODGERS, B., TAN, X., EASEAL, S., An association study of a functional polymorphism of the serotonin transporter gene with personality and psychiatric symptoms. *Mol. Psychiatry* **1998**, 3, 449–451.
- 53 GUSTAVSSON, J. P., NOTHEN, M. M., JONSSON, E. G., NEIDT, H., FORSLUND, K., RYLANDER, G., MATTILA-EVENDEN, M., SEDVALL, G. C., PROPPING, P., ASBERG, M., No association between serotonin transporter gene polymorphisms and personality traits. *Am. J. Med. Genet.* **1999**, 88, 430–436.
- 54 FLORY, J. D., MANUCK, S. B., FERRELL, R. E., DENT, K. M., PETERES, D. G., MULDOON, M. F., Neuroticism is not associated with the serotonin transporter (5-HTTLPR). *Mol. Psychiatry* **1999**, 4, 93–96.
- 55 EBSTEIN, R. P., GRITSSENKO, I., NEMANOV, L., FRISCH, A., OSHER, Y., BELMAKER, R. H., No association between the serotonin transporter gene regulatory region polymorphism and the Tridimensional Personality Questionnaire (TPQ) temperament of harm avoidance. *Mol. Psychiatry* **1997**, 2, 224–226.
- 56 HERBST, J. H., ZONDERMAN, A. B., MCCRAE, R. R., COSTA JR., P. T., Do the dimensions of the temperament and

- character inventory map a simple genetic architecture? Evidence from molecular genetics and factor analysis. *Am. J. Psychiatry* **2000**, 57, 1285–1290.
- 57 UMEKAGE, T., TOCHIGI, M., MARUI, T., KATO, C., HIBINO, H., OTANI, T., KOHDA, K., KATO, N., SASAKI, T., Serotonin transporter-linked promoter region polymorphism and personality traits in a Japanese population. *Neurosci. Lett.* **2003**, 337, 13–16.
 - 58 BURMEISTER, M., SEN, S., GHOSH, D., Association of serotonin transporter promoter variation with neuroticism: a meta-analysis. *Am. J. Med. Genet.* **2003**, 122, 30.
 - 59 GOTTESMAN, I. I., GOULD, T. D., The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* **2003**, 160, 636–645.
 - 60 MORENO, F. A., HENINGER, G. R., MCGAHUEY, C. A., DELGADO, P. L., Tryptophan depletion and risk of depression relapse: a prospective study of tryptophan depletion as a potential predictor of depressive episodes. *Biol. Psychiatry* **2000**, 48, 327–329.
 - 61 NEUMEISTER, A., KONSTANTINIDIS, A., STASTNY, J., SCHWARZ, M. J., VITOUCH, O., WILLEIT, M., PRASCHAK-RIEDER, N., ZACH, J., DE ZWAAN, M., BONDY, B., ACKENHEIL, M., KASPER, S., Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression. *Arch. Gen. Psychiatry* **2002**, 59, 613–620.
 - 62 MORENO, F. A., ROWE, D. C., KAISER, B., CHASE, D., MICHAELS, T., GELERNTER, J., DELGADO, P. L., Association between a serotonin transporter promoter region polymorphism and mood response during tryptophan depletion. *Mol. Psychiatry* **2002**, 7, 213–216.
 - 63 LOTRICH, F. E., POLLOCK, B. G., FERRELL, R. E., Polymorphism of the serotonin transporter: implications for the use of selective serotonin reuptake inhibitors. *Am. J. Pharmacogenomics* **2001**, 1, 153–164.
 - 64 MEYER, J. H., KAPUR, S., EISFELD, B., BROWN, G. M., HOULE, S., DASILVA, J., WILSON, A. A., RAFI-TARI, S., MAYBERG, H. S., KENNEDY, S. H., The effect of paroxetine on 5-HT(2A) receptors in depression: an [(18)F]setoperone PET imaging study. *Am. J. Psychiatry* **2001**, 158, 78–85.
 - 65 STOCKMEIER, C. A., Involvement of serotonin in depression: evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. *J. Psychiatr. Res.* **2003**, 37, 357–373.
 - 66 WARREN JR., J. T., PEACOCK, M. L., RODRIGUEZ, L. C., FINK, J. K., An MspI polymorphism in the human serotonin receptor gene (HTR2): detection by DGGE and RFLP analysis. *Hum. Mol. Genet.* **1993**, 2, 338.
 - 67 POLESSKAYA, O. O., SOKOLOV, B. P., Differential expression of the “C” and “T” alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *Neurosci. Res.* **2002**, 67, 812–822.
 - 68 SODHI, S. M., ANSAR, D. I., BUSH, E. S., HARRISON, P. J., Imprinting of the 5-HT2A receptor in schizophrenia. *Am. J. Med. Genet.* **2003**, 122B, 177.
 - 69 SPURLOCK, G., HEILS, A., HOLMANS, P., WILLIAMS, J., D'SOUZA, U. M., CARDNO, A., MURPHY, K. C., JONES, L., BUCKLAND, P. R., MCGUFFIN, P., LESCH, K. P., OWEN, M. J., A family based association study of T102C polymorphism in 5HT2A and schizophrenia plus identification of new polymorphisms in the promoter. *Mol. Psychiatry* **1998**, 3, 42–49.
 - 70 ERDMANN, J., SHIMRON-ABARBANEL, D., RIETSCHER, M., ALBUS, M., MAIER, W., KORNER, J., BONDY, B., CHEN, K., SHIH, J. C., KNAPP, M., PROPPING, P., NOTHEN, M. M., Systematic screening for mutations in the human serotonin-2A (5-HT2A) receptor gene: identification of two naturally occurring receptor variants and association analysis in schizophrenia. *Hum. Genet.* **1996**, 97, 614–619.
 - 71 OZAKI, N., MANJI, H., LUBIERMAN, V., LU, S. J., LAPPALAINEN, J., ROSENTHAL, N. E., GOLDMAN, D. J., A naturally occurring amino acid substitution of the human serotonin 5-HT2A receptor influences amplitude and timing of intracellular calcium mobilization. *Neurochem* **1997**, 68, 2186–2193.
 - 72 OZAKI, N., ROSENTHAL, N. E., PESONEN, U., LAPPALAINEN, J., FELDMAN-NAIM, S.,

- SCHWARTZ, P. J., TURNER, E. H., GOLDMAN, D., Two naturally occurring amino acid substitutions of the 5-HT_{2A} receptor: similar prevalence in patients with seasonal affective disorder and controls. *Biol. Psychiatry* **1996**, *40*, 1267–1272.
- 73 ENOCH, M. A., GOLDMAN, D., BARNETT, R., SHER, L., MAZZANTI, C. M., ROSENTHAL, N. E., Association between seasonal affective disorder and the 5-HT_{2A} promoter polymorphism, -1438G/A. *Mol. Psychiatry* **1999**, *4*, 89–92.
- 74 DU, L., BAKISH, D., LAPIERRE, Y. D., RAVINDRAN, A. V., HRDINA, P. D., Association of polymorphism of serotonin 2A receptor gene with suicidal ideation in major depressive disorder. *Am. J. Med. Genet.* **2000**, *96*, 56–60.
- 75 ZHANG, H. Y., ISHIGAKI, T., TANI, K., CHEN, K., SHIH, J. C., MIYASATO, K., OHARA, K., OHARA, K., Serotonin 2A receptor gene polymorphism in mood disorders. *Biol. Psychiatry* **1997**, *41*, 768–773.
- 76 ARIAS, B., GUTIERREZ, B., PINTOR, L., GASTO, C., FANANAS, L., Variability in the 5-HT_{2A} receptor gene is associated with seasonal pattern in major depression. *Mol. Psychiatry* **2001**, *6*, 239–242.
- 77 TECOTT, L. H., SUN, L. M., AKANA, S. F., STRACK, A. M., LOWENSTEIN, D. H., DALLMAN, M. F., JULIUS, D., Eating disorder and epilepsy in mice lacking 5-HT_{2c} serotonin receptors. *Nature* **1995**, *374*, 542–546.
- 78 SHAPIRA, B., COHEN, J., NEWMAN, M. E., LERER, B., Prolactin response to fenfluramine and placebo challenge following maintenance pharmacotherapy withdrawal in remitted depressed patients. *Biol. Psychiatry* **1993**, *33*, 531–535.
- 79 LAPPALAINEN, J., ZHANG, L., DEAN, M., OZ, M., OZAKI, N., YU, D. H., VIRKKUNEN, M., WEIGHT, F., LINNOILA, M., GOLDMAN, D., Identification, expression, and pharmacology of a Cys23-Ser23 substitution in the human 5-HT_{2c} receptor gene (HTR_{2C}). *Genomics* **1995**, *27*, 274–279.
- 80 QUESTED, D. J., WHALE, R., SHARPLEY, A. L., MCGAVIN, C. L., CROSSLAND, N., HARRISON, P. J., COWEN, P. J., Allelic variation in the 5-HT_{2C} receptor (HTR_{2C}) and functional responses to the 5-HT_{2C} receptor agonist, m-chlorophenylpiperazine. *Psychopharmacology* **1999**, *144*, 306–307.
- 81 LERER, B., MACCIARDI, F., SEGMAN, R. H., ADOLFSSON, R., BLACKWOOD, D., BLAIRY, S., DEL FAVERO, J., DIKEOS, D. G., KANEVA, R., LILLI, R., MASSAT, I., MILANOVA, V., MUIR, W., NOETHEN, M., ORUC, L., PETROVA, T., PAPADIMITRIOU, G. N., RIETSCHER, M., SERRETTI, A., SOUERY, D., VAN GESTEL, S., VAN BROECKHOVEN, C., MENDLEWICZ, J., Variability of 5-HT_{2C} receptor cys23ser polymorphism among European populations and vulnerability to affective disorder. *Mol. Psychiatry* **2001**, *6*, 579–585.
- 82 SPROUSE, J. S., AGHAJANIAN, G. K., Electrophysiological responses of serotonergic dorsal raphe neurons to 5-HT_{1A} and 5-HT_{1B} agonists. *Synapse* **1987**, *1*, 3–9.
- 83 ARTIGAS, F., BEL, N., CASANOVAS, J. M., ROMERO, L., Adaptive changes of the serotonergic system after antidepressant treatments. *Adv. Exp. Med. Biol.* **1996**, *398*, 51–59.
- 84 MELMER, G., SHERRINGTON, R., MANKOO, B., KALSI, G., CURTIS, D., GURLING, H. M. D., A cosmid clone for the 5HT_{1A} receptor (HTR_{1A}) reveals a TaqI RFLP that shows tight linkage to DNA loci D5S6, D5S39, and D5S76. *Genomics* **1991**, *11*, 767–769.
- 85 LEMONDE, S., TURECKI, G., BAKISH, D., DU, L., HRDINA, P. D., BOWN, C. D., SEQUEIRA, A., KUSHWAHA, N., MORRIS, S. J., BASAK, A., OU, X. M., ALBERT, P. R., Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J. Neurosci.* **2003**, *23*, 8788–8799.
- 86 ARIAS, B., ARRANZ, M. J., GASTO, C., CATALAN, R., PINTOR, L., GUTIERREZ, B., KERWIN, R. W., FANANAS, L., Analysis of structural polymorphisms and C-1018G promoter variant of the 5-HT_{1A} receptor gene as putative risk factors in major depression. *Mol. Psychiatry* **2002**, *7*, 930–932.
- 87 SERRETTI, A., LILLI, R., LORENZI, C., LATTUADA, E., SMERALDI, E., Serotonin-2C and serotonin-1A receptor genes are not associated with psychotic symptom-

- matology of mood disorders. *Am. J. Med. Genet.* **2000**, 96, 161–166.
- 88 NIELSEN, D. A., GOLDMAN, D., VIRKKUNEN, M., TOKOLA, R., RAWLINGS, R., LINNOILA, M., Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. *Arch. Gen. Psychiatry* **1994**, 51, 34–38.
 - 89 MOLCHAN, S. E., LAWLOR, B. A., HILL, J. L., MARTINEZ, R. A., DAVIS, C. L., MELLOW, A. M., RUBINOW, D. R., SUNDERLAND, T., CSF monoamine metabolites and somatostatin in Alzheimer's disease and major depression. *Biol. Psychiatry* **1991**, 29, 1110–1118.
 - 90 TAN, E. C., CHAN, A. O., TAN, C. H., MAHENDRAN, R., WANG, A., CHUA, H. C., Case-control and linkage disequilibrium studies of the tryptophan hydroxylase gene polymorphisms and major depressive disorder. *Psychiatr. Genet.* **2003**, 13, 151–154.
 - 91 TSAI, S. J., HONG, C. J., WANG, Y. C., Tryptophan hydroxylase gene polymorphism (218A>C) and suicidal behaviours. *Neuroreport* **1999**, 10, 3773–3775.
 - 92 DU, L., BAKISH, D., HRDINA, P. D., 2001 Tryptophan hydroxylase gene 218A/C polymorphism is associated with somatic anxiety in major depressive disorder. *J. Affect Disord.* **2001**, 65, 37–44.
 - 93 WAHLUND, B., SAAF, J., WETTERBERG, L., Clinical symptoms and platelet monoamine oxidase in subgroups and different states of affective disorders. *J. Affect Disord.* **1995**, 35, 75–87.
 - 94 BLACK, G. C., CHEN, Z. Y., CRAIG, I. W., POWELL, J. F., Dinucleotide repeat polymorphism at the MAOA locus. *Nucleic Acids Res.* **1991**, 19, 689.
 - 95 HOTAMISLIGIL, G. S., BREAKEFIELD, X. O., Human monoamine oxidase A gene determines levels of enzyme activity. *Am. J. Hum. Genet.* **1991**, 49, 383–392.
 - 96 TIVOL, E. A., SHALLOT, C., SCHUBACK, D. E., HSU, Y.-P., BREAKEFIELD, X. O., Mutational analysis of the human MAOA genes. *Am. J. Med. Genet.* **1996**, 67, 92–97.
 - 97 SABOL, S., HU, S., HAMER, D., A functional polymorphism in the monoamine oxidase A gene promoter. *Hum. Genet.* **1998**, 103, 273–279.
 - 98 DENNY, R. M., WAGUESPACK, A., KOCH, H., CRAIG, I. W., Association between monoamine oxidase A activity in human male skin fibroblasts and the genotype of the MAO promoter associated variable tandem repeat. *Hum. Genet.* **1999**, 105, 541–551.
 - 99 DECKERT, J., CATALANO, M., SYAGAILO, Y. V., BOSI, M., OKLADNOVA, O., DI BELLA, D., NÖTHEN, M. M., MAFFEI, P., FRANKE, P., FRITZE, J., MAIER, W., PROPPING, P., BECKMANN, H., BELLODI, L., LESCH, K. P., Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. *Hum. Mol. Genet.* **1999**, 8, 621–624.
 - 100 SCHULZE, T. G., MÜLLER, D. J., KRAUSS, H., SCHERK, H., OHLRAUN, S., SYAGAILO, Y. V., WINDEMUTH, C., NEIDT, H., GRÄSSLE, M., PAPASSOTIROPOULOS, A., HEUN, R., NÖTHEN, M. M., MAIER, W., LESCH, K.-P., RIETSCHEL, M., Association between a functional polymorphism in the monoamine oxidase A gene promoter and major depressive disorder. *Am. J. Med. Genet.* **2000**, 96, 801–803.
 - 101 JORM, A. F., HENDERSON, A. S., JACOMB, P. A., CHRISTENSEN, H., KORTEN, A. E., RODGERS, B., TAN, X., EASTEAL, S., Association of a functional polymorphism of the monoamine oxidase A gene promoter with personality and psychiatric symptoms. *Psychiatr. Genet.* **2000**, 10, 87–90.
 - 102 MAURA, G., THELLUNG, S., ANDRIOLI, G. C., RUELLE, A., RAITERI, M., Release-regulating serotonin 5-HT1D autoreceptors in human cerebral cortex. *J. Neurochem.* **1993**, 60, 1179–1182.
 - 103 HUANG, Y. Y., GRAILHE, R., ARANGO, V., HEN, R., MANN, J. J., Relationship of psychopathology to the human serotonin1B genotype and receptor binding kinetics in postmortem brain tissue. *Neuropsychopharmacology* **1999**, 21, 238–246.
 - 104 FEHR, C., GRINTSCHUK, N., SZEGEDI, A., ANGHELESCU, I., KLAWE, C., SINGER, P., HIEMKE, C., DAHMEN, N., The HTR1B 861G>C receptor polymorphism among patients suffering from alcoholism, major depression, anxiety disorders and narcolepsy. *Psychiatry Res.* **2000**, 97, 1–10.

- 105 HUANG, Y. Y., OQUENDO, M. A., FRIEDMAN, J. M., GREENHILL, L. L., BRODSKY, B., MALONE, K. M., KHAIT, V., MANN, J. J., Substance abuse disorder and major depression are associated with the human 5-HT1B receptor gene (HTR1B) G861C polymorphism. *Neuropsychopharmacology* **2003**, *28*, 163–169.
- 106 HONG, C. J., TSAI, S. J., CHENG, C. Y., LIAO, W. Y., SONG, H. L., LAI, H. C., Association analysis of the 5-HT(6) receptor polymorphism (C267T) in mood disorders. *Am. J. Med. Genet.* **1999**, *88*, 601–602.
- 107 BIRKETT, J. T., ARRANZ, M. J., MUNRO, J., OSBOURN, S., KERWIN, R. W., COLLIER, D. A., Association analysis of the 5-HT5A gene in depression, psychosis and antipsychotic response. *Neuroreport* **2000**, *11*, 2017–2020.
- 108 WONG, M. L., KLING, M. A., MUNSON, P. J., LISTWAK, S., LICINIO, J., PROLO, P., KARP, B., MCCUTCHEON, I. E., GERACIOTI JR., T. D., DeBELLIS, M. D., RICE, K. C., GOLDSTEIN, D. S., VELDHIJS, J. D., CHROUSOS, G. P., OLDFIELD, E. H., McCANN, S. M., GOLD, P. W., Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 325–330.
- 109 KLIMEK, V., STOCKMEIER, C., OVERHOLSER, J., MELTZER, H. Y., KALKA, S., DILLEY, G., ORDWAY, G. A., Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. *J. Neurosci.* **1997**, *17*, 8451–8458.
- 110 STÖBER, G., NOTH, M. M., PORZGEN, P., BRUSS, M., BONISCH, H., KNAPP, M., BECKMANN, H., PROPPING, P., Systematic search for variation in the human norepinephrine transporter gene: identification of five naturally occurring missense mutations and study of association with major psychiatric disorders. *Am. J. Med. Genet.* **1996**, *67*, 523–532.
- 111 ZILL, P., ENGEL, R., BAGHAI, T. C., JUCKEL, G., FRODL, T., MÜLLER-SIECHENEDER, F., ZWANGGER, P., SCHULE, C., MINOV, C., BEHRENS, S., RUPPRECHT, R., HEGERL, U., MÖLLER, H. J., BONDY, B., Identification of a naturally occurring polymorphism in the promoter region of the norepinephrine transporter and analysis in major depression. *Neuropsychopharmacology* **2002**, *26*, 489–493.
- 112 OWEN, D., DU, L., BAKISH, D., LAPIERRE, Y. D., HRDINA, P. D., Norepinephrine transporter gene polymorphism is not associated with susceptibility to major depression. *Psychiatry Res.* **1999**, *87*, 1–5.
- 113 IHALAINEN, J. A., TANILA, H., *In vivo* regulation of dopamine and noradrenaline release by alpha2A-adrenoceptors in the mouse prefrontal cortex. *Eur. J. Neurosci.* **2002**, *15*, 1789–1794.
- 114 GURGUIS, G. N., VO, S. P., GRIFFITH, J. M., RUSH, A. J., Platelet alpha2A-adrenoceptor function in major depression: Gi coupling, effects of imipramine and relationship to treatment outcome. *Psychiatry Res.* **1999**, *89*, 73–95.
- 115 LARIO, S., CALLS, J., CASES, A., ORIOLA, J., TORRAS, A., RIVERA, F., MspI identifies a biallelic polymorphism in the promoter region of the alpha 2A-adrenergic receptor gene. *Clin. Genet.* **1997**, *51*, 129–130.
- 116 OHARA, K., NAGAI, M., TANI, K., TSUKAMOTO, T., SUZUKI, Y., OHARA, K., Polymorphism in the promoter region of the alpha 2A adrenergic receptor gene and mood disorders. *Neuroreport* **1998**, *9*, 1291–1294.
- 117 MEYERS, B. S., ALEXOPOULOS, G. S., KAKUMA, T., TIRUMALASETTI, F., GABRIELE, M., ALPERT, S., BOWDEN, C., MELTZER, H. Y., Decreased dopamine beta-hydroxylase activity in unipolar geriatric delusional depression. *Biol. Psychiatry* **1999**, *45*, 448–452.
- 118 CRAIG, S. P., BUCKLE, V. J., LAMOUROUX, A., MALLET, J., CRAIG, I. W., Localization of the human dopamine beta hydroxylase (DBH) gene to chromosome 9q34. *Cytogenet. Cell Genet.* **1988**, *48*, 48–50.
- 119 CUBELLS, J. F., VAN KAMMEN, D. P., KELLEY, M. E., ANDERSON, G. M., O'CONNOR, D. T., PRICE, L. H., MALISON, R., RAO, P. A., KOBAYASHI, K., NAGATSU, T., GELERNTER, J., Dopamine beta-hydroxylase: two polymorphisms in linkage disequilibrium at the structural gene DBH associate with biochemical phenotypic variation. *Hum. Genet.* **1998**, *102*, 533–540.

- 120 KLIMEK, V., SCHENCK, J. E., HAN, H., STOCKMEIER, C. A., ORDWAY, G. A., Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. *Biol. Psychiatry* **2002**, *52*, 740–748.
- 121 LE CONIAT, M., SOKOLOFF, P., HILLION, J., MARTRES, M. P., GIROS, B., PILON, C., SCHWARTZ, J. C., BERGER, R., Chromosomal localization of the human D3 dopamine receptor gene. *Hum. Genet.* **1991**, *87*, 618–620.
- 122 LANNFELT, L., SOKOLOFF, P., MARTRES, M. P., PILON, C., GIROS, B., JÖNSSON, E., SEDVALL, G., SCHWARTZ, J. C., Amino acid substitution in the dopamine D3 receptor as a useful polymorphism for investigating psychiatric disorders *Psychiatr. Genet.* **1992**, *2*, 249–256.
- 123 DIKEOS, D. G., PAPADIMITRIOU, G. N., AVRAMOPOULOS, D., KARADIMA, G., DASKALOPOULOU, E. G., SOUERY, D., MENDLEWICZ, J., VASSILOPOULOS, D., STEFANIS, C. N., Association between the dopamine D3 receptor gene locus (DRD3) and unipolar affective disorder. *Psychiatr. Genet.* **1999**, *9*, 189–195.
- 124 MANKI, H., KANBA, S., MURAMATSU, T., HIGUCHI, S., SUZUKI, E., MATSUSHITA, S., ONO, Y., CHIBA, H., SHINTANI, F., NAKAMURA, M., YAGI, G., ASAI, M., Dopamine D2, D3 and D4 receptor and transporter gene polymorphisms and mood disorders. *J. Affect. Disord.* **1996**, *40*, 7–13.
- 125 HENDERSON, A. S., KORTEN, A. E., JORM, A. F., JACOMB, P. A., CHRISTENSEN, H., RODGERS, B., TAN, X., EASTEAL, S., 2000 COMT and DRD3 polymorphisms, environmental exposures, and personality traits related to common mental disorders. *Am. J. Med. Genet.* **2000**, *96*, 102–107.
- 126 ORUC, L., VERHEYEN, G. R., FURAC, I., JAKOVljeVIC, M., IVEZIC, S., RAEYMAEKERS, P., VAN BROECKHOVEN, C., Analysis of the tyrosine hydroxylase and dopamine D4 receptor genes in a Croatian sample of bipolar I and unipolar patients. *Am. J. Med. Genet.* **1997**, *74*, 176–178.
- 127 FRISCH, A., POSTILNICK, D., ROCKAH, R., MICHAELOVSKY, E., POSTILNICK, S., BIRMAN, E., LAOR, N., RAUCHVERGER, B., KREININ, A., POYUROVSKY, M., SCHNEIDMAN, M., MODAI, I., WEIZMAN, R., Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. *Mol. Psychiatry* **1999**, *4*, 389–392.
- 128 POLYMEROPOULOS, M. H., XIAO, H., RATH, D. S., MERRIL, C. R., Tetranucleotide repeat polymorphism at the human tyrosine hydroxylase gene (TH). *Nucleic Acids Res.* **1991**, *19*, 37–53.
- 129 MELONI, R., ALBANESE, V., RAVASSARD, P., TREILHOU, F., MALLET, J., A tetranucleotide polymorphic microsatellite, located in the first intron of the tyrosine hydroxylase gene, acts as a transcription regulatory element *in vitro*. *Hum. Mol. Genet.* **1998**, *7*, 423–428.
- 130 FURLONG, R. A., RUBINSZTEIN, J. S., HO, L., WALSH, C., COLEMAN, T. A., MUIR, W. J., PAYKEL, E. S., BLACKWOOD, D. H., RUBINSZTEIN, D. C., Analysis and metaanalysis of two polymorphisms within the tyrosine hydroxylase gene in bipolar and unipolar affective disorders. *Am. J. Med. Genet.* **1999**, *88*, 88–94.
- 131 LOTTA, T., VIDGREN, J., TILGMANN, C., ULMANEN, I., MELEN, K., JULKUNEN, I., TASKINEN, J., Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry* **1995**, *34*, 4202–4210.
- 132 OHARA, K., NAGAI, M., SUZUKI, Y., OHARA, K., Low activity allele of catechol-o-methyltransferase gene and Japanese unipolar depression. *Neuroreport* **1998**, *9*, 1305–1308.
- 133 KUNUGI, H., VALLADA, H. P., HODA, F., KIROV, G., GILL, M., AITCHISON, K. J., BALL, D., ARRANZ, M. J., MURRAY, R. M., COLLIER, D. A., No evidence for an association of affective disorders with high- or low-activity allele of catechol-o-methyltransferase gene. *Biol. Psychiatry* **1997**, *42*, 282–285.
- 134 JOHANSSON, C., WILLEIT, M., SMEDH, C., EKHOLM, J., PAUNIO, T., KIESEPPA, T., LICHTERMANN, D., PRASCHAK-RIEDER, N., NEUMEISTER, A., NILSSON, L. G., KASPER, S., PELTONEN, L., ADOLFSSON, R., SCHALLING, M., PARTONEN, T., Circadian clock-related polymorphisms

- in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* **2003**, *28*, 734–739.
- 135 DESAN, P. H., OREN, D. A., MALISON, R., PRICE, L. H., ROSENBAUM, J., SMOLLER, J., CHARNEY, D. S., GELERENTER, J., Genetic polymorphism at the CLOCK gene locus and major depression. *Am. J. Med. Genet.* **2000**, *96*, 418–421.
- 136 YU, Y. W., CHEN, T. J., WANG, Y. C., LIOU, Y. J., HONG, C. J., TSAI, S. J., Association analysis for neuronal nitric oxide synthase gene polymorphism with major depression and fluoxetine response. *Neuropsychobiology* **2003**, *47*, 137–140.
- 137 SEGMAN, R. H., SHAPIRA, Y., MODAI, I., HAMDAN, A., ZISLIN, J., HERESCO-LEVY, U., KANYAS, K., HIRSCHMANN, S., KARNI, O., FINKEL, B., SCHLAFMAN, M., LERNER, A., SHAPIRA, B., MACCIARDI, F., LERER, B., Angiotensin converting enzyme gene insertion/deletion polymorphism: case-control association studies in schizophrenia, major affective disorder, and tardive dyskinesia and a family-based association study in schizophrenia. *Am. J. Med. Genet.* **2002**, *114*, 310–314.
- 138 PAULS, J., BANDELOW, B., RUTHER, E., KORNUBER, J., Polymorphism of the gene of angiotensin converting enzyme: lack of association with mood disorder. *J. Neural Transm.* **2000**, *107*, 1361–1366.
- 139 FURLONG, R. A., KERAMATIPOUR, M., HO, L. W., RUBINSZTEIN, J. S., MICHAEL, A., WALSH, C., PAYKEL, E. S., RUBINSZTEIN, D. C., No association of an insertion/deletion polymorphism in the angiotensin I converting enzyme gene with bipolar or unipolar affective disorders. *Am. J. Med. Genet.* **2000**, *96*, 733–735.
- 140 VILLAFUERTE, S. M., DEL-FAVERO, J., ADOLFSSON, R., SOUERY, D., MASSAT, I., MENDLEWICZ, J., VAN BROECKHOVEN, C., CLAES, S., Gene-based SNP genetic association study of the corticotropin-releasing hormone receptor-2 (CRHR2) in major depression. *Am. J. Med. Genet.* **2002**, *114*, 222–226.
- 141 COMINGS, D. E., WU, S., ROSTAMKHANI, M., MCGUE, M., IACONO, W. G., MACMURRAY, J. P., Association of the muscarinic cholinergic 2 receptor (CHRM2) gene with major depression in women. *Am. J. Med. Genet.* **2002**, *114*, 527–529.
- 142 LAI, I. C., HONG, C. J., TSAI, S. J., Association study of nicotinic-receptor variants and major depressive disorder. *J. Affect Disord.* **2001**, *66*, 79–82.
- 143 YAMADA, K., WATANABE, A., IWAYAMA-SHIGENO, Y., YOSHIKAWA, T., Evidence of association between gamma-aminobutyric acid type A receptor genes located on 5q34 and female patients with mood disorders. *Neurosci. Lett.* **2003**, *349*, 9–12.
- 144 ORUC, L., VERHEYEN, G. R., FURAC, I., IVEZIC, S., JAKOVljeVIC, M., RAEYMAEKERS, P., VAN BROECKHOVEN, C., Positive association between the GABRA5 gene and unipolar recurrent major depression. *Neuropsychobiology* **1997**, *36*, 62–64.
- 145 JUN, T. Y., PAE, C. U., CHAE, J. H., BAHK, W. M., KIM, K. S., Polymorphism of CTLA-4 gene for major depression in the Korean population. *Psychiatry Clin. Neurosci.* **2001**, *55*, 533–537.
- 146 ARINAMI, T., LI, L., MITSUSHIO, H., ITOKAWA, M., HAMAGUCHI, H., TORU, M., An insertion/deletion polymorphism in the angiotensin converting enzyme gene is associated with both brain substance P contents and affective disorders. *Biol. Psychiatry* **1996**, *40*, 1122–1127.
- 147 KRAMER, M. S., CUTLER, N., FEIGHNER, J., SHRIVASTAVA, R., CARMAN, J., SRAMEK, J. J., REINES, S. A., LIU, G., SNAVELY, D., WYATT-KNOWLES, E., HALE, J. J., MILLS, S. G., MACCOSS, M., SWAIN, C. J., HARRISON, T., HILL, R. G., HEFTI, F., SCOLNICK, E. M., CASCIERI, M. A., CHICCHI, G. G., SADOWSKI, S., WILLIAMS, A. R., HEWSON, L., SMITH, D., RUPNIAK, N. M., et al., Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* **1998**, *281*, 1640–1645.
- 148 BJELLAND, I., TELL, G. S., VOLLSET, S. E., REFSUM, H., UELAND, P. M., Folate, vitamin B12, homocysteine, and the MTHFR 677C>T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. *Arch. Gen. Psychiatry* **2003**, *60*, 618–626.
- 149 UELAND, P. M., HUSTAD, S., SCHNEEDE, J., REFSUM, H., VOLLSET, S. E., 2001 Biological and clinical implications of the

- MTHFR C677T polymorphism. *Trends Pharmacol. Sci.* **2001**, *22*, 195–201.
- 150 ARINAMI, T., YAMADA, N., YAMAKAWA-KOBAYASHI, K., HAMAGUCHI, H., TORU, M., Methylenetetrahydrofolate reductase variant and schizophrenia/depression. *Am. J. Med. Genet.* **1997**, *74*, 526–528.
 - 151 KUNUGI, H., FUKUDA, R., HATTORI, M., KATO, T., TATSUMI, M., SAKAI, T., HIROSE, T., NANKO, S., C677T polymorphism in methylenetetrahydrofolate reductase gene and psychoses. *Mol. Psychiatry* **1998**, *3*, 435–437.
 - 152 CLAPHAM, D. E., NEER, E. J., G protein beta gamma subunits. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 167–203.
 - 153 LEVINE, M. A., MODI, W. S., O'BRIEN, S. J., Chromosomal localization of the genes encoding two forms of the G protein beta polypeptide, beta 1 and beta 3, in man. *Genomics* **1990**, *8*, 380–386.
 - 154 SIFFERT, W., ROSSKOPF, D., SIFFERT, G., BUSCH, S., MORITZ, A., ERBEL, R., SHARMA, A. M., RITZ, E., WICHMANN, H. E., JAKOBS, K. H., HORSTHEMKE, B., Association of a human G-protein beta3 subunit variant with hypertension. *Nature Genet.* **1998**, *18*, 45–48.
 - 155 SERRETTI, A., LORENZI, C., CUSIN, C., ZANARDI, R., LATTUADA, E., ROSSINI, D., LILLI, R., PIROVANO, A., CATALANO, M., SMERALDI, E., SSRIs antidepressant activity is influenced by G beta 3 variants. *Eur. Neuropsychopharmacol.* **2003**, *13*, 117–122.
 - 156 ZILL, P., BAGHAI, T. C., ZWANZGER, P., SCHULE, C., MINOV, C., RIEDEL, M., NEUMEIER, K., RUPPRECHT, R., BONDY, B., Evidence for an association between a G-protein beta3-gene variant with depression and response to antidepressant treatment. *Neuroreport* **2000**, *11*, 1893–1897.
 - 157 ZILL, P., BAGHAI, T. C., ZWANZGER, P., SCHULE, C., MINOV, C., BEHRENS, S., RUPPRECHT, R., MOLLER, H. J., ENGEL, R., BONDY, B., Association analysis of a polymorphism in the G-protein stimulatory alpha subunit in patients with major depression. *Am. J. Med. Genet.* **2002**, *114*, 530–532.
 - 158 WILLEIT, M., PRASCHAK-RIEDER, N., ZILL, P., NEUMEISTER, A., ACKENHEIL, M., KASPER, S., BONDY, B., C825T polymorphism in the G protein beta3-subunit gene is associated with seasonal affective disorder. *Biol. Psychiatry* **2003**, *54*, 682–686.
 - 159 KUNUGI, H., KATO, T., FUKUDA, R., TATSUMI, M., SAKAI, T., NANKO, S., Association study of C825T polymorphism of the G-protein b3 subunit gene with schizophrenia and mood disorders. *J. Neural Transm.* **2002**, *109*, 213–218.
 - 160 MANJI, H. K., DREVETS, W. C., CHARNEY, D. S., The cellular neurobiology of depression. *Nature Med.* **2001**, *7*, 541–547.
 - 161 EGAN, M. F., KOJIMA, M., CALLICOTT, J. H., GOLDBERG, T. E., KOIACHANA, B. S., BERTOLINO, A., ZAITSEV, E., GOLD, B., GOLDMAN, D., DEAN, M., LU, B., WEINBERGER, D. R., The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **2003**, *112*, 257–269.
 - 162 NEVES-PEREIRA, M., MUNDO, E., MUGLIA, P., KING, N., MACCIARDI, F., KENNEDY, J. L., The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am. J. Hum. Genet.* **2002**, *71*, 651–655.
 - 163 HONG, C. J., HUO, S. J., YEN, F. C., TUNG, C. L., PAN, G. M., TSAI, S. J., Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology* **2003**, *48*, 186–189.
 - 164 ZUBENKO, G. S., HUGHES 3RD, H. B., MAHER, B. S., STIFFLER, J. S., ZUBENKO, W. N., MARAZITA, M. L., Genetic linkage of region containing the CREB1 gene to depressive disorders in women from families with recurrent, early-onset, major depression. *Am. J. Med. Genet.* **2002**, *114*, 980–987.
 - 165 THOME, J., SAKAI, N., SHIN, K., STEFFEN, C., ZHANG, Y. J., IMPEY, S., STORM, D., DUMAN, R. S., cAMP response element-mediated gene transcription is up-regulated by chronic antidepressant treatment. *J. Neurosci.* **2000**, *20*, 4030–4036.
 - 166 CASPI, A., SUGDEN, K., MOFFITT, T. E., TAYLOR, A., CRAIG, I. W., HARRINGTON, H., MCCRAY, J., MILL, J., MARTIN, J.,

- BRAITHWAITE, A., POULTON, R., Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **2003**, *301*, 386–389.
- 167 JOHNSON, G. C., ESPOSITO, L., BARRATT, B. J., SMITH, A. N., HEWARD, J., DI GENOVA, G., UEDA, H., CORDELL, H. J., EAVES, I. A., DUDBRIDGE, F., TWELLS, R. C., PAYNE, F., HUGHES, W., NUTLAND, S., STEVENS, H., CARR, P., TUOMILEHTO-WOLF, E., TUOMILEHTO, J., GOUGH, S. C., CLAYTON, D. G., TODD, J. A., Haplotype tagging for the identification of common disease genes. *Nature Genet.* **2001**, *29*, 233–237.
- 168 PURCELL, S., CHERNY, S. S., SHAM, P. C., Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* **2003**, *19*, 149–150.
- 169 NUFFIELD COUNCIL ON BIOETHICS. *Mental Disorders and Genetics: The Ethical Context*, 1998.
- 170 OHARA, K., NAGAI, M., TSUKAMOTO, T., TANI, K., SUZUKI, Y., OHARA, K., Functional polymorphism in the serotonin transporter promoter at the SLC6A4 locus and mood disorders. *Biol. Psychiatry* **1998**, *44*, 550–554.
- 171 MINOV, C., BAGHAI, T. C., SCHULE, C., ZWANZGER, P., SCHWARZ, J., ZILL, P., RUPPRECHT, R., BONDY, B., Serotonin-2A-receptor and -transporter polymorphisms: lack of association in patients with major depression. *Neurosci. Lett.* **2001**, *303*, 119–122.
- 172 SERRETTI, A., LILLI, R., LORENZI, C., LATTUADA, E., CUSIN, C., SMERALDI, E., Serotonin transporter gene (5-HTTLPR) and major psychoses. *Mol. Psychiatry* **2002**, *7*, 95–99.
- 173 BONDY, B., KUZNIK, J., BAGHAI, T., SCHULE, C., ZWANZGER, P., MINOV, C., DE JONGE, S., RUPPRECHT, R., MEYER, H., ENGEL, R. R., EISENMENGER, W., ACKENHEIL, M., Lack of association of serotonin-2A receptor gene polymorphism (T102C) with suicidal ideation and suicide. *Am. J. Med. Genet.* **2000**, *96*, 831–835.
- 174 TSAI, S. J., HONG, C. J., HSU, C. C., CHENG, C. Y., LIAO, W. Y., SONG, H. L., LAI, H. C., Serotonin-2A receptor polymorphism (102T/C) in mood disorders. *Psychiatry Res.* **1999**, *87*, 233–237.
- 175 OSWALD, P., SOUERY, D., MASSAT, I., DEL-FAVERO, J., LINOTTE, S., PAPADIMITRIOU, G., DIKEOS, D., KANEVA, R., MILANOVA, V., ORUC, L., IVEZIC, S., SERRETTI, A., LILLI, R., VAN BROECKHOVEN, C., MENDLEWICZ, J., Lack of association between the 5HT2A receptor polymorphism (T102C) and unipolar affective disorder in a multicentric European study. *Eur. Neuropsychopharmacol.* **2003**, *13*, 365–368.
- 176 KUNUGI, H., ISHIDA, S., KATO, T., SAKAI, T., TATSUMI, M., HIROSE, T., NANKO, S., No evidence for an association of polymorphisms of the tryptophan hydroxylase gene with affective disorders or attempted suicide among Japanese patients. *Am. J. Psychiatry* **1999**, *156*, 774–776.
- 177 KUNUGI, H., ISHIDA, S., KATO, T., TATSUMI, M., SAKAI, T., HATTORI, M., HIROSE, T., NANKO, S., A functional polymorphism in the promoter region of monoamine oxidase-A gene and mood disorders. *Mol. Psychiatry* **1999**, *4*, 393–395.
- 178 SYAGAILO, Y. V., STOBER, G., GRASSLE, M., REIMER, E., KNAPP, M., JUNGKUNZ, G., OKLADNOVA, O., MEYER, J., LESCH, K. P., Association analysis of the functional monoamine oxidase A gene promoter polymorphism in psychiatric disorders. *Am. J. Med. Genet.* **2001**, *105*, 168–171.
- 179 SASAKI, T., HATTORI, M., SAKAI, T., KATO, T., KUNUGI, H., HIROSE, T., NANKO, S., The monoamine oxidase-A gene and major psychosis in Japanese subjects. *Biol. Psychiatry* **1998**, *44*, 922–924.
- 180 TADIC, A., RUJESCU, D., SZEGEDI, A., GIEGLING, I., SINGER, P., MOLLER, H. J., DAHMEN, N., 2003. Association of a MAOA gene variant with generalized anxiety disorder, but not with panic disorder or major depression. *Am. J. Med. Genet.* **2003**, *117B*, 1–6.

32

Molecular Effects of Antidepressant Treatments*Pierre Sokoloff***Abstract**

Antidepressant drugs mainly target plasma membrane transporters for monoamines with various selectivities for serotonin, noradrenaline and dopamine, and inhibit reuptake of these amines after their release, thus increasing their extracellular levels. In addition, antidepressant drugs share the property of being able to block the serotonin-gated cation channel (5-HT₃ receptor). Drugs targeting receptors for substance P or corticotrophin-releasing factor have also been proposed as antidepressants. Chronic treatments with antidepressants induce changes in the activity of serotonin and dopamine neurons, notably by desensitizing inhibitory autoreceptors. After chronic antidepressant treatment, all these primary interactions seem to result in convergent adaptive changes mediated through the cyclic AMP/CREB/BDNF cascade. These changes are responsible for enhancement of the responsiveness to the mesolimbic dopamine system mediating motivation and reward, and for an increase of neurogenesis in the hippocampus, which is involved in the control of the hypothalamus–pituitary–adrenal axis mediating stress responses. This rather coherent chain of events accounts for most of the observations made in animals receiving chronic antidepressant treatments, and has received some, as yet limited, support from clinical studies.

32.1**Introduction**

The treatment of depression was revolutionized about half-century ago by the serendipitous discovery of tricyclic antidepressants (TCAs, for instance imipramine), derived from antihistamine agents, and of monoamine oxidase inhibitors (MAOIs), derived from an antitubercular drug, iproniazide. Both classes of drugs have dominated the treatment of major depression between 1960 and 1980. TCAs were demonstrated to predominantly target the monoamine systems in the brain (noradrenaline, serotonin, dopamine) by increasing the extracellular levels of

transmitters, which points to a crucial role of these systems in the etiology of depression and the action of antidepressant drugs. Indeed, TCAs were found to act mainly as inhibitors of monoamine reuptake, principally targeting noradrenaline and serotonin. TCAs also target various other brain effectors, which may explain the side-effects of these drugs.

Second-generation antidepressant drugs appeared during late 1980s, following the earlier discovery of the antidepressant efficacy of the serotonin-uptake inhibitor zimelidine [1], a drug whose development was discontinued because of rare but serious side-effects. Drugs of this class include serotonin-selective reuptake inhibitors (SSRIs, for instance paroxetine, fluoxetine) and norepinephrine-selective reuptake inhibitors (NaRIs, for instance reboxetine), and are widely used today. More recently, antagonism of neurokinins has been suggested to produce antidepressant effects [2]. Hence, it is difficult to define a common mechanism of action for antidepressant drugs, and the situation is even less clear regarding other antidepressant treatments such as electroconvulsive seizures (ECT), which remains the most effective treatment for major depression to date.

Most antidepressant drugs are active after an acute administration in some rodent behavioral tests which have been suggested to predict antidepressant activity, such as the forced swim test [3] and the tail suspension test [4]. However, the antidepressant effect emerges in patients after chronic, but not acute treatment, emphasizing the crucial importance of adaptive changes in promoting this activity. Thus, in spite of the long-standing clinical use of antidepressant drugs, the neural mechanisms underlying the therapeutic effects of these drugs are still incompletely understood. We still lack a fundamental understanding of the genes and gene-environment interactions that determine the vulnerability to depression, and of the changes in the brain that underlie symptoms. A better knowledge of these mechanisms may obviously have a considerable impact on the development of novel medications, which are indeed, needed. Thus, an assessment of the clinical effectiveness of antidepressant therapies [5] reveals that the response rate is only of 50% for the newer antidepressants (compared with 32% for placebo) in a survey of more than 80 placebo-controlled studies. In addition, the newer antidepressants appear as effective as first- and second-generation tricyclic antidepressants (TCAs). Moreover, many patients experience intolerable side-effects.

This aims of this chapter are not only to describe the primary molecular targets of antidepressant drugs within various neurotransmitter systems, but also to examine the possible secondary, long-term effects of antidepressant treatments, notably genomic effects, which could produce enduring changes in brain function and eventually participate in the clinical effects of these treatments.

32.2

Primary Molecular Targets for Antidepressant Drugs

32.2.1

Monoamine Oxidases

Monoamine oxidases (MAOs) convert catecholamines (dopamine, noradrenaline) and serotonin into their respective inactive aldehydes, which are rapidly catabolized into the corresponding acids by aldehyde dehydrogenases. Monoamine oxidases are present in neuronal and non-neuronal cells as membrane-bound enzymes associated with the outer membrane of mitochondria. MAOs are widely distributed in the brain, but the highest concentrations of these enzymes are found in the liver and kidney. IMAOs were introduced into the clinics for major depression in 1957, following the observation that iproniazid, an antituberculosis agent, had antidepressant effects; the use of irreversible hydrazine IMAOs has however, been limited by their high liver toxicity. Nevertheless, the efficacy of IMAOs as antidepressant drugs provided the first indications that dysfunction of monoamine systems may play a role in the pathophysiology of depression.

Non-hydrazine compounds, such as tranylcypromine, were subsequently developed, but their use has been associated with life-threatening hypertensive reactions. Nevertheless, the interest in IMAOs has been rejuvenated by the discovery that there are two MAO isoforms, A and B, which have different substrate specificities and pharmacological profiles with respect to inhibitors. As an attempt to minimize the complications of earlier agents, both selective and reversible MAO-A inhibitors (RIMAs), such as moclobemide, brofaromide, cimoxatone and befloxatone, were identified and found efficacious in pre-clinical studies. However, RIMAs appear to be less effective for the treatment of depression as compared to other MOAIs and TCAs [5] and their use in clinics is very limited at the present time.

32.2.2

Noradrenaline

Noradrenergic systems are involved in physiological processes such as learning and memory, sleep, arousal and adaptation, all of which are relevant to the autonomic response to stress and in depression [6]. Central noradrenergic neurons emerge from two brain structures, the locus coeruleus and lateral tegmentum, which project into regions of the brain which are concerned with fear and stress, including the thalamus, amygdala, cortex, and raphe nucleus [7]. In animals, chronic stress reduces β -adrenergic receptors and cyclic AMP responses, and increases α_1 - and α_2 -adrenoreceptors; changes in density of these receptors in depressed patients are more controversial [8, 9]. Thus, the involvement of noradrenergic systems in depression is rather indirect. The strongest evidence comes from the clinical efficacy in depression of selective noradrenaline uptake inhibitors (desipramine, reboxetine, maprotiline, see Table 32.1), which appear to have equivalent efficacy to other

antidepressant drugs, yet some of them have significant disadvantages with respect to side-effects related to lateral pharmacological effects on muscarinic, cholinergic, adrenergic or histaminergic receptors [9]. Thus, blockade of noradrenaline reuptake elevates extracellular levels of noradrenaline, but this rise is limited by the activation of inhibitory α_2 -autoreceptors [10]. Similarly, mianserin and mirtazapine, two atypical antidepressant drugs that block α_2 -autoreceptors controlling noradrenaline release, increase noradrenaline, but this rise is limited by reuptake. Therefore, it should be advantageous to combine noradrenaline reuptake and α_2 -autoreceptors blockade [11], a concept that has not yet been supported by clinical evidence.

Table 32.1 Pharmacological profile of antidepressant drugs at recombinant human transporters

Antidepressant	<i>K_i values (nM) for transporters</i>		
	Serotonin	Noradrenaline	Dopamine
Amitriptyline	4.3	35	3250
Amoxapine	58	16	4310
Bupropion	9100	52,000	520
Butriptyline	1360	5100	3940
Citalopram	1.2	4070	28,100
Clomipramine	0.28	38	2190
Desipramine	18	0.83	3190
Desmethylcitalopram	3.6	1820	18,300
Desmethylsertraline	3.0	390	129
Dothiepin	8.6	46	5310
Doxepin	68	29.5	12,100
Etoferidone	890	20,000	52,000
Femoxetine	11	760	2050
Fluoxetine	0.81	240	3600
Fluvoxamine	2.2	1300	9200
Imipramine	1.4	37	8500
Lofepamine	70	5.4	18,000
Maprotiline	5,800	11	1000
Mianserine	4,000	71	9400
Mirtazapine	> 100,000	2900	> 100,000
Nomifensine	1,010	16	56
Norfluoxetine	1.5	1430	420
Nortriptyline	18	4.4	1140
Oxaprotiline	3900	4.9	4340
Paroxetine	0.13	40	490
Sertraline	0.29	420	25
Tomoxetine	8.9	2.0	1080
Trazodone	160	8500	7400
Trimipramine	149	2450	3780
Venlafaxine	8.9	1060	9300
Vilofaxine	17,300	155	> 100,000
Zimelidine	152	9400	11,700

Data from [164].

32.2.3

Serotonin

Serotonin (5HT-tryptamine) is the neurotransmitter that has received by far the most attention in the area of depression. Direct evidence for the involvement of serotonin in this disorder is provided by clinical studies. Thus, low concentrations of 5-hydroxyindolacetic acid, the major metabolite of serotonin, have been reported in the cerebrospinal fluid of depressed patients [12, 13]. A diet low in tryptophan, the serotonin precursor, precipitates relapse in remitted depressed patients [14]. Moreover, regional brain glucose metabolism after administration of the serotonin-releasing drug dl-fenfluramine is blunted in unmedicated depressed patients [15]. Nevertheless, even though the aforementioned evidence supports the hypothesis of serotonin dysfunction in depression, this dysfunction could be secondary to disturbances in other neural systems. However, the observation that selective drugs acting at different levels of the serotonin system, notably on reuptake, have clinical efficacy comparable to that of non-selective drugs, indicates that serotonin has a pivotal role in antidepressant effects. Thus, the introduction of SSRIs (for instance fluoxetine, fluvoxamine, paroxetine, setraline, citalopram; see Table 32.1) for the treatment of major depression represented a revolution in the pharmacotherapy of this disorder, as these drugs are potent antidepressants and free of the typical side-effects of TCAs. They are now the mainstay of treatment for depression, not only in the psychiatrist's clinic, but also in general practitioners' surgeries. It is important to realize that serotonin and noradrenaline neurons are anatomically and functionally interconnected and that their reciprocal regulation of activity by blockade of the uptake of serotonin and noradrenaline and synergism in the action of drugs acting on one of these, may play a role in the actions of antidepressant drugs. Hence, newer antidepressants (for instance venlafaxine, milnacipram) combine the inhibition of both serotonin and noradrenaline uptake.

Another line of evidence points to a specific involvement of serotonin systems in the mode of action of antidepressant drugs. Thus, compelling electrophysiological data documented that various types of antidepressant treatment enhance serotonin neurotransmission. All TCAs, irrespective of their selectivity towards monoamine uptake, progressively increase the responsiveness of post-synaptic 5HT-_{1A} receptors in the rat hippocampus and this effect is specific to antidepressant drugs, since it is not reproduced by the antipsychotic chlorpromazine nor by the anxiolytic diazepam [16]. The time course of sensitization of 5HT-_{1A} receptors (2–3 weeks) is congruent with the delayed onset of action of antidepressant drugs in major depression and is obtained at clinically relevant dosages. Moreover, repeated, but not single, ECTs also induce sensitization of serotonin in the dorsal hippocampus [17]. Furthermore, all MAOIs targeting the type A isoenzyme (for instance clorgyline, moclobemide, phenelzine and tranylcipromine) or SSRIs initially induce an attenuation of the firing activity of serotonin neurons, which gradually recovers; eventually these compounds enhance serotonin transmission after prolonged administration. These effects are due to an initial stimulation of 5HT-_{1A} auto-receptors by serotonin, the extracellular concentration of which is increased in the

raphe nucleus, the brain region containing serotonin neuron cell bodies; the period of stimulation is then followed by desensitization of these receptors which normally exert an inhibitory influence on serotonin neuron activity [18]. This desensitization is an adaptive process which typically takes 2–3 weeks to become apparent and adequately explains the time-lag seen in the clinical action of antidepressant drugs [16]; it is also accompanied by downregulation of 5HT_{1A} mRNA in the raphe nucleus [19]. Indirect evidence supports the fact that the changes found in laboratory animals also occur in humans. For instance, prolactin secretion induced by intravenous administration of L-tryptophan which is mediated via post-synaptic 5-HT_{1A}, is blunted in depressed patients and significantly enhanced after treatment with amitriptyline or desipramine [20]. Since desipramine is selective for noradrenaline uptake, this effect cannot be due to the direct action of antidepressants on serotonin availability, but rather to a decrease in 5-HT_{1A} receptor responsiveness.

As a corollary to the above considerations, it may be possible to directly manipulate the 5-HT_{1A} receptors to obtain novel antidepressants, or to improve the efficacy or reduce the time-lag of existing antidepressants. Thus, pindolol, a β -adrenergic/5-HT_{1A} receptor antagonist, has been proposed to augment antidepressants in the early phase of treatment, based on the concept that blockade of 5-HT_{1A} somatodendritic receptors would eliminate the need to desensitize these receptors and would thus hasten the therapeutic effects. Such a concept is consistent with the larger occupancy by pindolol of postsynaptic compared to somatodendritic 5-HT_{1A} receptors [21–23], suggesting that antagonism of postsynaptic 5-HT_{1A} receptors would not hinder the manifestation of antidepressant effects. Most of the placebo-controlled clinical studies published so far support this concept and have found that pindolol accelerates the onset of antidepressant effects; some studies even found an augmentation of antidepressant effects [24]. Nevertheless, the combination of pindolol with other antidepressant drugs has not yet become routine in clinical practice.

A related, but opposite proposition is the use of a 5-HT_{1A} receptor agonist as an antidepressant, based on the concept that direct and prolonged stimulation of somatodendritic 5-HT_{1A} receptors would accelerate their desensitization and eventually produce an enhancement of serotonin neuron firing which is necessary to achieve an antidepressant effect. Buspirone is such an agent, and has been associated with significant antidepressant effects in clinic and has good tolerability [25]; in addition, the desirable anxiolytic action of this agent makes it a sound therapeutic option for the treatment of depression. Nevertheless, the poor pharmacokinetic properties of buspirone and other 5-HT_{1A} receptor agonists (ipsapirone, gepirone) may be responsible for their modest clinical efficacy [26].

Another principle of action of antidepressant drugs was established by the seminal, yet unrecognized, discovery by Fan in 1994 that antidepressant drugs (TCA, SSRI and MAOIs) inhibit, at clinically relevant concentrations, serotonin inward currents mediated via 5-HT₃ receptors in rat nodose ganglion neurons [27]. The 5-HT₃ receptor is distinct from other serotonin receptors which all belong to the large G protein-coupled receptor family; it constitutes a cation-permeable ligand-gated channel that shares structural features and sequence homology with γ -amino-

butyric acid type A, glycine and nicotinic acetylcholine receptors [28]. In the brain, 5-HT₃ receptors are expressed in the area postrema in which they mediate the antiemetic effects of 5-HT₃ receptor antagonists which are commonly used in cancer therapy, and they are also expressed in the hippocampus and the amygdala [29, 30]. Acute activation of 5-HT₃ receptors results in transmitter release, especially dopamine in the mesolimbic pathways [31]. Recently, a thorough examination of the effects of antidepressant drugs belonging to various classes on Na⁺ and Ca²⁺ currents mediated by recombinant and native 5-HT₃ receptors [32], revealed that these drugs act as non-competitive antagonists (with the exception of mirtazapine), in a voltage-independent manner. Some, but not all antidepressant drugs also accelerate desensitization of serotonin-evoked currents. Importantly, this study shows that trimipramine, an antidepressant (and also an antipsychotic) drug which is structurally related to imipramine, but whose action is weak at the human serotonin transporter (Table 32.1) and which has no effect on noradrenaline, serotonin or dopamine uptake [33], also shares the property of other antidepressant drugs in inhibiting serotonin-evoked currents. In addition, an analysis of structure–activity relationships in the series of desipramine and carbamazepine reveals structural determinants of potency at 5-HT₃ receptors, which are correlated with clinical efficacy [32]. Further studies are necessary to understand the link which exists between non-competitive blockade of 5-HT₃ receptors and antidepressant effects. For instance, it would be interesting to assess the ultimate adaptive changes in the function of neurotransmitters, notably serotonin, noradrenaline and dopamine which are believed to be involved in depression, and antidepressant effects following chronic 5-HT₃ receptor blockade. Nevertheless, the discovery of a novel common site of action for antidepressant drugs is an important finding challenging current views on these drugs and offering provocative possibilities for future research on depression and development of novel therapies.

32.2.4

Dopamine

Considerable emphasis has been placed upon the putative role of dopamine systems in appetitive motivation and positive reinforcement [34, 35]. Hence, mesolimbic dopaminergic neurons projecting into the nucleus accumbens have been suggested to be involved in the pathogenesis of depression, particularly anhedonia, a core symptom of the disease, and in the therapeutic actions of some antidepressant drugs [36–39]. This hypothesis postulates that decreased dopamine activity is involved in depression, while increased dopamine function contributes to mania. Accordingly, dopaminergic drugs (e.g. amphetamine or cocaine) can produce effects in humans that are remarkably similar to an idiopathic manic episode [40, 41] and the discontinuation of such drugs [42] or the acute administration of dopamine receptor antagonists can result in a psychopathological state similar to a depressive episode [43]. Clinical imaging studies in depressed patients have found increased [¹²³I]IBZM binding in the striatum, probably reflecting reduced dopamine function in depression [44, 45]. Furthermore, dopaminergic drugs such as the selective

dopamine uptake inhibitors amineptine [46], nomifensin and bupropion (Table 32.1) have been successfully used for treating major depression [46–48].

Dopamine exerts its actions by interacting with receptors belonging to a family comprising five subtypes, the D₁–D₅ receptors [49, 50]. The D₃ receptor is expressed mainly in the limbic ventral part of the striatal complex, particularly in the shell of the nucleus accumbens [51, 52]; other dopamine receptor subtypes are also expressed in the nucleus accumbens or in structures connected to this region. Hence, it can be hypothesized that increasing dopamine input in the nucleus accumbens by blocking dopamine uptake can mediate therapeutic effects, notably with respect to anhedonia, of those antidepressant drugs that display some selectivity for this uptake system.

Hence, although dopamine systems are usually thought to be secondary targets of antidepressant drugs, some of their components constitute primary targets for atypical antidepressants. In addition, a large body of evidence suggests that these systems are an important substrate for adaptive changes following stress and chronic antidepressant treatments (see Section 32.3.4).

32.2.5

Substance P

Substance P is a peptide composed of 11 aminoacids and is the most abundant neurokinin in the mammalian central nervous system (CNS). The substance P-preferring neurokinin-1 (NK1) receptor is highly expressed in brain regions, including the amygdala, hypothalamus, hippocampus and locus coeruleus [53], which receive convergent monoaminergic innervations and/or co-ordinate stress responses. A fraction of noradrenaline- and serotonin-containing cell bodies also co-express substance P [53], which suggests interactions with neurotransmitters involved in the action of established antidepressant drugs. The potential for such functional interactions *in vivo* is supported by the observation that repeated administration of antidepressant drugs downregulates substance P biosynthesis in discrete brain regions in the rat [54, 55], raising speculation that alterations in neurokinin systems may contribute to their antidepressant efficacy. Nevertheless, studies measuring substance P in the cerebrospinal fluid of depressed patients are controversial [56, 57]; one study found an elevation of substance P serum levels [58]. The aforementioned results suggest that substance P antagonists might have utility in the treatment of depression.

The development of centrally active non-peptide NK1 antagonists, such as MK-0869 (Aprepitant, a compound initially developed as an anti-emetic drug for cancer therapy) and its analog L-760,735, and the generation of NK1 receptor-knockout mice offered the opportunity to test this hypothesis more directly. Thus, pharmacological blockade or deletion of NK1 receptors causes an increase in the firing rate of serotonin neurons in the dorsal raphe, without increasing the extracellular efflux of serotonin in the cortex [59, 60]. NK1 receptor antagonists also increase burst firing of noradrenergic neurons [61]. Behavioral studies demonstrate that NK1 antagonists exhibit antidepressant- and anxiolytic-like

activities in a range of animal models: increased glucose intake after chronic mild stress [62], increased social interactions [63], decreased distress vocalizations [2] and increased time spent in an aversive environment [64]. Moreover, NK1 receptor-knockout mice display reduced stress responses [65].

These results provided rationale for testing NK1 antagonists in depression. A double-blind, placebo-controlled clinical trial found MK-0869 to have antidepressant efficacy versus placebo in patients with major depression and high anxiety, comparable to that of paroxetine [2]. In a subsequent dose-finding study, MK-0869 and another NK1 antagonist were found to be as active as placebo; however, an SSRI used as an active control also produced similar effects as placebo [66]. Nevertheless, clinical development of MK-0869 as an antidepressant has recently been halted because the compound failed to demonstrate efficacy for the treatment of depression in a Phase III clinical trial (see Research and Development news provided by Merck at <http://www.merck.com>). This disappointing result highlights two main areas of speculation: (1) the efficacy of NK1 antagonists as antidepressants, and especially that of MK-0869, might be low; in any event these novel drugs do not seem to represent a breakthrough for the treatment of major depression with respect to existing medications; (2) the animal models of depression that predicted the efficacy of MK-0869 might not be adequate for extrapolation to the human disease. Nevertheless, it should be pointed out that these pessimistic conclusions derive from clinical studies which used only a single compound.

32.2.6

Corticotropin-releasing Factor

Corticotrophin-releasing factor (CRF) is a neuropeptide composed of 41 amino acids that initiates hypothalamic–pituitary–adrenal (HPA) axis response to stress, by releasing adrenocorticotrophic hormone (ACTH) from the anterior pituitary into the general circulation; ACTH acting on the adrenal cortex stimulates the secretion of glucocorticoids which mediate stress responses. CRF acts through two types of receptors, CRF₁ and CRF₂. In addition to the secretion of ACTH, CRF participates in other functions related to stress, since CRF neurons also project into other regions involved in stress responses, such as the amygdala, lateral septum, locus coeruleus and raphe nucleus in which CRF receptors are also found [67]. The CRF₁ receptor appears to be involved in the response to stress: CRF₁ mutant mice display decreased anxiety-like behaviors and blunted responses to stress [68] and CRF₁ antagonists attenuate behavioral, neuroendocrine and autonomic responses to stress [69, 70]. Interestingly, some studies found that the responses to CRF₁ antagonists is more pronounced in animals submitted to stressors, suggesting that CRF₁ antagonists may block pathological CRF-mediated responses to stress, while having minimal effects on the HPA axis under normal conditions. Preliminary outcomes of the first clinical open trial of a CRF₁ antagonist in depression are encouraging [71], even though this potential novel approach to the treatment of this disorder is still awaiting proof-of-concept.

32.2.7

Glutamate

There is circumstantial evidence to suggest that drugs acting at glutamate receptors of the N-methyl-D-aspartate subtype have antidepressant-like properties in pre-clinical and clinical studies. Moreover, chronic administration of antidepressants to mice alters both the mRNA levels encoding N-methyl-D-aspartate (NMDA) receptor subunits and radioligand binding to these receptors within discrete areas of the brain [72, 73]. The first placebo-controlled study of an NMDA antagonist, ketamine, in depression revealed a significant improvement of depressive symptoms [74]. However, treatment with ketamine was associated with the typical psychotic symptoms elicited by NMDA antagonists, such as phencyclidine [75].

32.3

Adaptive Molecular Changes Following Chronic Antidepressant Treatment

32.3.1

Antidepressant Treatment-induced Changes in G Protein Signaling

A relevant issue concerning the molecular effects of antidepressant drugs are the changes occurring after chronic treatment beyond the primary events related to receptor occupancy by either the drug itself or the neurotransmitter released or increased by the drug. Since most primary targets of antidepressant drugs are G protein-coupled receptors or neurotransmitters acting through this kind of receptor, it is interesting to assess the changes at the G protein level. G proteins are heterotrimeric proteins composed of α , β and γ subunits. They are activated by the stimulation of G protein-coupled receptors, which initiates heterotrimer dissociation of the G protein, exchange of guanosine 5'-diphosphate (GDP) for guanosine 5'-triphosphate (GTP) on its $G\alpha$ subunit and activation of the effector proteins which mediate intracellular signals. Thus, antidepressant drugs may be effective because they modulate intracellular signaling generated in response to neurotransmitters, particularly adenylyl cyclase and its product adenosine 3',5'-cyclic monophosphate (cAMP), which is the main intracellular second messenger [76]. Accordingly, it was found that *in vitro* stimulation of adenylyl cyclase activity by forskolin or a GTP analog is reduced in membranes from suicide cases with a history of depression [77]. Moreover, chronic administration of various antidepressants, including ECT, in animals enhances adenylyl cyclase activation [76]. The intrinsic properties of adenylyl cyclase are unchanged, as are G protein expression and GTP-binding capacity. It is therefore likely that this effect of antidepressants occurs at the level of the stimulatory α subunit of the G_s protein, which more readily couples to the enzyme. This was subsequently confirmed in immunoprecipitation experiments with an anti- $G_s\alpha$ antibody [76].

G protein signaling complexes are associated with specific components of the plasma membrane and cytoskeleton [78]. These domains are cholesterol- and

sphingolipid-rich and detergent-resistant membrane caveolae and rafts [79]. It is noteworthy that different G protein α subunits are found in distinct plasma membrane microdomains and that receptors, G proteins and effectors are constrained from lateral mobility within the plane of the plasma membrane in part by the cytoskeletal structures bound to the inner membrane face, most probably through bifunctional scaffolding proteins. Supercomplexes can form between the various components of the signaling system according to both receptor activation and preferential localization of the individual components within distinct microdomains. For instance, while both $G_{s\alpha}$ and $G_{i\alpha}$ can move in and out of caveolae, they are predominantly associated with lipid rafts complexed with $G\beta\gamma$ [76]. Biochemical data demonstrate that $G_{s\alpha}$ localizes to a different membrane microdomain upon antidepressant treatment [80]. These data suggest that chronic antidepressant treatments can change the lipid environment of the G protein in plasma membrane microdomains, resulting in changes in the signaling cascade, particularly increasing the coupling to adenylyl cyclase [76]. Hence, increased coupling between $G_{s\alpha}$ and adenylyl cyclase by antidepressants is an intriguing finding that has not as yet been confirmed by clinical studies. Nevertheless, since it is expected that such an effect would evoke an increase in the generation of cAMP, and therefore would enhance the function of many cAMP-dependent pathways (see below), it may be highly relevant to the mode of action of antidepressants [81].

32.3.2

Cyclic AMP-Responsive Element Binding (CREB) Protein as an Intermediate Mediator of Antidepressant Effects

Cyclic AMP-dependent pathways are initially activated by a cAMP-dependent protein kinase (PKA). Increases in cAMP binding to PKA or PKA activity was observed after chronic, but not acute treatment with antidepressants [82, 83]. Among PKA substrates, cAMP-Responsive Element Binding (CREB) protein has received much attention in the area of depression following the demonstration that chronic, but not acute antidepressant treatments increase CREB expression and CRE binding [84]. The transcription activity of CREB is also increased, as assessed using a transgenic mouse expressing a reporter gene [85]. Moreover, overexpression of CREB in the dentate gyrus, mediated through *Herpes simplex* virus-mediated gene transfer, elicits antidepressant-like effects in behavioral tests, including the forced swim test and the learned helplessness model [86]. However, blockade of CREB function in the nucleus accumbens using animals carrying an inducible CREB-negative dominant gene has the opposite effect [87]. These results support the contention that the cAMP pathway and CREB in particular, plays an important role in the effect of antidepressants and in depression. However, not all the data are consistent with this view [88, 89], and the clinical relevance of these observations in animals remains to be established, since post-mortem studies in suicide cases are rather contradictory [90, 91]. It is noteworthy that CREB is also activated by a Ca^{2+} -dependent pathway [92] and that numerous G protein-coupled receptors, targeted

by the neurotransmitters whose levels are increased by antidepressants, produce signals by increasing the levels of intracellular Ca^{2+} , thus extending the possibilities for the mechanisms of regulation of CREB by these drugs.

32.3.3

Brain-derived Neurotrophic Factor as a Secondary Target for Antidepressants

The brain-derived neurotrophic factor (BDNF) gene is a CREB-regulated gene [93, 94]. BDNF, like other neurotrophins, was initially regarded as being responsible for neuronal proliferation, differentiation and survival, following its neuronal uptake and retrograde transport to the soma [95]. A more diverse role for BDNF as an extracellular transmitter has nevertheless, been inferred from observations that its transport is anterograde [96, 97], it is released upon neuron depolarization and that it triggers rapid intracellular signals [98] and action potentials in central neurons [99] via intracellular transduction of its high-affinity membrane receptor TrkB. BDNF can alter fast synaptic transmission not only by speeding up the development of excitatory and inhibitory synapses [100], but also by modulating synaptic efficacy [101, 102]. In particular, BDNF is necessary for the induction and maintenance of long-term hippocampal potentiation [103–105].

The first hint of a link between BDNF and depression came from the observation that acute immobilization stress markedly reduces BDNF mRNA levels in the dentate gyrus and hippocampus. In contrast, neurotrophin-3, neurotrophin-4, TrkB and TrkC mRNA levels were unchanged [106]. These changes also occur in adrenalectomized rats, indicating that corticosterone negative feedback does not contribute to the observed changes in BDNF. The second suggestion of a link came from the observation that chronic, but not acute antidepressant treatments, including TCA, SSRI, MAOI, and ECT, all increase BDNF mRNA in the hippocampus (Table 32.2, see [107]). Upregulation of BDNF by antidepressant requires CREB, because the upregulation is abolished in CREB-deficient animals, although behavioral and endocrine responses to antidepressants are maintained [108]. Furthermore, TrkB signaling is necessary for antidepressant drugs to have a positive effect, as assessed by the forced swim test, since the antidepressant effect is lost in mice expressing the TrkB-negative dominant gene [109]. Direct evidence for the involvement of BDNF in the effects of antidepressants comes from the observation that a single bilateral infusion of BDNF into the dentate gyrus of the hippocampus produced an antidepressant effect in two animal models of depression (the forced swim test and the learned helplessness) that was comparable in magnitude with repeated systemic administration of a chemical antidepressant [110].

These animal data are consistent with clinical data showing increased BDNF expression in the dentate gyrus, hilus and supragranular regions in subjects treated with antidepressant medications at the time of death, compared with subjects who had not been treated with antidepressant [111]. They also suggest that CREB-dependent BDNF upregulation is critical for long-term adaptation of the central nervous system to antidepressant drug treatment.

Table 32.2 Effects of acute and chronic antidepressant treatment on BDNF and its receptor TrkB mRNA expression in the hippocampus

	<i>BDNF mRNA</i> (%)	<i>TrkB mRNA</i> (%)
Chronic antidepressant drug treatments		
Electroconvulsive shocks*	161	275
Tranylcypromine	181†	139†
Mianserin	144†	91
Sertraline	120†	136†
Desipramine	126†	141†
Acute antidepressant drug treatments		
Electroconvulsive shock*	180	170
Tranylcypromine	112	91
Mianserin	104	119
Sertraline	93	98
Desipramine	112	94
Chronic non antidepressant treatments		
Morphine	102	96
Cocaine	95	100
Haloperidol	106	106

Data from [107]. The animals were sacrificed 2–3 h after the last administration of treatment.

* In the CA3 region only.

† Significantly different from the vehicle-treated group.

32.3.4

BDNF-mediated Adaptive Changes in the Mesolimbic Dopamine System

BDNF is an important factor in the plasticity of the dopamine mesolimbic system, whose role in appetitive motivation and positive reinforcement has been emphasized above. Thus, chronic infusion of BDNF into the nucleus accumbens or the ventral tegmental area durably increases responses to cocaine or to cocaine cues [112]. At least part of these effects might be mediated by a BDNF-mediated increase in dopamine D₃ receptors [113], a major target of dopamine mesolimbic neurons involved in responses to reward-related stimuli [114, 115].

Experimental evidence also supports the view that secondary adaptive changes in the function of dopamine systems contribute to the effects of stress and chronic antidepressant treatments. Acute stress activates the mesocortical dopaminergic system [116], but chronic stress triggers adaptive processes leading to decreased dopaminergic transmission in the shell of the nucleus accumbens [117, 118]. In contrast, antidepressant drugs [119] and ECT [120] induce subsensitivity of dopamine autoreceptors, leading to a persistent enhancement of dopamine neuron electrical activity [121, 122]. Although antidepressant drug treatments have variable effects on basal extracellular dopamine in the nucleus accumbens [123], they increase amphetamine-evoked dopamine release [124, 125] and ECT treatments enhance

spontaneous dopamine release [126]. Hence, the data in the literature are consistent with the suggestion that decreased activity of mesolimbocortical dopamine neurons is induced by chronic stress and depression, and is reversed by chronic antidepressant treatment. The convergent effects of antidepressant drugs acting through different serotonin/norepinephrine receptors on dopamine neuron activity can be explained as an adaptation of these neurons to the inhibitory actions of both serotonin and norepinephrine, as evidenced by various anatomical and functional studies [127, 128]

BDNF is expressed by mesolimbic dopamine neurons [129] and is released in a neuron activity-dependent manner [130]. Therefore, changes in mesolimbic dopamine neuron activity after stress or chronic antidepressant treatment would alter the expression of BDNF-regulated genes in the target neurons. In support of this theory, it has been shown that various antidepressant treatments, including TCAs, SSRIs, IMAOs and ECT all selectively increase D₃ receptor expression in the shell subdivision of the nucleus accumbens [131, 132] (Table 32.3), whereas changes in D₁ or D₂ receptor expression, which are not regulated by BDNF [113], are more variable, limited in amplitude, short-lasting or occur in other brain regions [123, 132–134]. These results are in agreement with previous observations that treatment with antidepressant drugs produces a variety of changes in dopamine responsiveness in rats, most notably sensitization of behavioral responses to agonists acting at dopamine D₂/D₃ receptors within the nucleus accumbens [39, 135–137].

Some features of the response to these antidepressant treatments suggest that enhanced dopamine neurotransmission through this receptor contributes to the adaptive changes leading to antidepressant activity. First, antidepressant drugs enhanced D₃ receptor expression after chronic, but not acute treatment (Table 32.3), which is in agreement with the delayed therapeutic action of these drugs in depressed patients. Several antidepressant drugs had limited or even reverse effects when tested after a single administration [131, 132] (see Table 32.3). Moreover, in animal studies progressive and strong downregulation of D₃ receptor binding was observed after repeated handling and injection of the animals, even though no

Table 32.3 Changes in D receptor expression in the shell of the nucleus accumbens after antidepressant treatment

	<i>Acute</i>	<i>Chronic</i>	
Treatment	D ₃ R mRNA	D ₃ R mRNA	D ₃ R binding
Desipramine	nd	+ 54%**	nd
Imipramine	– 24%*	+ 35%**	nd
Amirypiline	– 31%**	+ 35%**	+ 46%*
Fluoxetine	+ 24%	– 30%*	+ 42%*
Tranylcypromine	– 22%*	+ 38%*	nd
Electroconvulsive shocks	nd	+ 49%*	+ 42%**

nd, not determined; * $P < 0.05$, ** $P < 0.01$ versus saline-treated animals. Data from [132]. Antidepressant drugs were administered for 21 and 42 days (twice daily) before measuring D₃ receptor (D₃R) mRNA and binding, respectively. Electroconvulsive shocks were administered once a day for 5 days.

drug was administered; this might be interpreted as a stress-induced effect [132]. Second, this common effect of antidepressant drugs is restricted to the shell of the nucleus accumbens which various studies have shown to mediate the effects of dopamine in appetitive motivation, positive reinforcement, and the pleasurable effects of reinforcing stimuli. Interestingly enough, ECT produced the most rapid and robust increase in D₃ receptor protein and mRNA expression (Table 32.3) as compared to antidepressant drugs, which is in line with its therapeutic efficacy in refractory depression.

These results indicate that D₃ receptor expression and function are downregulated in stress and, possibly, depression, and that these changes are reversed by antidepressant treatment. This hypothesis is in agreement with data showing that pramipexole, a preferential D₃ receptor agonist [138, 139], displays antidepressant-like effects in animals [140, 141] and is efficacious as an antidepressant in humans [142, 143].

32.3.5

Effects of Antidepressant Treatments on Neurogenesis

Post-mortem and brain imaging studies have revealed multiple abnormalities in the brain of patients with depression and mood disorders, including loss of glial cells and neurons (reviewed in [73, 144, 145]) and reduced regional blood flow and glucose metabolism in limbic and frontal cortex areas (reviewed in [73, 146–148]). Such changes may underlie either the vulnerability to abnormal mood episodes or compensatory changes to other pathological processes. Nevertheless, the former hypothesis is supported by the well-documented influence of stress in mood disorders and the effects of stress on cellular morphology in the hippocampus, which is the brain region that expresses the highest levels of glucocorticoid receptors and is important in the control of the HPA axis [149, 150]. The subgranular zone of the hippocampus and the subventricular zone in both rodents and primates constitute the two areas where adult neurogenesis occurs, that is, the generation of new neurons in an adult brain. In addition, chronic stress results in persistent inhibition of granule cell production and changes in the structure of the dentate gyrus, raising the possibility that stress alters hippocampal function through this mechanism [151]. That hippocampal neurogenesis is necessary for the behavioral effects of antidepressants to become apparent, was demonstrated by showing that suppression of neurogenesis by restricted X-irradiation or by genetic manipulation (the use of a 5-HT_{1A} knockout mouse which is insensitive to the neurogenic effects of fluoxetine) blocked the behavioral effects produced by two classes of antidepressant drugs [152].

Evidence also indicates that chronic treatment with rolipram, an activator of the cAMP pathway, increases phospho-CREB and neurogenesis in the adult hippocampus [153]. Additional studies demonstrated that infusion of BDNF increases cell proliferation [154] and that antidepressant treatment increases the appearance of new cells in the hippocampus, which mature and become neurons [155]. These findings raise the possibility that BDNF-dependent increases in cell proliferation

and in neuronal number may constitute the mechanism by which antidepressant treatment overcomes stress-induced atrophy and loss of hippocampal neurons and may contribute to the therapeutic actions of antidepressant treatment.

Increased neurogenesis in conditions that stimulate neuronal activity, for instance learning, exercise and exposure to an enriched environment [156], is generally believed to result in a positive outcome. Nevertheless, even the link between increased neurogenesis and memory, which is also impaired in depression, remains to be established. Thus, although a correlation exists between performances on memory tasks and neurogenesis among various mouse strains, old mice, which have about one-tenth of the neurogenic activity of young animals, are not impaired to the same degree [157]. Moreover, no evidence exists for a relationship between neurogenesis and mood and emotions. Hence, although hippocampal neurogenesis indeed plays a crucial role in the actions of antidepressants in animals [152], its clinical relevance for the pathogenesis of depression in man remains to be established.

32.4

Conclusions

The various antidepressant drugs currently used in clinic appear to have distinct primary molecular targets, which leads to the puzzling conclusion that none of these targets, taken individually, is essential for clinical efficacy. The partial clinical efficacy of existing antidepressant drugs also suggests that all of these targets may contribute to the therapeutic effects. An alternative hypothesis is that a common target for antidepressant drugs remains to be identified. The demonstration that 5-HT₃ receptors are blocked by various antidepressant drugs at clinically relevant concentrations [27, 32] is an interesting finding in this respect, although the relationship between blockade of these receptors and the therapeutic effects has not been established as yet.

A rather coherent picture can be drawn from the examination of the secondary targets of antidepressant drugs and their relationships. It is suggested that these drugs activate cAMP pathways (and also probably Ca²⁺-dependent pathways), which results in an enhancement of CREB-dependent adaptive changes. Various studies also indicate a crucial role for one of the CREB-controlled gene products, BDNF. The neurotrophic property of this compound seems to be responsible for its action on neurogenesis, particularly in the hippocampus, and the BDNF-dependent action of antidepressant drugs has been evaluated in animal models of depressive symptoms. In addition to its neurotrophic action, BDNF acts as an extracellular transmitter, responsible for the remote control of genes involved in the antidepressant drug effects on the plasticity of the mesolimbic dopamine system, notably through the control of dopamine D₃ receptor expression. Both adrenergic and serotonergic systems, targeted by antidepressant drugs, are connected to dopamine cell bodies. Hence, the convergent action of antidepressants on the mesolimbic dopamine system mediating motivation and reward may underlie their therapeutic

effects on anhedonia, a core symptom of depression. It is probable that other CREB- or BDNF-dependent genes are involved, as well as other cascades. For instance, antidepressant drugs blunt some effects of glucocorticoids and inhibit corticosterone-induced gene transcription [158]. In addition, functional genomic studies have identified a number of genes whose expression is altered by chronic antidepressant treatments and new candidate genes have also emerged from these studies (see [159, 160] and also Section 32.2.4)

This chain of events adequately explains why antidepressant drugs are associated with a delay in onset of clinical action. However, it does not explain the rapid relapse of remitted SSRI-treated patients subjected to experimental depletion of tryptophan [161–163]. A more tenable hypothesis posits that treatment of depression is attained by providing both trophic and neurochemical support, which reinstates the optimal function of neurotransmitters in restored synaptic connections [73].

References

- CARLSSON, A., Some current problems related to the mode of action of antidepressant drugs. *Acta Psychiatr. Scand.* **1981**, 290 (Suppl.), 63–66.
- KRAMER, M. S., CUTLER, N., FEIGHNER, J., et al., Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* **1998**, 281, 1640–1645.
- PORSOLT, R. D., ANTON, G., BLAVET, N., JALFRE, M., Behavioral despair in rats: a new model sensitive to antidepressant treatments. *Eur. J. Pharmacol.* **1978**, 47, 379–391.
- STERU, L., CHERMAT, R., THIERRY, B., SIMON, P., The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology (Berl.)* **1985**, 85, 367–370.
- PARKER, G., ROY, K., WILHEM, K., MITCHELL, P., Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. *J. Clin. Psychiatry* **2001**, 62, 117–125.
- LEONARD, B. E., The role of noradrenaline in depression. *J. Psychopharmacol.* **1997**, 11 (4 Suppl.), S39–S47.
- MOORE, R. Y., CARD, J. P., Noradrenaline-containing neurons systems. In Björklund, A., Hökfelt, T. (Eds.), *Classical Transmitters in the CNS, Part I*. Amsterdam: Elsevier, **1984**, 123–156.
- LEONARD, B. E., Nordrenaline in basic models of depression. *Eur. Neuropsychopharmacol.* **1997**, 7 (Suppl. 1), S11–S16.
- BRUNELLO, N., MENDLEWICZ, J., KASPER, S., et al., The role of noradrenaline and selective noradrenaline reuptake inhibition in depression. *Eur. Neuropsychopharmacol.* **2002**, 12, 461–475.
- SVENSSON, T. H., USDIN, T., Feedback inhibition of brain noradrenaline neurones by tricyclic antidepressants: a-receptor mediation. *Science* **1978**, 202, 1089–1091.
- NUTT, D. J., The neuropharmacology of serotonin and noradrenaline in depression. *Int. Clin. Psychopharmacology* **2002**, 17 (Suppl. 1), S1–S12.
- VAN PRAAG, H. M., KORF, J., A pilot study of some kinetic aspects of the metabolism of 5-hydroxytryptamine in depressive patients. *Biol. Psychiatry* **1971**, 3, 105–112.
- ASBERG, M., THORÉN, P., TRÄKSMAN, L., BERTILSSON, L., RINGBERGER, V., “Serotonin depression” – a biochemical subgroup within the affective disorder? *Science* **1976**, 191, 478–480.
- DELGADO, P. L., CHARNEY, D. S., PRICE, L. H., AGHAJANIAN, G. K., LANDIS, H., HENINGER, G. R., Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced

- remission by rapid depletion of plasma tryptophan. *Arch. Gen. Psychiatry* **1990**, *47*, 411–418.
- 15 MANN, J. J., MALONE, K. M., DIEHL, D. J., PEREL, J., COOPER, T. B., MINTUN, M. A., Demonstration *in vivo* of reduced serotonin responsivity in the brain of untreated depressed patients. *Am. J. Psychiatry* **1996**, *153*, 174–182.
 - 16 BLIER, P., DE MONTIGNY, C., Possible serotonergic mechanisms underlying the antidepressant and anti-obsessive-compulsive disorder responses. *Biol. Psychiatry* **1998**, *44*, 313–323.
 - 17 DE MONTIGNY, C., Electroconvulsive treatments enhance responsiveness of forebrain neurons to serotonin. *J. Pharmacol. Exp. Ther.* **1984**, *228*, 230–234.
 - 18 AGHAJANIAN, G. K., LAKOSKI, J. M., Hyperpolarization of serotonin neurons by serotonin and LSD: studies in brain slices showing increased K⁺ conductance. *Brain Res.* **1984**, *305*, 181–185.
 - 19 LE POUL, E., BONI, C., HANOUN, N., et al., Differential adaptation of brain 5-HT_{1A} and 5-HT_{1B} receptors and 5-HT transporter in rats treated chronically with fluoxetine. *Neuropharmacology* **2000**, *39*, 110–122.
 - 20 CHARNEY, D. S., HENINGER, G. R., STERNBERG, D. E., Serotonin function and mechanism of action of antidepressant treatment. Effects of amitriptyline and desipramine. *Arch. Gen. Psychiatry* **1984**, *41*, 359–365.
 - 21 HIRANI, E., OPACKA-JUFFRY, J., GUNN, R., KHAN, I., SHARP, T., HUME, S., Pindolol occupancy of 5-HT_{1A} receptors measured *in vivo* using small animal positron emission tomography with carbon-11 labeled WAY 100635. *Synapse* **2000**, *36*, 330–341.
 - 22 RABINER, E. A., GUNN, R. N., WILKINS, M. R., et al., Drug action at the 5-HT_{1A} receptor *in vivo*: autoreceptor and postsynaptic receptor occupancy examined with PET and [carbonyl-¹¹C]WAY-100635. *Nucl. Med. Biol.* **2000**, *27*, 509–513.
 - 23 MARTINEZ, D., HWANG, D., MAWLAWI, O., et al., Differential occupancy of somatodendritic and postsynaptic 5HT(1A) receptors by pindolol: a dose-occupancy study with [11c]WAY 100635 and positron emission tomography in humans. *Neuropsychopharmacology* **2001**, *24*, 209–229.
 - 24 BLIER, P., The pharmacology of putative early-onset antidepressant strategies. *Eur. Neuropsychopharmacology* **2003**, *13*, 57–66.
 - 25 APTER, J. T., ALLEN, L. A., Buspirone: future directions. *J. Clin. Psychopharmacol.* **1999**, *19*, 86–93.
 - 26 BLIER, P., WARD, N. M., Is there a role for 5-HT_{1A} agonists in the treatment of depression? *Biol. Psychiatry* **2003**, *53*, 193–203.
 - 27 FAN, P., Effects of antidepressants on the inward current mediated by 5-HT₃ receptors in rat nodose ganglion neurones. *Br. J. Pharmacol.* **1994**.
 - 28 MARICQ, A. V., PETERSON, A. S., BRAKE, A. J., MYERS, R. M., JULIUS, D., Primary structure and functional expression of the 5-HT₃ receptor, a serotonin-gated ion channel. *Science* **1991**, *254*, 432–437.
 - 29 KILPATRICK, G. J., JONES, B. J., TYERS, M. B., Identification and distribution of 5-HT₃ receptor, a serotonin-gated ion channel. *Nature* **1987**, *330*, 746–748.
 - 30 TECOTT, L. H., MARICQ, A. V., JULIUS, D., Nervous system distribution of the 5-HT₃ receptor in rat brain using radioligand binding. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1430–1443.
 - 31 DE DEURWAERDERE, P., STINUS, L., SPAMPINATO, U., Opposite change of *in vivo* dopamine release in the rat nucleus accumbens and striatum that follows electrical stimulation of dorsal raphe nucleus: role of 5-HT₃ receptors. *J. Neurosci.* **1998**, *18*, 6528–6538.
 - 32 EISENSAMER, B., RAMMES, G., GIMPL, G., et al., Antidepressants are functional antagonists at the serotonin type 3 (5-HT₃) receptor. *Mol. Psychiatry* **2003**, *8*, 994–1007.
 - 33 RICHELSON, E., PFENNING, M., Blockade by antidepressants and related compounds of biogenic amine uptake into rat synaptosomes: most antidepressants selectively block norepinephrine uptake. *Eur. J. Pharmacol.* **1984**, *104*, 277–286.
 - 34 KOOB, G. F., Dopamine, addiction and reward. *Sem Neurosci* **1992**, *4*, 139–148.
 - 35 SALAMONE, J. D., The involvement of nucleus accumbens dopamine in

- appetitive and aversive motivation. *Behav. Brain Res.* **1994**, *61*, 117–133.
- 36 KAPUR, S., MANN, J., Role of the dopaminergic system in depression. *Biol. Psychiatry* **1992**, *32*, 1–17.
 - 37 BROWN, A. S., GERSHON, S., Dopamine and depression. *J. Neural. Transm.* **1993**, *91*, 75–109.
 - 38 FIBIGER, H. C., Neurobiology of depression: focus on dopamine. *Adv. Biochem. Psychopharmacol.* **1995**, *49*, 1–17.
 - 39 WILLNER, P., The mesolimbic dopamine system as a target for rapid antidepressant action. *Int. Clin. Psychopharmacol.* **1997**, *12* (Suppl. 3), S7–S14.
 - 40 SILVERSTONE, T., Dopamine in manic depressive illness. A pharmacological synthesis. *J. Affect Dis.* **1985**, *8*, 225–231.
 - 41 GESSA, G. L., PANI, L., SERRA, G., FRATTA, W., Animal models of mania. *Adv. Biochem. Psychopharmacol.* **1995**, *49*, 43–66.
 - 42 MARKOU, A., KOOB, G. F., Postcocaine anhedonia. An animal model of cocaine withdrawal. *Neuropsychopharmacology* **1991**, *4*, 17–26.
 - 43 BELMAKER, R. H., WALD, D., Haloperidol in normals. *Br. J. Psychiatry* **1977**, *131*, 222–223.
 - 44 D'HAENEN, H. A., BOSSUYT, A., Dopamine D2 receptors in depression measured with single photon emission computed tomography. *Biol. Psychiatry* **1994**, *35*, 128–132.
 - 45 SHAH, P. J., OGILVIE, A. D., GOODWIN, G. M., EBMEIER, K. P., Clinical and psychometric correlates of dopamine D2 binding in depression. *Psychol. Med.* **1997**, *27*, 1247–1256.
 - 46 GARATTINI, S., Pharmacology of amineptine, an antidepressant agent acting on the dopaminergic system: a review. *Int. Clin. Psychopharmacol.* **1997**, *12* (Suppl. 3), S15–S19.
 - 47 ZUNG, W. W., Review of placebo-controlled trials with bupropion. *J. Clin. Psychiatry* **1983**, *44*, 104–114.
 - 48 KINNEY, J. L., Nomifensine maleate: a new second-generation antidepressant. *Clin. Pharmacol.* **1984**, 625–636.
 - 49 SOKOLOFF, P., SCHWARTZ, J.-C., The novel dopamine receptors half a decade later. *Trends Pharmacol. Sci.* **1995**, *16*, 270–275.
 - 50 MISSALE, C., NASH, S. R., ROBINSON, S. W., JABER, M., CARON, M. G., Dopamine receptors: from structure to function. *Physiol. Rev.* **1998**, *78*, 189–225.
 - 51 SOKOLOFF, P., GIROS, B., MARTRES, M.-P., BOUTHENET, M.-L., SCHWARTZ, J.-C., Molecular cloning and characterization of a novel dopamine receptor (D₃) as a target for neuroleptics. *Nature* **1990**, *347*, 146–151.
 - 52 LÉVESQUE, D., DIAZ, J., PILON, C., et al., Identification, characterization and localization of the dopamine D₃ receptor in rat brain using 7-[³H]-hydroxy-N,N-di-n-propyl-2-aminotetralin. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 8155–8159.
 - 53 HOLMES, A., HEILIG, M., RUPNIAK, N. M. J., STECKLER, T., GRIEBEL, G., Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. *Trends Neurosci.* **2003**, *24*, 580–588.
 - 54 BRODIN, E., OGREN, S. O., THEODORSSON-NORHEIM, E., Effects of subchronic treatment with imipramine, zimelidine and alaproclate on regional tissue levels of substance P- and neurokinin A/neurokinin B-like immunoreactivity in the brain and spinal cord of the rat. *Neuropharmacology* **1987**, *26*, 581–590.
 - 55 SHIRAYAMA, Y., MITSUSHIO, H., TAKASHIMA, M., ICHIKAWA, H., TAKAHASHI, K., Reduction of substance P after chronic antidepressants treatment in the striatum, substantia nigra and amygdala of the rat. *Brain Res.* **1996**, *739*, 70–78.
 - 56 RIMON, R., LE GREVES, P., NYBERG, F., HEIKKILA, L., SALMELA, L., TERENIUS, L., Elevation of substance P-like peptides in the CSF of psychiatric patients. *Biol. Psychiatry* **1984**, *19*, 509–516.
 - 57 BERRETTINI, W. H., RUBINOW, D. R., NURNBERGER, J. I. J., SIMMONS-ALLING, S., POST, R. M., GERSHON, E. S., CSF substance P immunoreactivity in affective disorders. *Biol. Psychiatry* **1985**, *20*, 965–970.
 - 58 BONDY, B., BAGHAI, T. C., MINOV, C., et al., Substance P serum levels are increased in major depression: preliminary results. *Biol. Psychiatry* **2003**, *53*, 538–542.
 - 59 FROGER, N., GARDIER, A. M., MORATALLA, R., et al., 5-hydroxytryptamine (5-HT)_{1A} autoreceptor adaptive changes in substance P (neurokinin 1) receptor

- knock-out mice mimic antidepressant-induced desensitization. *J. Neurosci.* **2001**, *21*, 8188–8197.
- 60 CONLEY, R. K., CUMBERBATCH, M. J., MASON, G. S., et al., Substance P (neurokinin 1) receptor antagonists enhance dorsal raphe neuronal activity. *J. Neurosci.* **2002**, *22*, 7730–7736.
 - 61 MAUBACH, K. A., MARTIN, K., CHICCHI, G., et al., Chronic substance P (NK1) receptor antagonist and conventional antidepressant treatment increases burst firing of monoamine neurones in the locus coeruleus. *Neuroscience* **2002**, *109*, 609–617.
 - 62 PAPP, M., VASSOUT, A., GENTSCH, C., The NK1-receptor antagonist NKP608 has an antidepressant-like effect in the chronic mild stress model of depression in rats. *Behav. Brain Res.* **2000**, *115*, 19–23.
 - 63 FILE, S. E., NKP608, an NK1 receptor antagonist, has an anxiolytic action in the social interaction test in rats. *Psychopharmacol. (Berl.)* **2000**, *152*, 105–109.
 - 64 VARTY, G. B., COHEN-WILLIAMS, M. E., MORGAN, C. A., et al., The gerbil elevated plus-maze II: anxiolytic-like effects of selective neurokinin NK1 receptor antagonists. *Neuropsychopharmacology* **2002**, *27*, 371–379.
 - 65 DE FELIPE, C., HERRERO, J. F., O'BRIEN, J. A., et al., Altered nociception, analgesia and aggression in mice lacking the receptor for substance P, *Nature* **1998**, *392*, 394–397.
 - 66 RANGA, K., KRISHNAN, R., Clinical experience with substance P receptor (NK1) antagonists in depression. *J. Clin. Psychiatry* **2002**, *63* (Suppl. 11), 25–29.
 - 67 REUL, J. M., HOLSBOER, F., Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Curr. Opin. Pharmacol.* **2002**, *2*, 23–33.
 - 68 TIMPL, P., SPANAGEL, R., SILLABER, I., et al., Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. *Nature Med.* **1998**, *19*, 162–166.
 - 69 HABIB, K. E., WELD, K. P., RICE, K. C., et al., Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 6079–6084.
 - 70 OKUYAMA, S., CHAKI, S., KAWASHIMA, N., et al., Receptor binding, behavioral, and electrophysiological profiles of non-peptide corticotropin-releasing factor subtype 1 receptor antagonists CRA1000 and CRA1001. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 926–935.
 - 71 ZOBEL, A. W., NICKEL, T., KUNZEL, H. E., et al., Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J. Psychiatr. Res.* **2000**, *34*, 171–181.
 - 72 SKOLNICK, P., Antidepressants for the new millennium. *Eur. J. Pharmacol.* **1999**, *375*, 31–40.
 - 73 MANJI, H. K., QUIROZ, J. A., SPORN, J., et al., Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol. Psychiatry* **2003**, *53*, 707–742.
 - 74 BERMAN, R. M., CAPPIELLO, A., ANAND, A., et al., Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* **2000**, *47*, 351–354.
 - 75 SNYDER, S., Psychogenic drugs as models of schizophrenia. *Neuropsychopharmacology* **1988**, *1*, 197–199.
 - 76 DONATI, R. J., RASENICK, M. M., G protein signaling and the molecular basis of antidepressant action. *Life Sci.* **2003**, *73*, 1–17.
 - 77 COWBURN, R. F., MARCUSON, J. O., ERIKSSON, A., WIEHAGER, B., O'NEILL, C., Adenylyl cyclase activity and G-protein subunit levels in postmortem frontal cortex of suicide victims. *Brain Res.* **1994**, *633*, 297–304.
 - 78 HUANG, C., HEPLER, J. R., CHEN, L. T., GILMAN, A. G., ANDERSON, R. G., MUMBY, S. M., Organization of G proteins and adenylyl cyclase at the plasma membrane. *Mol. Biol. Cell* **1997**, *8*, 2365–2378.
 - 79 LI, S., OKAMOTO, T., CHUN, M., et al., Evidence for a regulated interaction between heterotrimeric G proteins and caveolin. *J. Biol. Chem.* **1995**, *270*, 15693–15701.
 - 80 TOKI, S., DONATI, R. J., RASENICK, M. M., Treatment of C6 glioma cells and rats with antidepressant drugs increases the

- detergent extraction of G(s alpha) from plasma membrane. *J. Neurochem.* **1999**, 73, 1114–1120.
- 81 DUMAN, R. S., HENINGER, G. R., NESTLER, E. J., A molecular and cellular theory of depression. *Arch. Gen. Psychiatry* **1997**, 54, 597–606.
 - 82 MORI, S., ZANARDI, R., POPOLI, M., et al., cAMP-dependent phosphorylation system after short and long-term administration of moclobemide. *J. Psychiatr. Res.* **1998**, 32, 111–115.
 - 83 TADOKORO, C., KIUCHI, Y., YAMAZAKI, Y., OGUCHI, K., KAMIJIMA, K., Effects of imipramine and sertraline on protein kinase activity in rat frontal cortex. *Eur. J. Pharmacol.* **1998**, 342, 51–54.
 - 84 NIBUYA, M., NESTLER, E. J., DUMAN, R. S., Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J. Neurosci.* **1996**, 16, 2365–2372.
 - 85 THOME, J., SAKAI, N., SHIN, K., et al., cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *J. Neurosci.* **2000**, 20, 4030–4036.
 - 86 CHEN, A. C., SHIRAYAMA, Y., SHIN, K. H., NEVE, R. L., DUMAN, R. S., Expression of the cAMP response element binding protein (CREB) in hippocampus produces an antidepressant effect. *Biol. Psychiatry* **2001**, 49, 753–762.
 - 87 NEWTON, S. S., THOME, J., WALLACE, T. L., et al., Inhibition of cAMP response element-binding protein or dynorphin in the nucleus accumbens produces an antidepressant-like effect. *J. Neurosci.* **2002**, 22, 10883–10890.
 - 88 MANIER, D. H., SHELTON, R. C. F. S., Noradrenergic antidepressants: does chronic treatment increase or decrease nuclear CREB-P? *J. Neural. Transm.* **2002**, 109, 91–99.
 - 89 SCHWANINGER, M., SCHOFL, C., BLUME, R., ROSSIG, L., KNEPEL, W., Inhibition by antidepressant drugs of cyclic AMP response element-binding protein/cyclic AMP response element-directed gene transcription. *Mol. Pharmacol.* **1995**, 47, 1112–1118.
 - 90 ODAGAKI, Y., GARCIA-SEVILLA, J. A., HUGUELET, P., LA HARPE, R., KOYAMA, T., GUIMON, J., Cyclic AMP-mediated signaling components are upregulated in the prefrontal cortex of depressed suicide victims. *Brain Res.* **2001**, 898, 224–231.
 - 91 DWIVEDI, Y., RAO, J. S., RIZAVI, H. S., et al., Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. *Arch. Gen. Psychiatry* **2003**, 60, 273–282.
 - 92 SHENG, M., MCFADDEN, G., GREENBERG, M. E., Membrane depolarization and calcium induce c-fos transcription via phosphorylation of transcription factor CREB. *Neuron* **1990**, 4, 571–582.
 - 93 TAO, X., FINKBEINER, S., ARNOLD, D. B., SHAYWITZ, A. J., GREENBERG, M. E., Ca^{2+} influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. *Neuron* **1998**, 20, 709–726.
 - 94 SHIEH, P. B., HU, S. C., BOBB, K., TIMMUS, T., GHOSH, A., Identification of a signaling pathway involved in calcium regulation of BDNF expression. *Neuron* **1998**, 20, 727–740.
 - 95 THOENEN, H., Neurotrophins and neuronal plasticity. *Science* **1995**, 270, 593–598.
 - 96 ALTAR, C. A., CAI, N., BLIVEN, T., et al., Anterograde transport of brain-derived neurotrophic factor and its role in the brain. *Nature* **1997**, 389, 856–860.
 - 97 VON BARTHELD, C. S., BYERS, M. R., WILLIAMS, R., BOTHWELL, M., Anterograde transport of neurotrophins and axodendritic transfer in the developing visual system. *Nature* **1996**, 379, 830–833.
 - 98 ALTAR, C. A., DISTEFANO, P. S., Neurotrophin trafficking by anterograde transport. *Trends Neurosci.* **1998**, 21, 433–437.
 - 99 KAFITZ, K. W., ROSE, C. R., THOENEN, H., KONNERTH, A., Neurotrophin-evoked rapid excitation through TrkB receptors. *Nature* **1999**, 401, 918–921.
 - 100 VICARIO-ABEJON, C., COLLIN, C., MCKAY, R. D. G., SEGAL, M., Neurotrophins induce formation of functional excitatory and inhibitory synapses between cultured hippocampal neurons. *J. Neurosci.* **1998**, 18, 7256–7271.
 - 101 HUANG, Z. J., KIKWOOD, A., PIZZORUSSO, T., et al., BDNF regulates the maturation

- of the inhibition of the critical period of plasticity in mouse visual cortex. *Cell* **1999**, 98, 739–755.
- 102 LOHOF, A. M., IP, N. Y., POO, M. M., Potentiation of developing neuromuscular synapses by the neurotrophin NT-3 and BDNF. *Nature* **1993**, 363, 350–353.
 - 103 FIGUROV, A., POZZO-MILLER, L. D., OIAFSSON, P., WANG, T., LU, B., Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* **1996**, 381, 706–709.
 - 104 KORTE, M., CARROLL, P., WOLF, E., BREM, G., THOENEN, H., BONHOEFFER, T., Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proc. Natl. Acad. Sci. USA* **1995**, 92, 8856–8860.
 - 105 KOVALCHUK, Y., HANSE, E., KAFITZ, K. W., KONNERTH, A., Postsynaptic induction of BDNF-mediated long-term potentiation. *Science* **2002**, 295, 1651–1653.
 - 106 SMITH, M. A., MAKINO, S., KVENANSKY, R., POST, R. M., Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J. Neurosci.* **1995**, 15, 1768–1777.
 - 107 NIBUYA, M., MORINOBU, S., DUMAN, R. S., Regulation of BDNF and TrkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci.* **1995**, 15, 7539–7547.
 - 108 CONTI, A. C., CRYAN, J. F., DAIVI, A., LUCKI, I., BLENDY, J. A., cAMP response element-binding protein is essential for the upregulation of brain-derived neurotrophic factor transcription, but not the behavioral or endocrine responses to antidepressant drugs. *J. Neurosci.* **2002**, 22, 3262–3268.
 - 109 SAARELAINEN, T., HENDOLIN, P., LUCAS, G., et al., Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.* **2003**, 23, 349–357.
 - 110 SHIRAYAMA, Y., CHEN, A. C., NAKAGAWA, S., RUSSELL, D. S., DUMAN, R. S., Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J. Neurosci.* **2002**, 22, 3251–3261.
 - 111 CHEN, B., DOWLATSHAHI, D., MACQUEEN, G. M., WANG, J. F., YOUNG, L. T., Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol. Psychiatry* **2001**, 50, 260–265.
 - 112 HORGER, B. A., LYASERE, C. A., BERHOW, M. T., MESSER, C. J., NESTLER, E. J., TAYLOR, J. R., Enhancement of locomotor activity and conditioned reward to cocaine by brain-derived neurotrophic factor. *J. Neurosci.* **1999**, 19, 4110–4122.
 - 113 GUILLIN, O., DIAZ, J., CARROLL, P., GRIFFON, N., SCHWARTZ, J.-C., SOKOLOFF, P., BDNF controls dopamine D₃ receptor expression and triggers behavioural sensitization. *Nature* **2001**, 411, 86–89.
 - 114 PILLA, M., PERACHON, S., SAUTEL, F., et al., Selective inhibition of cocaine-seeking behaviour by a partial dopamine D₃ receptor agonist. *Nature* **1999**, 400, 371–375.
 - 115 LE FOLL, B., FRANCÈS, H., DIAZ, J., SCHWARTZ, J.-C., SOKOLOFF, P., Role of the dopamine D₃ receptor in reactivity to cocaine-associated cues in mice. *Eur. J. Neurosci.* **2002**, 15, 2016–2026.
 - 116 THIERRY, A.-M., TASSIN, J.-P., BLANC, G., GLOWINSKI, J., Selective activation of mesocortical DA systems by stress. *Nature* **1976**, 263, 242–244.
 - 117 FINLAY, J. M., ZIGMOND, M. J., The effects of stress on central dopaminergic neurons: possible clinical implications. *Neurochem. Res.* **1997**, 22, 1387–1394.
 - 118 GAMBARANA, C., MASI, F., TAGLIAMONTE, A., SCHEGGI, S., GHIGLIERI, O. G., DMM. A chronic stress that impairs reactivity in rats also decreases dopaminergic transmission in the nucleus accumbens: a microdialysis study. *J. Neurochem.* **1999**, 72, 2039–2046.
 - 119 CHIODO, L. A., ANTELMAN, S. M., Repeated tricyclics induce a progressive dopamine autoreceptor subsensitivity. *Nature* **1980**, 287, 451–454.
 - 120 CHIODO, L. A., ANTELMAN, S. M., Electroconvulsive shock: progressive dopamine autoreceptor subsensitivity independent of repeated treatment. *Science* **1980**, 210, 799–801.
 - 121 CHIODO, L. A., BUNNEY, B. S., Typical and atypical neuroleptics: differential effects of chronic administration on the activity

- of A9 and A10 midbrain dopaminergic neurons. *J. Neurosci.* **1983**, 3, 1607–1619.
- 122 WHITE, F. J., WANG, R. Y., Differential effects of classical and atypical antipsychotic drugs on A9 and A10 dopamine neurons. *Science* **1983**, 221, 1054–1057.
 - 123 AINSWORTH, K., SMITH, S. E., ZETTERSTROM, T. S., FRANKLIN, M., SHARP, T., Effects of antidepressant drugs on dopamine D₁ and D₂ receptor expression and dopamine release in the nucleus accumbens of the rat. *Psychopharmacology (Berl.)* **1998**, 140, 470–477.
 - 124 BROWN, E. E., NOMIKOS, G. G., WILSON, C., FIBIGER, H. C., Chronic desipramine enhances the effect of locally applied amphetamine on interstitial concentrations of dopamine in the nucleus accumbens. *Eur. J. Pharmacol.* **1991**, 202, 125–127.
 - 125 STEWART, J., RAJABI, H., Initial increases in extracellular dopamine in the ventral tegmental area provide a mechanism for the development of desipramine-induced sensitization within the midbrain dopamine system. *Synapse* **1996**, 23, 258–264.
 - 126 NOMIKOS, G. G., ZIS, A. P., DAMSMA, G., FIBIGER, H. C., Electroconvulsive shock produces large increases in interstitial concentrations of dopamine in the rat striatum: an *in vivo* microdialysis study. *Neuropsychopharmacology* **1991**, 4, 65–69.
 - 127 PRISCO, S., ESPOSITO, E., Differential effects of acute and chronic fluoxetine administration on the spontaneous activity of dopaminergic neurones in the ventral tegmental area. *Br. J. Pharmacol.* **1995**, 116, 1923–1931.
 - 128 GRENHOFF, J., NISELL, M., FERRE, S., ASTON-JONES, G., SVENSSON, T. H., Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat. *J. Neural. Transm.* **1993**, 93, 11–25.
 - 129 SEROOGY, K. B., LUNDGREN, K. H., TRAN, T. M. D., GUTHRIE, K. M., ISACKSON, P. J., GALL, C., Dopaminergic neurons in rat ventral midbrain express brain-derived neurotrophin factor and neurotrophin-3 mRNAs. *J. Comp. Neurol.* **1994**, 342, 321–334.
 - 130 ZAFRA, F., HENGERER, B., LEIBROCK, J., THOENEN, H., Activity-dependent regulation of BDNF and NGF mRNAs in the rat hippocampus is mediated by non-NMDA glutamate receptors. *EMBO J.* **1990**, 9, 3545–3550.
 - 131 MAJ, J., DZIEDZICKA-WASYLEWSKA, M., ROGOZ, E., ROGOZ, Z., Effect of anti-depressant drugs administered repeatedly on the dopamine D₃ receptors in the rat brain. *Eur. J. Pharmacol.* **1998**, 351, 31–37.
 - 132 LAMMERS, C. H., DIAZ, J., SCHWARTZ, J.-C., SOKOLOFF, P., Selective increase of dopamine D₃ receptor gene expression as a common effect of chronic antidepressant treatments. *Mol. Psychiatry* **2000**, 5, 378–388.
 - 133 DZIEDZICKA-WASYLEWSKA, M., ROGOZ, R., KLIMEK, V., MAJ, J., Repeated administration of antidepressant drugs affects the levels of mRNA coding for D1 and D2 dopamine receptors in the rat brain. *J. Neural. Transm.* **1997**, 104, 515–524.
 - 134 DZIEDZICKA-WASYLEWSKA, M., WILLNER, P., PAPP, M., Changes in dopamine receptor mRNA expression following chronic mild stress and chronic antidepressant treatment. *Behav. Pharmacol.* **1997**, 8, 607–618.
 - 135 MAJ, J., ROGOZ, Z., SKUZA, G., SOWINSKA, H., Repeated treatment with antidepressant drugs potentiates the locomotor response to (+)-amphetamine. *J. Pharm. Pharmacol.* **1984**, 36, 127–130.
 - 136 BARKAI, A. I., DURKIN, M., NELSON, H. D., Localized alterations of dopamine receptor binding in rat brain by repeated electroconvulsive shock: an autoradiographic study. *Brain Res.* **1990**, 529, 208–213.
 - 137 SMITH, S. E., SHARP, T., Evidence that the enhancement of dopamine function by repeated electroconvulsive shock requires concomitant activation of D1-like and D2-like receptors. *Psychopharmacology* **1997**, 133, 77–84.
 - 138 SAUTEL, F., GRIFFON, N., LÉVESQUE, D., PILON, C., SCHWARTZ, J.-C., SOKOLOFF, P., A functional test identifies dopamine agonists selective for D₃ versus D₂ receptors. *Neuroreport* **1995**, 6, 329–332.
 - 139 MIERAU, J., SCHINGNITZ, G., Biochemical and pharmacological studies on pramipexole, a potent and selective dopamine D₂ receptor agonist. *Eur. J. Pharmacol.* **1992**, 215, 161–170.

- 140 MAJ, J., ROGOZ, Z., SKUZA, G., KOLODZIEJCZYK, K., Antidepressant effects of pramipexole, a novel dopamine receptor agonist. *J. Neural. Transm.* **1997**, *104*, 525–533.
- 141 WILLNER, P., LAPPAS, S., CHEETA, S., MUSCAT, R., Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. *Psychopharmacology (Berl.)* **1994**, *115*, 454–462.
- 142 GOLDBERG, J. F., FRYE, M. A., DUNN, R. T., Pramipexole in refractory bipolar depression. *Am. J. Psychiatry* **1999**, *156*, 798.
- 143 SZEGEDI, A., WETZEL, J., HILLERT, A., KLEISER, E., GAEBEL, W., BENKERT, O., Pramipexole, a novel selective dopamine agonist in major depression. *Mov. Disord.* **1996**, *11* (Suppl. 1), 266.
- 144 COTTER, D. R., PARIANTE, C. M., EVERALL, I. P., Glial cell abnormalities in major psychiatric disorders: the evidence and implications. *Brain Res. Bull.* **2001**, *55*, 585–595.
- 145 RAJKOWSKA, G., Cell pathology in mood disorders. *Semin. Clin. Neuropsychiatry* **2002**, *7*, 281–292.
- 146 DREVETS, W., Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr. Opin. Neurobiol.* **2001**, *11*, 240–249.
- 147 BEYER, J. L., KRISHNAN, K. R., Volumetric brain imaging findings in mood disorders. *Bipolar Disord.* **2002**, *4*, 89–104.
- 148 STRAKOWSKI, S. M., ADLER, C. M., DELBELLO, M. P., Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? *Bipolar Disord.* **2002**, *4*, 80–88.
- 149 SAPOLSKY, R. M., KREY, L. C., McEWEN, B. S., Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 6174–6177.
- 150 HERMAN, J. P., SCHAFER, M. K., YOUNG, E. A., et al., Evidence for hippocampal regulation of neuroendocrine neurons of the hypothalamo–pituitary–adrenal axis. *J. Neurosci.* **1989**, *9*, 3072–3082.
- 151 GOULD, E., TANAPAT, P., McEWEN, B. S., FLUGGE, G., FUCHS, E., Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3168–3171.
- 152 SANTARELLI, L., SAXE, M., GROSS, C., et al., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **2003**, *301*, 805–809.
- 153 NAKAGAWA, S., KIM, J. E., LEE, R., et al., Regulation of neurogenesis in adult mouse hippocampus by cAMP and the cAMP response element-binding protein. *J. Neurosci.* **2002**, *22*, 3673–3682.
- 154 PENCEA, V., BINGAMAN, K. D., WIEGAND, S. J., LUSKIN, M. B., Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. *J. Neurosci.* **2001**, *21*, 6706–6717.
- 155 MALBERG, J. E., EISCH, A. J., NESTLER, E. J., DUMAN, R. S., Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.* **2000**, *20*, 9104–9110.
- 156 VAN PRAAG, H., KEMPERMANN, G., GAGE, F. H., Neural consequences of environmental enrichment. *Nature Rev. Neurosci.* **2000**, *1*, 191–198.
- 157 KEMPERMANN, G., Regulation of adult hippocampal neurogenesis-implications for novel theories of major depression. *Bipolar Disord.* **2002**, *4*, 17–33.
- 158 BUDZISZEWSKA, B., JAWORSKA-FEIL, L., KAJTA, M., LASON, W., Antidepressant drugs inhibit glucocorticoid receptor-mediated gene transcription – a possible mechanism. *Br. J. Pharmacol.* **2000**, *130*, 1385–1393.
- 159 LANDGREBE, J., WEIZL, G., METZ, T., et al., Molecular characterisation of antidepressant effects in the mouse brain using gene expression profiling. *J. Psychiatr. Res.* **2002**, *36*, 119–129.
- 160 YAMADA, M., HIGUCHI, T., Functional genomics and depression research. Beyond the monoamine hypothesis. *Eur. Neuropsychopharmacol.* **2002**, *12*, 235–244.
- 161 DELGADO, P. L., CHARNEY, D. S., PRICE, L. H., AGHAJANIAN, G. K., LANDIS, H., HENINGER, G. R., Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch. Gen. Psychiatry* **1990**, *47*, 411–418.

- 162 ABERG-WISTEDT, A., HASSELMARK, L., STAIN-MALMGREN, R., APERIA, B., KJELLMAN, B. F., MATHE, A. A., Serotonergic "vulnerability" in affective disorder: a study of the tryptophan depletion test and relationships between peripheral and central serotonin indexes in citalopram-responders. *Acta Psychiatr. Scand.* **1998**, 97, 374–380.
- 163 MORENO, F. A., GELENBERG, A. J., HENINGER, G. R., et al., Tryptophan depletion and depressive vulnerability. *Biol. Psychiatry* **1999**, 46, 498–505.
- 164 TATSUMI, M., GROSHAN, K., BLAKELY, R. D., RICHELSON, E., Pharmacological profile of antidepressant and related compounds at human monoamine transporters. *Eur. J. Pharmacol.* **1997**, 340, 249–258.

33

The Role of Transcription Factors in the Biology of Depression

Robert D. Beech and Ronald S. Duman

Abstract

An emerging hypothesis for the pathophysiology of depression proposes that the mechanisms underlying the therapeutic actions of antidepressants and mood stabilizers, as well as the etiology of mood disorders themselves are more complex than simple changes in the synaptic level of monoamine neurotransmitters. In this hypothesis depression is understood as a failure of various forms of neuronal plasticity, resulting in the inability to make appropriate adaptive responses to stress or other aversive stimuli. While the immediate actions of chemical antidepressants at the synapse are in many cases now well understood, the time course of these

Abbreviations

Akt, protein kinase identified in the AKT virus, also known as protein kinase B; **AMPA**, α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; **AP-1**, activator protein 1; **Bcl-2**, B-cell lymphoma protein 2, an anti-apoptotic protein; **BDNF**, brain derived neurotrophic factor; **CaMK II**, calcium/calmodulin-dependent protein kinase II; **CaMK IV**, calcium/calmodulin-dependent protein kinase IV; **CaMKK**, calcium/calmodulin-dependent protein kinase-kinase (an upstream activator of CaMK IV); **CREB**, cyclic AMP response element binding protein; **CREM**, cyclic AMP response element modulator; **DNA**, deoxyribonucleic acid; **Elk-1**: an E twenty-six (Ets) domain transcription factor, binds to serum response element along with serum response factor; **ERK**, extracellular-signal regulated kinase; **GPBP**, G+C rich binding protein; **GPCRs**, G protein-coupled receptors; **5-HT**, 5-hydroxy tryptamine, more commonly known as serotonin; **5-HTT**, 5-hydroxy tryptamine transporter; **ICER**, inducible cyclic AMP early repressor; **I κ B**, inhibitor of κ B (see NF κ B); **I κ BK**, inhibitor of κ B kinase, phosphorylates I κ B, releasing active NF κ B; **IP₃**, Inositol 4,5 triphosphate; **MAPK**, mitogen-activated protein kinase; **MAPKAP K2**, MAPK activated protein kinase 2; **MARCKS**, myristolated alanine-rich protein kinase C substrate; **MEK**, mitogen-activated protein kinase kinase; **MMTV**, mouse mammary tumor virus; **NF κ B**, nuclear factor of kappa light chain gene enhancer in B cells; **NMDA**, N-methyl-D-aspartate; **pCREB**, phospho-CREB (the activated form CREB); **PI**, phosphatidyl inositol; **PI3K**, phosphatidyl inositol 3-kinase; **Pyk2**, proline-rich tyrosine kinase; **RAS**, family of guanosine triphosphate binding proteins; **RAS-GRF2**, RAS protein-specific guanine nucleotide-releasing factor 2; **RNA**, ribonucleic acid; **RSK**, ribosomal S6 kinases, also known as p90^{rsk}, or MAPKAP K1 (a, b, and c); **Shc**, Sarc-homologous and collagen-like, couples BDNF to signaling pathways; **SOS1**, named after the Drosophila gene, son of sevenless, SOS1 is a RAS-guanine nucleotide exchange factor (see above); **Sp1**, Signaling protein 1; **SSRI**, selective serotonin reuptake inhibitor; **SRC-1**, steroid receptor coactivator-1; **SynGAP1**, Synaptic RAS-guanosine triphosphatase-activating protein 1; **TNF- α** , tumor necrosis factor- α ; **Wnt**, wingless-type MMTV integration site family, homologs of the Drosophila "wingless" gene; **Zif268**, zinc finger protein, 268 amino acids.

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actions is much more rapid than the clinical response to treatment which typically takes 6–8 weeks for a full response. Thus, attention has shifted to the long-term adaptations that follow from these acute changes. Work in our laboratory and others has identified a number of genes whose expression in the brain changes markedly when animals are treated with different classes of antidepressants. These include the cyclic AMP response element binding protein (CREB), and the immediate early genes *c-fos* and *zif268*. Changes in the expression of many of these same transcription factors are also seen in response to both physical and psychological stress. Cell type-specific changes in the concentration and activity of transcription factors allow the expression of different genes to vary in response to developmental programs or changes in the environment. The initiation of transcription is a key event in the organism's response to changes in the outside world and it is the target of many converging signaling pathways. Changes in gene expression, and in particular the levels of different transcription factors, are integral to both the deleterious effects of chronic stress on the brain, and the therapeutic effects of antidepressants.

33.1

Introduction: Genetic and Environmental Causes of Depression

The causes of depression include both genetic and environmental factors. Genetic and epidemiological studies suggest that 40–50% of the risk for developing depression is genetic. However, depression itself is not inherited. Rather it is the result of a complex interplay between genetic and environmental factors, which in susceptible individuals gives rise to the clinical phenotype recognized as depression. One important genetic variant, a polymorphism in the promoter region of the serotonin transporter (5-HTT) gene has recently been identified. As explained in greater detail below, the promoter is the short sequence of DNA found near the beginning of a gene which serves as the assembly site for the protein machinery needed to make an RNA copy from that gene. The process of copying information from genes, which are made of DNA, into messenger RNAs, which direct the production of specific proteins, is referred to as transcription. A polymorphism is a naturally-occurring variation in the DNA sequences found in the human population. The 5-HTT gene comes in two versions, or alleles: a long form and a short form. The short form is associated with decreased transcription of the 5-HTT gene, and thus with lower levels of transporter. Individuals who inherit the short allele have a greater likelihood of developing depression, but only if they have experienced a number of major life stressors. In a study by Caspi et al. [1] people who had one or two copies of the short allele of the 5-HTT gene and had experienced four or more major life stressors as adults (such as break-up of a romantic relationship, bereavement, major illness or job loss) were twice as likely to have had a major depressive episode in the past year than people with two copies of the long form who had experienced an equal number of stressful events. Thoughts about suicide and suicide attempts were also greatly increased among carriers of the short allele who had experienced multiple stressors. In contrast, carriers of the

short allele who had experienced two or fewer major stressors did not show an increased risk of depression or suicidality.

This example illustrates the important concept of a gene–environment interaction. Genes encode specific proteins, including those that regulate our bodies’ responses to stressful stimuli. Variation in these genes can affect how we react to stressful situations and under some circumstances increase the likelihood of our becoming depressed. Also it is important to note that in the study by Caspi et al., some people who had two copies of the “good” version of the 5-HTT gene still became depressed, despite having no history of childhood abuse and no reported major life stressors. Conversely, the majority of people with two “bad” copies of the 5-HTT gene did not become depressed, even if they had experienced multiple stressors. Many other genes, and gene–environment interactions, many of which are still unknown, are likely to be involved in the pathogenesis of depression.

33.2

A Dialog between Genes and Synapses

The “central dogma” of molecular biology, first formulated by Francis Crick, posits that genes (made of DNA) encode RNA messages that encode proteins. Thus, genes provide the information for the synthesis of all of the proteins in a cell, and ultimately for the development of the entire organism. However, the flow of information is not unidirectional. Environmental factors including nutritional status, toxins, viruses, hormonal factors, sensory inputs, learning (including psychotherapy), physical and psychological stressors, and psychoactive medications can all affect the expression of specific genes, and thereby change the production of specific proteins within a cell. These in turn can affect the functional properties of that cell including its ability to multiply and generate new cells, and in the case of neurons its ability to form and maintain functional connections with other cells. Activation of different signaling pathways by neurotransmitters leads to changes in expression of a variety of genes, including those encoding neurotransmitter receptors themselves. This in turn affects the cell’s future responses to the same and other neurotransmitters. This process produces what Eric Kandel, who received the Nobel Prize in 2000, referred to as “a dialog between genes and synapses”.

An emerging hypothesis for the pathophysiology of depression [2–4] proposes that the mechanisms underlying the therapeutic actions of antidepressants and mood stabilizers, as well as the etiology of mood disorders themselves, are more complex than simple changes in the synaptic level of monoamine neurotransmitters. In this hypothesis depression is understood as a failure of various forms of neuronal plasticity, including adult hippocampal neurogenesis, resulting in the inability to make appropriate adaptive responses to stress or other aversive stimuli. While the immediate actions of chemical antidepressants at the synapse are in many cases now well understood [5, 6], the time course of these actions is much more rapid than the clinical response to treatment which typically takes 6–8 weeks for a full response. Evidence from a variety of sources, including neuroimaging [7–11] and

postmortem studies [12, 13] indicates that there are subtle structural changes in the brains of depressed patients. Even more exciting recent evidence indicates that some of these structural changes may be reversible in patients who are treated with antidepressants [14–16]. A number of structural changes can be induced in experimental animals by exposure to either psychological or physical forms of stress (reviewed in [17, 18]). These include decreased proliferation of neuronal precursors in the dentate gyrus of the hippocampus and reduced number and length of apical dendrites in CA3 pyramidal neurons. These effects are opposed by the actions of a variety of classes of chemical antidepressants as well as electroconvulsive seizures. Work in our laboratory and others have identified a number of genes whose expression in the brain changes markedly when animals are treated with different classes of antidepressants. These include the cyclic AMP response element binding protein (CREB) [19], and the immediate early genes *c-fos* [20, 21] and *zif268* [20]. Thus, changes in gene expression, and in particular the levels of different transcription factors, are integral to both the deleterious effects of chronic stress on the brain, and the therapeutic effects of antidepressants.

33.3

Getting the Message Out: From Gene to Transcript to Protein

The human genome consists of approximately 40,000 genes. These genes, like those of all eukaryotes, are organized into chromosomes, extremely long molecules of DNA that contain thousands of genes each. Within the cell nucleus, these DNA molecules are wrapped around a group of core proteins referred to as histones, to form bead-like structures termed nucleosomes. These nucleosomes are the “beads on a string” seen in electron micrographs of uncoiled DNA. The nucleosomes are themselves arranged into higher order structures referred to as chromatin.

The process of producing an RNA copy or message from the corresponding DNA gene is referred to as transcription. In order for transcription to be initiated, the chromatin containing the DNA encoding the specific gene to be transcribed must be unpacked, and the DNA unwound from its associated histones. This process involves the actions of specific transcription factors and co-factors, some of which are discussed in more detail below. Approximately 5% of all genes are believed to encode transcription factors [22], and a large number of these are expressed in the adult brain. Transcription factors bind to sites located in or near the promoter and are important in regulating when and where tissue-specific genes are expressed. The particular combination and spacing of the transcription factor binding sites give each promoter its unique tissue and developmental specificity. Changes in the concentration and activity of these factors allow the expression of different genes to vary in response to developmental programs or changes in the environment. Thus, the initiation of transcription is a key event in the organism’s response to changes in the outside world and the target of many converging signaling pathways.

A group of proteins termed histone acetyl transferases that acetylate specific residues of the histone proteins are of particular importance to the transcription

process. This acetylation procedure permits general transcription factors to bind to the DNA and initiate transcription, and this step in the initiation of transcription is highly regulated by a variety of extracellular signals [23, 24]. Histone deacetylases return DNA to the coiled/bound nucleosome state and contribute to inactivation of gene transcription. Interestingly, histone deacetylases are inhibited by valproic acid, an anticonvulsant drug used for the treatment of bipolar disorder [25]. Inhibition of histone deacetylase leads to increased expression of genes that are thought to contribute to the therapeutic action of valproic acid and other mood stabilizing drugs, as well as its side-effects.

The key steps involved in going from signals received at the cell surface to production of new proteins are illustrated in Figure 33.1. These include (1) receptor activation and dimerization (illustrated here for the neurotrophic factor BDNF), (2) activation of the intracellular messenger cascades, (3) activation and (4) nuclear localization of specific transcription factors, (5) binding of these factors to the appropriate “response elements” in the genome, (6) transcript initiation, (7) chain elongation, (8) formation of a 5' cap structure at the end of the growing RNA chain, (9) splicing, and (10) termination and cleavage of the newly generated RNA strand. Most genes in eukaryotes are interrupted by non-protein coding sequences referred to as introns. The introns are spliced from the growing RNA chain even as new sequences are being added to the growing 3' end. After reaching the end of the transcribed sequence, the nascent RNA strand is cleaved, and a polyadenosine tail is added to the 3' end of the transcript (11). The newly synthesized RNA must then be packaged by appropriate factors in order for it to be transported out of the nucleus (12) where it can be “translated” by large ribonucleoprotein complexes called ribosomes (13), which “read” the RNA message and assemble the new protein. Finally, the protein must be folded into the appropriate three-dimensional shape (14) in order to carry out its function within the cells. While these processes have been thought of, and largely studied as if they were discrete events, recent evidence suggests that the various aspects of signaling, transcription, and translation are coordinately regulated, so that events at each step are coupled to the succeeding one (reviewed in [26]).

Transcription is initiated by the binding of general transcription factors, including RNA polymerase II, to DNA regulatory sequences near the start site of transcription, referred to as core promoter sequences (reviewed in [27]). Core promoters for protein-coding genes fall into at least two distinct classes. Promoters for approximately half of the known genes contain a sequence known as the TATA box located 25–30 basepairs upstream of a unique transcription start site. Transcription at TATA box-containing promoters is initiated by the binding of a multi-protein subunit complex referred to as the basal transcription complex, which includes the RNA polymerase II.

Promoters for the remaining genes lack the typical TATA sequence. These non-TATA box promoters are typically rich in GC base pairs, have one or more binding sites for the transcription factor Sp1, and have multiple transcription start sites. Genes with this class of promoter include a number of genes expressed in the CNS including those involved in cell-cycle progression, DNA repair, and apoptosis,

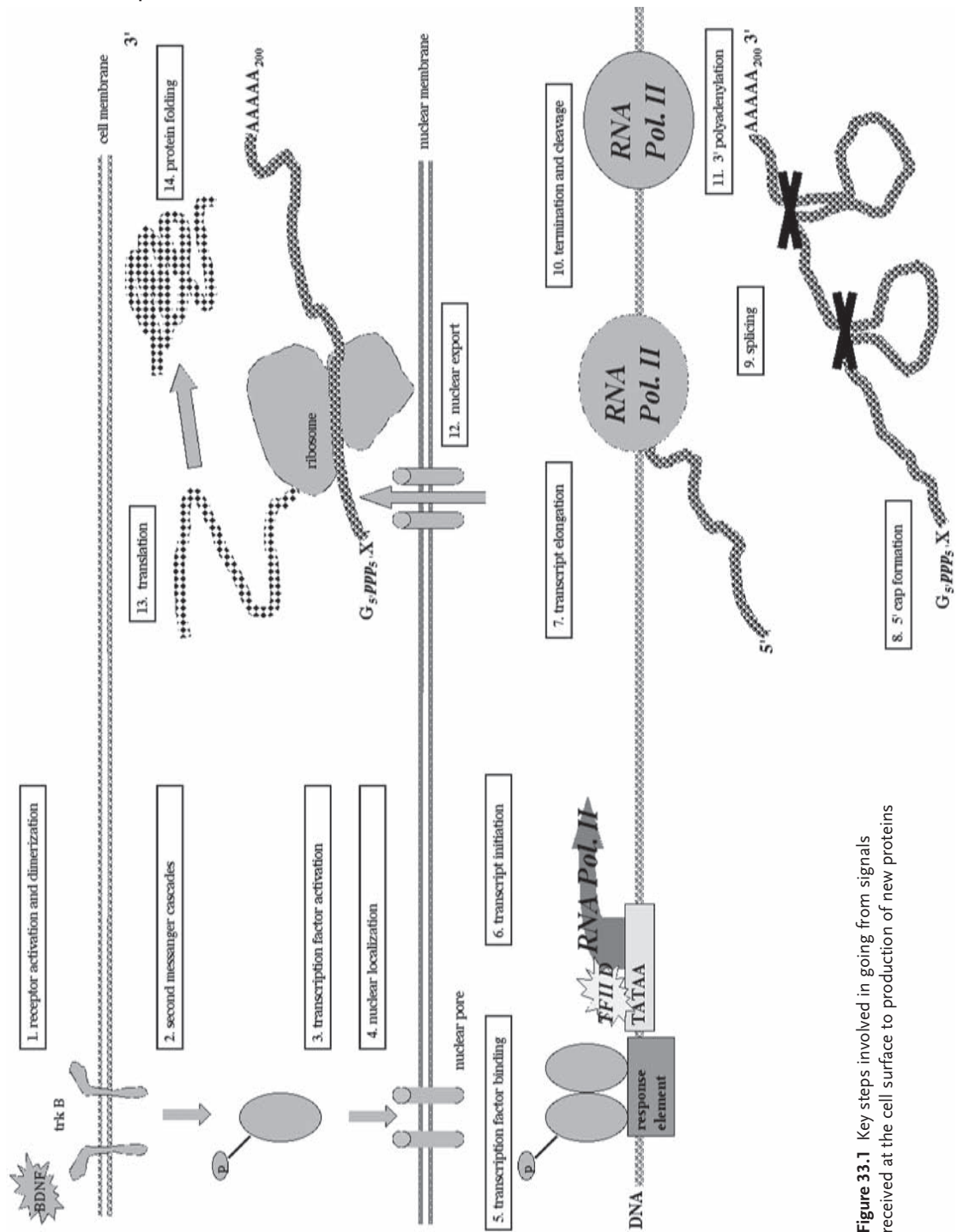


Figure 33.1 Key steps involved in going from signals received at the cell surface to production of new proteins

as well as many widely expressed “house-keeping” genes [28]. Transcription at this class of promoters is initiated by the binding of G + C-rich promoter binding protein (GPBP) in a sequence-independent manner to a particular secondary conformation of the DNA at the promoter region, which then promotes the binding of the basal transcription machinery including RNA polymerase II [28]. GPBP also binds to the CREB-binding protein (see below). However, the two types of core promoters appear to interact differentially with some gene-specific transcription factors. For example, while cyclic AMP response elements sites (see below), are found in both TATA-containing and TATA-less promoters, only in TATA-containing promoters do these elements confer responsiveness to cyclic AMP [29]. Similarly, the transcription factor c-fos has been shown to interact selectively with TATA-containing promoters [30], while Elf-1, a member of the E twenty-six (Ets) family of transcription factors, interacts preferentially with non-TATA promoters [27].

A large number of genes that encode transcription factors are expressed in the adult brain. Transcription factors are important in regulating the temporal and spatial patterns of gene expression, and elements such as the CRE (cyclic AMP response element) and AP-1 (activator protein 1) sites serve as modular binding sites for the different transcription factors that regulate the expression of different genes (see below). The unique tissue and developmental specificity depends on particular combination and spacing of the transcription factor binding sites on each promoter, and the changes in the expression of different genes parallel variations in concentration and activity of transcription factors. This process is a key element in the organism’s response to changes to the internal or external milieu as it reflects the conversion of multiple signaling pathways. Some of these pathways are discussed in more detail in the following sections.

33.3.1

The Cyclic AMP/CREB Cascade

One important signaling pathway that is activated by antidepressant treatment is the cyclic AMP signal transduction pathway. Chronic, but not acute, treatment with antidepressants leads to up-regulation of both the function and expression of the transcription factor CREB (cyclic AMP response element binding protein) in brain regions implicated in mood disorders, including the hippocampus and the amygdala (reviewed in [31]). Increased phosphorylation of CREB in T-lymphocytes has been associated with improvement of depressive symptoms in patients treated with either psychotherapy or antidepressant medications [32], and the region containing the CREB1 gene in humans has been linked to depressive disorders in women from families with recurrent, early-onset, major depression [33]. Post-mortem studies also demonstrate that levels of CREB are decreased in the temporal cortex of non-medicated depressed patients, but elevated in those patients taking antidepressant medication at the time of death [34]. These findings suggest that changes in CREB-mediated gene transcription may be important in both the pathogenesis and treatment of depression.

As illustrated in Figure 33.2, activation of either β_2 adrenergic receptors, or a number of serotonin receptors leads to activation of adenylyl cyclase. This activation is mediated by the α subunit of the G_s class of G-proteins. Receptors which act via G-proteins are referred to as G-protein coupled receptors or GPCRs. GPCRs typically have a seven-transmembrane domain structure with the amino terminus of the protein facing out into the extracellular space and the carboxyl terminus facing the inside of the cell or cytoplasm. The activity of G-proteins results in the production of a variety of molecules termed second messengers (the first messenger is the neurotransmitter). These second messengers include calcium ions, cyclic AMP, cyclic GMP and inositol 4,5 triphosphate (IP_3). Second messengers in turn activate specific signaling cascades, which often involve the sequential activation of a series of kinases. Two different families of proteins regulate the activity of the GPCRs. One family, G protein-coupled receptor kinases, act by phosphorylating GPCRs. Phosphorylation of GPCRs uncouples them from their respective G-proteins. A second family, guanosine triphosphatase (or GTPase)-activating proteins (also called regulators of G protein signaling proteins) acts by accelerating the intrinsic guanosine triphosphatase activity of the α subunit of the G-protein, leading to a faster return to the resting state.

Activation of G_s leads to increased production of the second messenger cyclic AMP. Cyclic AMP activates protein kinase A (or PKA) which phosphorylates CREB at a specific site (serine 133). CREB can also be phosphorylated at this site in a stimulus-dependent manner by a number of other kinases including CaMK IV (calcium calmodulin-dependent kinase IV), MAPKAP2, and members of the ribosomal S6 kinases (RSK, also called MAPKAP K1) and stress-activated protein kinases families (reviewed in [35]). Thus, phosphorylation of CREB at serine 133 is an important convergence point for many different signaling pathways. CREB binds to a specific DNA sequence [5'-TGACGTCA-3'] termed the cyclic AMP response element (or CRE). This sequence is found in the promoter elements of a large number of genes expressed in the brain, including the genes encoding c-fos, BDNF, and CREB itself, and coordinates the response of those genes to a variety of extracellular signals. A partial list of genes containing cyclic AMP response element sequences is given in Table 33.1.

Phosphorylated CREB is able to interact with a co-activator, CREB-binding protein that acetylates histones of CRE-containing genes (HAT-activity) when bound to CREB, and also recruits other histone acetyl transferases and co-factors including components of the basal transcription complex. The combined activity of CREB and CREB-binding protein leads to increased transcription of a number of different target genes (Figure 33.2). The activity of CREB in increasing transcription is thought to be due, at least in part, to its interaction with a specific TATA binding protein-associated factor, hTAF_{II}135 [36]. The presence or absence of this particular TATA binding protein-associated factor in different transcription factor IID complexes may thus contribute to the specificity of promoter activation by CREB, as well as the lack of cyclic AMP-responsiveness of non-TATA promoters even if they contain a CRE.

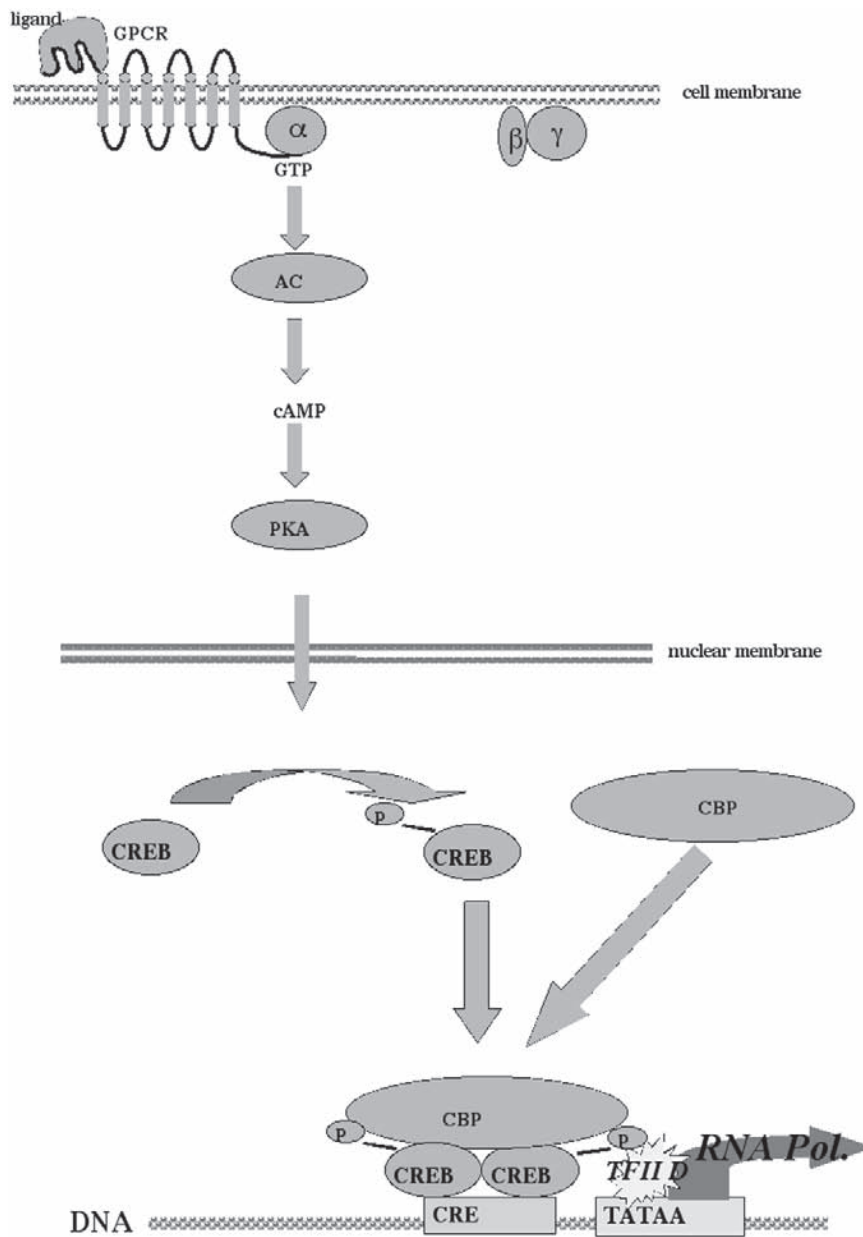


Figure 33.2 Activation of CREB by the cyclic AMP/PKA pathway

Table 33.1 A partial list of genes containing a cyclic AMP response element sequence**Growth factors**

Brain-derived neurotrophic factor (BDNF); Fibroblast growth factor-6 (FGF-6); Flt-1;
Insulin-like growth factor I (IGF-I); Inhibin α ; leptin; Transforming growth factor- β 2 (TGF- β 2)

Neurotransmitter receptors

α 1-GABAA receptor; β_1 , β_2 adrenergic receptors; Galanin Receptor (GalR1); Gonadotropin-releasing hormone receptor (GnRHR); murine gastrin-releasing peptide receptor(mGRP-R); Somatostatin receptor (sstr-2); Trk B

Neuropeptides

Calcitonin gene-related peptide (CGRP); Cholecystokinin (CCK); Corticotropin releasing hormone (CRH); Galanin; Pituitary adeny cyclase activating polypeptide (PACAP); Preprotachykinin A; Proenkephalin; Prodynorphin; Proglucagon; Vasopressin; VGF

Transcription factors

Activating transcription factor-3 (ATF-3); C/EBP- β ; c-fos; CREB; Egr-1; ICER; JunD; Krox-20; mPer1; mPer2; Nurr1; Pit-1; STAT3

Transporters

Norepinephrine transporter (NET); Glucose transporter-2; Vesicular monoamine transporter; (VMAT)

Adapted from [35].

The activity of the cyclic AMP system is regulated by phosphodiesterases. These are enzymes that break down cyclic AMP, and thus turn off the cyclic AMP signal transduction pathway. Inhibition of one particular phosphodiesterase (phosphodiesterase 4) by rolipram has been shown to have antidepressant-like properties in animal models. Thus, inhibitors of specific phosphodiesterases may be promising targets for the development of new antidepressants. CREB activity is also regulated by the actions of related CREB-family proteins including cyclic AMP response element modulator (CREM) and inducible cyclic AMP early repressor (ICER) (reviewed in [35, 37]). CREM isoforms α , β , and γ , negatively regulate CREB activity by forming inactive heterodimers with CREB, while the τ isoform of CREM acts as a positive regulator. The activity of the CREM proteins is regulated in turn by ICER. ICER is expressed as an alternately spliced transcript of the CREM gene (using an alternative promoter located inside one of the CREM introns). Thus the rate of transcription of cyclic AMP response element-containing genes reflects not only the activation state of CREB itself, but also the relative concentrations of positively- and negatively-acting CREB family members present in the cell nucleus.

33.3.2

BDNF and the MAP Kinase Cascade

A second pathway leading to the activation of CREB is the MAP kinase (mitogen-activated protein kinase) cascade. MAP kinases, also referred to as extracellular-signal regulated kinases, are a family of kinases that phosphorylate a variety of different substrates in response to extracellular signals. Decreased levels of extracellular signal-regulated kinase activity and expression have been found in

the cortex and hippocampus of subjects who committed suicide [38], suggesting that this may be a key signaling pathway in the regulation of mood in these subjects. Much of the work carried out on the MAPK cascade in antidepressant response has focused on the role of BDNF (brain derived neurotrophic factor). A substantial body of evidence implicates BDNF in the mechanism of action of antidepressants (reviewed in [39]). Stress decreases the expression of BDNF in the hippocampus, while treatment with either antidepressant drugs or induction of electroconvulsive seizures increases expression of both BDNF and its receptor trk B. Direct infusion of BDNF into the hippocampus as well as the cortex has been shown to have an antidepressant-like effect in animal models of depression [40]. Conversely, expression of a dominant-negative trk B mutant blocks the behavioral effects of antidepressants in animal models of depression demonstrating that this signaling pathway is necessary for antidepressant activity [41]. Post-mortem studies have shown evidence of increased BDNF in the hippocampus of subjects treated with antidepressant medications [42], while serum levels of BDNF were found to be decreased in depressed subjects [43]. These findings suggest that increasing BDNF is important to the therapeutic action of antidepressants.

Expression of the BDNF gene is highly regulated by neuronal activity, and BDNF is released by active neurons during periods of activity. The BDNF gene is one of the downstream genes activated by cyclic AMP/CREB signaling. BDNF is a member of the neurotrophin family of growth factors (reviewed in [44]). Neurotrophins regulate a wide range of activities in the central nervous system including neuronal survival, axonal and dendritic growth, synaptic structure and connections, neurotransmitter release and long-term potentiation. Long-term potentiation is a form of synaptic plasticity characterized by an enduring increase in the response to stimulation of a pathway that has been previously activated. It is thought to be a cellular model of learning and memory in vertebrates. Interestingly, genes for the neurotrophins and their receptors are not found in *Drosophila* or *C. elegans*, suggesting that these genes are not essential for establishment of basic neuronal circuitry, but may be selectively involved in higher order cognitive functions.

Intracellular signaling pathways activated by BDNF are illustrated in Figure 33.3. Binding of BDNF to the trk B receptor leads to receptor dimerization and activation of its intrinsic kinase activity, and autophosphorylation of the dimerized receptor. The adapter protein Src homologous and collagen-like (Shc), links activated trk B to two separate pathways. One pathway links activation of the trk B receptor to important cell-survival mechanisms. Shc, together with the associated protein growth factor receptor-bound protein 2 and its associated binder-1, links activated trk B receptors to PI3K (phosphatidylinositol 3-kinase). PI3K in turn activates 3-phosphoinositide-dependent kinase-1 (or PDK1) and Akt (protein kinase identified in the AKT virus, also known as protein kinase B). Akt activation is further enhanced by 3-phosphoinositide-dependent kinase-1. Akt has a number of important functions related to cell survival and proliferation, two of which are illustrated here. Akt inhibits the pro-apoptotic protein bcl-2 antagonist of cell death (or BAD). It also inhibits glycogen synthase kinase. Glycogen synthase kinase 3 is a serine threonine kinase with a number of important substrates including CREB, immediate early genes

(c-Jun and Jun-D), proto-oncogenes (c-Myb and c-Myc), and protein kinase A (reviewed in [45]). Protein kinase A also directly phosphorylates glycogen synthase kinase 3 and inactivates it, providing cross-talk between the cyclic AMP/protein kinase A and PI3K pathways. Inhibition of glycogen synthase kinase 3 has been proposed to be an important mechanism of action of the mood stabilizer lithium, and inhibition of glycogen synthase kinase 3 by lithium blocks the c-Jun-mediated stress response which leads to expression of the pro-apoptotic Bcl-2 family member, Bcl-2 interacting mediator of cell death (or BIM) [46]. This suggests that glycogen synthase kinase 3 may act in concert with JNK (c-Jun N-terminal kinase) to promote apoptotic cell death. However, the precise mechanism by which activated glycogen synthase kinase 3 promotes cell death is unknown.

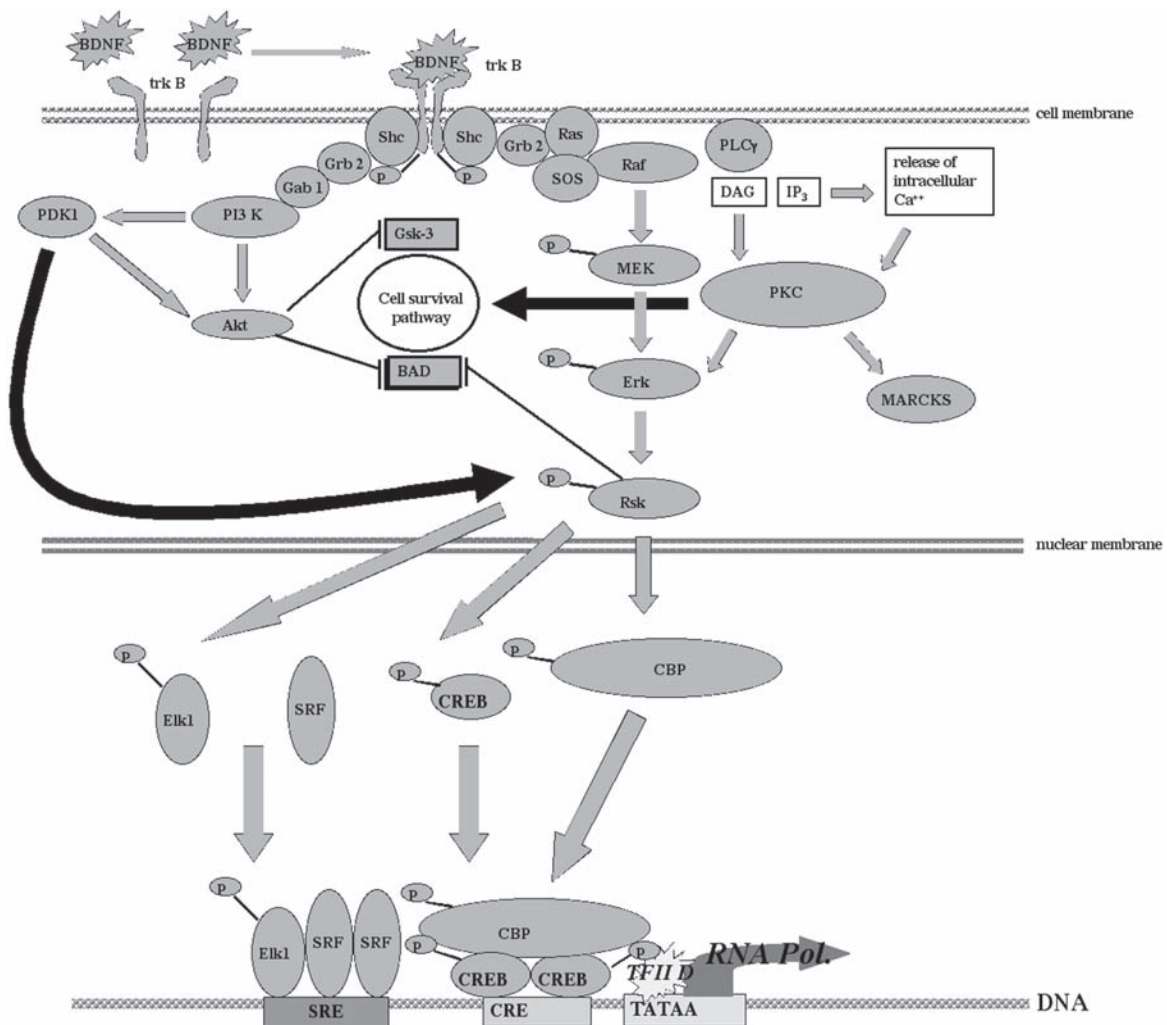


Figure 33.3 Intracellular signaling pathways activated by BDNF

The second pathway linked to activation of trk B receptors by BDNF involves recruitment of SOS1 (son of sevenless) via the linking proteins Shc and growth factor receptor-bound protein 2. The SOS1 gene is a Ras-guanine nucleotide exchange factor. Exchange of guanosine diphosphate (or GDP) for guanosine triphosphate (or GTP) leads to activation of the RAS family of guanosine triphosphate binding proteins. The guanosine triphosphate-bound active form of RAS interacts with and activates the serine-threonine kinase RAF. This in turn leads to the sequential activation of MEK (mitogen-activated protein kinase kinase), ERK (extracellular-signal regulated kinase), and ribosomal S6 kinases (RSK). Ribosomal S6 kinases can also be phosphorylated by 3-phosphoinositide-dependent kinase-1, which provides cross-talk between the two pathways. Indeed, recent observations suggest that full activation of RSK requires that both pathways phosphorylate ribosomal S6 kinases. RSK activates both CREB and CREB-binding protein (and the related protein p300) leading to the activation of CREB-regulated genes. RSK also phosphorylates, and inactivates pro-apoptotic protein bcl-2 antagonist of cell death, the same pro-apoptotic Bcl-2 family member that is inhibited by glycogen synthase kinase 3, thus providing further cross-talk between the two pathways. Although shown in the diagram as single representative protein, each of these proteins (RAS, RAF, MEK, ERK, and RSK) are actually families of related proteins that, at least *in vitro*, have overlapping substrate specificities. For example ribosomal S6 kinase family members, RSK1, RSK2, and RSK3, and mitogen- and stress-activated protein kinase family members MSK1 and MSK2 have all been shown to phosphorylate CREB *in vitro* at the same site utilized by the protein kinase A signaling pathway (reviewed in [47]). The particular kinase or kinases that phosphorylate CREB at this site *in vivo* may vary depending on the cell type and which signaling pathways have been activated by a given stimulus.

Mitogen- and stress-activated protein kinase-mediated phosphorylation of CREB-binding protein and the related protein p300 also allow them to interact with a number of other important transcription regulators. These include the immediate early genes c-Fos and c-Jun (discussed below), STAT, MyoD, E2F, NF κ B, and steroid receptors including estrogen receptor- α . Thus activation of the ras-raf-MEK-ERK-RSK pathway by BDNF binding to the trk B receptor can lead to changes in a wide variety of signaling pathways in addition to CREB.

A third major pathway activated by BDNF signaling is the phospholipase C pathway. Activation of phospholipase C leads to hydrolysis of PIP2 (phosphoinositide 4,5 bisphosphate). This generates two important second messengers: IP3 (inositol 4,5-triphosphate) and diacyl glycerol. IP3 mobilizes calcium from intracellular stores, while diacyl glycerol activates protein kinase C. Protein kinase C can also be directly activated by calcium.

Protein kinase C has been proposed as a major site of action for lithium in regulating gene expression. Lithium treatment initially activates protein kinase C, however long-term treatment with lithium leads to reductions of the α and ϵ isoforms of protein kinase C. Protein kinase C isoforms have a number of important neuroprotective functions in the cell. These include inhibition of glycogen synthase kinase 3 β , activation of MAP kinases and phosphorylation of a protein referred to

as MARCKS (myristolated alanine-rich protein kinase C substrate). MARCKS is a filamentous actin cross-linking protein whose activity is inhibited when it is phosphorylated by protein kinase C and by binding to calcium-calmodulin [48]. Knockout mice lacking MARCKS die within a few hours of birth and have high frequencies of midline defects particularly in cranial neurulation [49], suggesting that the function of this protein is important in the development of the nervous system.

33.3.3

Immediate Early Genes

The end-point of the various signal transduction cascades described above is changes in gene transcription. One important class of target genes for all of these signaling pathways is the immediate early genes. Immediate early genes are a group of genes first identified in fibroblasts stimulated to divide by serum. The defining characteristic of immediate early genes is their rapid induction following stimulation, without the need for *de novo* protein synthesis (reviewed in [50]). The immediate early genes thus constitute a set of “first responders”, overlapping subsets of which are activated by different extracellular signals. Immediate early genes encode a wide variety of structurally unrelated proteins including secreted proteins (e.g. BDNF), cytoplasmic enzymes, ligand-dependent transcription factors and inducible transcription factors such as the members of the fos and jun families discussed below.

One of the best-studied immediate early genes is the inducible transcription factor, *c-fos*. The ras-raf-MEK-ERK-RSK pathway described above regulates transcription of the *c-fos* gene in two complementary ways. First, as mentioned above, RSK2 phosphorylates both CREB and CREB-binding protein, allowing the CREB–CREB-binding protein complex to bind to the cyclic AMP response element. The *c-fos* promoter contains at least three cyclic AMP response elements that are required for growth factor induction of *c-fos*. Second, ERK, the kinase upstream of RSK, phosphorylates a transcription factor called Elk-1 (an E-twenty six (Ets) domain transcription factor). Phosphorylated Elk-1 binds to a second protein serum response factor that binds to a DNA sequence termed the “serum response element”. The serum response element consists of a core sequence [CC(A/t)₆GG] termed the CArG box, which serves as the binding site for the dimerized serum response factor, and an adjacent sequence CAGGAT, which is bound by Elk-1. The complex formed by Elk-1, serum response factor, and the serum response element is referred to as a ternary complex. Elk-1 and related transcription factors (Sap1a, Sap1b, and Net) are sometimes referred to as ternary complex factors. Binding of Elk-1 and serum response factor to the serum response element, and CREB to the three CREB sites turns on transcription of the *c-fos* gene (Figure 33.3). *c-Fos* is an inducible transcription factor; *c-Fos* and other fos family members (FosB, Fra-1 and Fra-2) form heterodimers with members of the Jun family of immediate early genes (*c-Jun*, JunB, JunD). These heterodimers bind to a site [5'TGAG/CTCA-3'] termed the AP-1 (activator protein 1) site. AP-1 is not a single protein, but a sequence-specific

binding activity shared by the various Fos–Jun heterodimers. To complicate matters even further this same site can be bound by Jun–Jun homodimers as well as homo- and heterodimers containing members of the Maf and ATF families. Note that the AP-1 sequence is very similar to the cyclic AMP response element site [5′-TGACGTCA-3′] and some AP-1 family members can bind to the cyclic AMP response element site as well, although with lower affinity. Like the cyclic AMP response element the AP-1 site is found in the promoters of a large number of genes and serves to coordinate the response of these genes to a variety of extracellular signals. Among the genes regulated by binding of fos and jun family members are a number of genes involved in regulating cell survival (reviewed in [51]). These include the pro-apoptotic genes Fas ligand (or FasL), Bcl-2 interacting mediator of cell death, and Fas, as well as the anti-apoptotic gene Bcl-3. The role of AP-1 family proteins in the regulation of cell survival is complex and likely to be context dependent. For example in most cellular contexts c-Jun appears to be a positive regulator of cell proliferation, while JunB has the opposite effect. However, persistent activation of c-Jun by JNK (e.g. following UV irradiation) leads to induction of pro-apoptotic genes such as Bcl-2 interacting mediator of cell death gene. Inhibition of this pathway may be important in the neuroprotective actions of the mood stabilizer lithium.

33.3.4

Glutamate Receptors, Calcium/Calmodulin Signal Cascades, and Long-term Potentiation

The hypothesis that antidepressants act, at least in part, by restoring neuronal plasticity suggests that changes in synaptic connections are essential to the mechanism of action of antidepressants. Changes in the number and strength of synaptic connections are believed to underlie many different forms of learning and memory. The best-studied paradigm for this process is long-term potentiation in the hippocampus. Long-term potentiation refers to a long lasting increase in the strength of an excitatory connection following repeated stimulation. A related phenomenon, long-term depression can occur with low frequency stimulation of the same pathways. Induction of long-term potentiation requires new protein synthesis and is associated with activation of many of the transcription factors discussed above.

BDNF has been shown to induce transcription-dependent late-phase long-term potentiation in animal models, and ERK, CREB, and the immediate early genes have all been shown to be required for some forms of memory.

Glutamate receptors, in particular the NMDA (N-methyl-D-aspartate) class of glutamate receptors, have been shown to play a key role in the induction of both long-term potentiation and long-term depression. They have been proposed as possible targets of antidepressant action (reviewed in [52]). Administration of the NMDA antagonist ketamine has been shown to have antidepressant-like properties in depressed patients [53] and chronic administration of antidepressants has been shown to affect both the subunit composition [54] and function [55] of NMDA receptors. NMDA-type glutamate receptors play a key role in the regulation of long-

term potentiation because of their dual requirement for depolarization of the post-synaptic dendrite (which relieves blockade of the channel by Mg^{2+} ions) and activation by the neurotransmitter glutamate. Activation of NMDA receptors thus serves as an activity-dependent coincidence detector that signals the simultaneous depolarization and activation of particular pathways. Calcium entry through NMDA receptors regulates gene expression through a number of complex and not fully understood mechanisms (reviewed in [56]). Some of the pathways activated by calcium entry are shown in Figure 33.4.

One pathway alluded to previously is the activation of CaM kinases (Calcium Calmodulin-Dependent Kinases). Calmodulin is an important calcium-binding protein that plays a key role as a sensor of intracellular calcium. Calmodulin has four calcium binding sites. When all four of these sites are bound by calcium, calmodulin undergoes a conformation shift that allows it to interact with a wide variety of effector proteins. CaMK I, CaMK II, and CaMK IV can all phosphorylate CREB at serine 133, the same site phosphorylated by the protein kinase A and RSK pathways described above. CaMK IV is located primarily in the nucleus (and requires phosphorylation by CaMKK in addition to binding to calmodulin to become active) while CaMK I and CaMK II are primarily cytoplasmic, however there is evidence which suggests that both CaMK I and CaMK II can translocate to the nucleus upon neuronal stimulation. Thus all three CaM kinases may contribute to activation of CREB-dependent gene expression under different circumstances. Activated CaMK II also undergoes autophosphorylation. This autophosphorylation event allows CaMK II to remain active after the initial spike in local calcium concentration has dissipated. Persistent activation of CaMK II has been proposed as one of the key events in the induction of long-term potentiation. Activated CaMK II may also play a role in recruiting additional AMPA (α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid) receptors to the synapse, which is important for the change in conductance in the early (protein-synthesis independent) phase of long-term potentiation.

Of particular relevance to the possible role of CaM kinases in depression are experiments looking at fear-related memory in mutant mice lacking the CaMK IV gene. The CaMK IV mutant mice showed normal responses to acute noxious stimuli, but deficits in fear-related memory [57]. These mice also failed to show increases in CREB phosphorylation following fear conditioning in several brain areas including the CA1 region of the hippocampus, basolateral amygdala, anterior cingulate cortex, primary somatosensory cortex, and agranular insular cortex. Thus activation of CREB-dependent genes in one or more of these areas by CaMK IV appears to be necessary for the retention of fearful memories, while over activation of this signaling pathway could potentially contribute to later vulnerability to depression.

A second pathway involves the calcium-calmodulin-mediated activation of PI3K (PI3-kinase). Activation of PI3K leads to activation of the ras-raf-MEK-ERK-RSK pathway described above, and the induction of a number of immediate early genes, including BDNF. In addition, PI3K phosphorylates Akt, leading to activation of cell-survival pathways. Akt can also be phosphorylated directly by CaMKK in a PI3K-independent pathway.

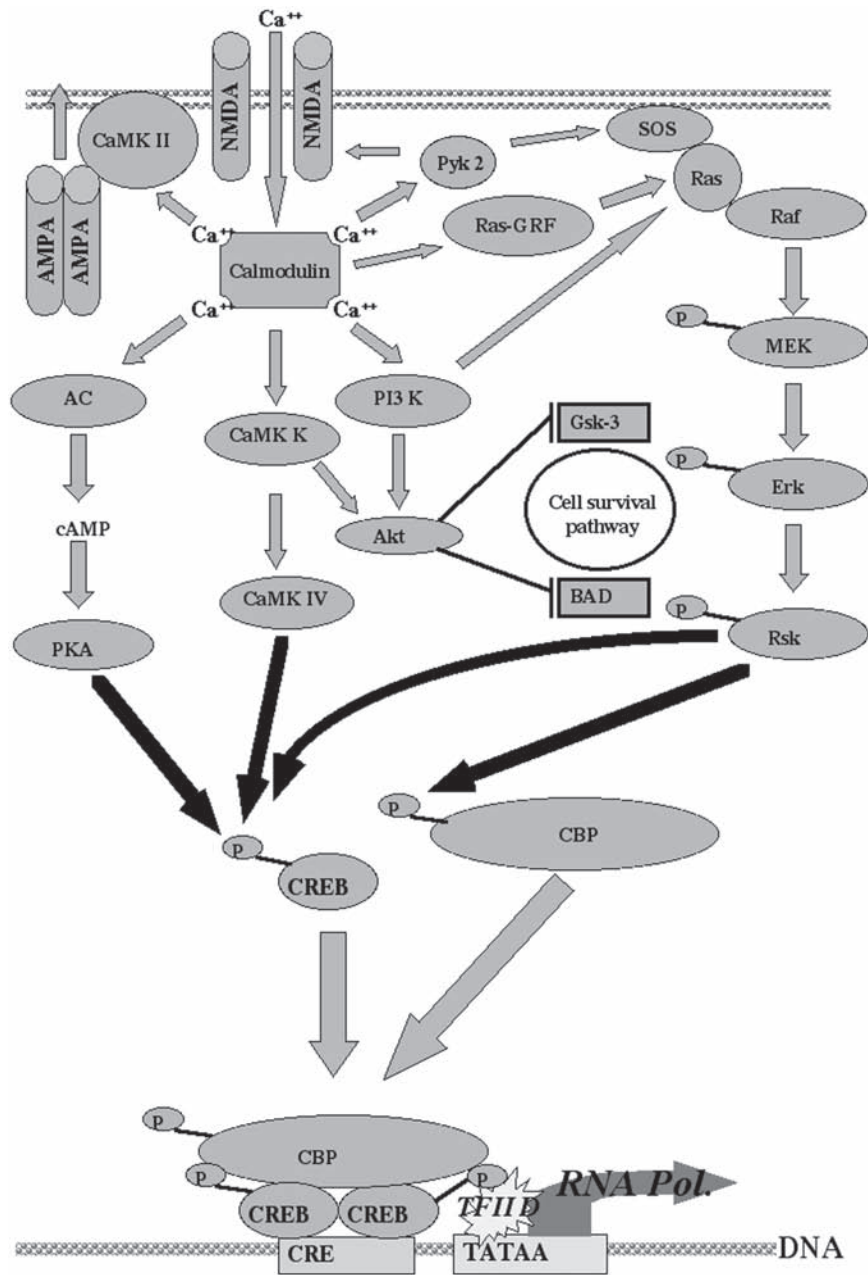


Figure 33.4 Signaling pathways activated by calcium entry

A third pathway activated by calcium entry involves the tyrosine non-receptor kinase Pyk2 (proline-rich tyrosine kinase 2, also known as focal adhesion kinase 2). Pyk2 has a number of important actions related to long-term potentiation. First, Pyk2 phosphorylates the NMDA receptors leading to enhanced calcium influx. It also phosphorylates voltage-gated potassium channels leading to decreased potassium efflux and prolonging the period of neuronal depolarization and thus contributes to the induction of long-term potentiation. Second, Pyk2 activates the Ras-guanine nucleotide exchange factors, SOS1 (son of sevenless). SOS1 promotes the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) by Ras, and leads to activation of the ras-raf-MEK-ERK-RSK pathway. Calcium entry also leads to activation of the related protein RAS-GRF2 (RAS protein-specific guanine nucleotide-releasing factor 2). Expression of Pyk2 in the lateral septum has recently been shown to have anti-depressant like properties in a learned helplessness model of depression [58] and Pyk2 expression is decreased by stress, suggesting that these pathways may be important in coping responses to stressful stimuli.

Finally calcium entry leads (via activation of the calcium sensitive adenylate cyclase) to activation of the protein kinase A pathway. While all of the pathways are shown converging on CREB phosphorylation, CREB is only one of the many transcription factors whose activity is regulated by calcium entry into the cell. The timing and route of calcium entry are also important determinants of the specific response to calcium. Calcium can enter the cell through at least four routes: through the NMDA channels as shown in Figure 33.4, through some types of AMPA receptors, through L-type voltage-gated Ca^{2+} channels and by release from internal stores. Each of these routes of calcium entry is thought to have specific effects on cell physiology and on gene-transcription. For example, while entry of calcium through NMDA receptors plays a key role in the induction of long-term potentiation and leads to the expression of many immediate early genes, the induction of BDNF is particularly dependent upon calcium entry through L-type voltage-gated calcium channels. Thus while calcium entry activates a wide variety of signaling mechanisms, not all of these mechanisms will be engaged every time calcium enters the cell.

33.3.5

β -Catenins and the Wnt Signaling Pathway

Another signaling pathway that has been the subject of recent study is the β -catenin/Wnt (wingless-type MMTV integration site family) signaling pathway (Figure 33.5). β -Catenin is a transcription factor and the effector of the Wnt signaling pathway. Wnt receptors are seven-transmembrane domain proteins encoded by members of the *Frizzled* gene family. Activation of Wnt membrane receptors by extracellular Wnt ligands leads to activation of the *disheveled* protein (both *frizzled* and *disheveled* are named for the appearance of strains of the fruit fly, *Drosophila*, with mutations of the homologous genes). Disheveled inhibits GSK3 β , relieving the tonic inhibition of glycogen synthase kinase 3 β on β -catenin, and allowing β -catenin to translocate to the nucleus where it interacts with members of the lymphoid enhancer-binding

factor/Tcf class of transcription factors to stimulate the expression of a numbers of genes that are important in the development of the nervous system (reviewed in [59, 60]). These genes seem to be particularly important in the ontogeny of hippocampal dentate gyrus granule cells as mutant mice that lack the lymphoid enhancer-binding factor 1 gene do not develop dentate gyrus cells. Even more strikingly mice with a dominant negative form of lymphoid enhancer-binding factor 1, which also interferes with β -catenin-mediated activation with other lymphoid enhancer-binding factor/Tcf proteins, lack the entire hippocampus [61]. Conversely, when a constitutively active form of β -catenin was expressed in transgenic mice during development, these mice developed enlarged brains with increased cerebral cortical surface area and folds resembling the sulci and gyri of higher mammals [62]. Thus, appropriate regulation of the β -catenin/Wnt signaling pathway appears to be extremely important in the development of the CNS. Brief exposure to lithium blocks the tonic inhibition of glycogen synthase kinase 3 β on β -catenin, and thus mimics the effects of Wnt signaling [63, 64]. This effect may be important in lithium's actions in stimulating hippocampal neurogenesis [65]. Activation of gene expression by valproate regulation of histone deacetylases (HDAC, discussed above) may provide common gene expression targets for these two different mood-stabilizing drugs.

Wnt signaling also leads to activation of phospholipase C. As noted above, activation of phospholipase C leads to generation of the second messengers, IP3 and diacyl glycerol, and this in turn leads to activation of various PKC isoforms. An atypical variant of protein kinase C referred to as PKC ζ is responsible for the activation of the survival factor NF- κ B [66]. NF- κ B (nuclear factor of kappa light chain gene enhancer in B cells) was discovered and named for its role in the regulation of genes encoding the immunoglobulin κ light chain. However, it has subsequently been shown to play an important role in a variety of cellular processes. NF- κ B-regulated genes include a variety of genes that are involved in protecting cells from apoptotic cell death including Mn-SOD (manganese superoxide dismutase), calbindin, and Bcl-2, however, persistent and inappropriate expression of NF- κ B can induce apoptosis. Like the AP-1 complex, the NF- κ B complex can contain a variety of different protein subunits. Transcriptionally-inactive NF- κ B consists of homodimers of either the p65 or p50 subunits complexed with the histone deacetylase HDAC1 [67]. p50-HDAC1 complexes bind to DNA and suppress the expression of NF- κ B-dependent genes. The NF- κ B complex is inhibited by I κ B (inhibitor of κ B) proteins that bind to NF- κ B, trapping it in the cytoplasm. Phosphorylation of NF- κ B by PKC ζ leads to ubiquitination and degradation of I κ B and translocation of the p65 complexes to the nucleus. NF- κ B complexes containing phosphorylated p65 are then able to bind to CREB-binding protein and displace the p50-HDAC1 complexes leading to transcription of NF- κ B-dependent genes.

In addition to its roles in promoting or suppressing apoptosis NF- κ B is thought to play a role in regulating synaptic transmission (reviewed in [68]). In hippocampal slices, NF- κ B is located in the distal dendrites and translocates to the nucleus following activation of NMDA receptors or L-type calcium channels. NF- κ B-regulated genes include both NMDA and AMPA glutamate receptor subunits [69]. NF- κ B is

activated in response to membrane depolarization, low-frequency stimulation, and during long-term potentiation of synaptic transmission. Furthermore, pre-treatment with κ B decoy DNA (to “soak up” activated NF κ B) in hippocampal slices suppresses both long-term potentiation and long-term depression [70]. Thus, NF κ B-mediated changes in gene expression may be essential to some forms of plasticity.

33.3.6

Glucocorticoid and Other Nuclear Hormone Receptors

In addition to the pathways discussed above that involve signaling from receptors located at the cell surface a number of important signaling molecules are able to cross the cell membrane and interact directly with receptors inside the cell. These include androgen receptors, estrogen receptors (α and β), glucocorticoid receptors, mineralocorticoid receptors, progesterone receptors, all-*trans* and 9-*cis* retinoic acid receptor alpha and retinoic X receptor, thyroid hormone receptor, and vitamin D receptor, as well as a number of putative receptors identified based on DNA sequence homology to known hormone receptors for which no ligand has yet been identified, termed orphan nuclear receptors (reviewed in [71]).

Of particular relevance to the biology of depression are those changes induced by the glucocorticoids. Over half of the patients with major depression have been found to have abnormalities of the hypothalamic–pituitary–adrenal axis, as evidenced by the failure of dexamethasone to suppress the secretion of endogenous cortisol [72]. This function is thought to result from a failure of negative feedback control at the level of the hypothalamus, and may involve reverberating positive feedback loops involving the effects of cortisol on the amygdala, hippocampus, and locus coeruleus-noradrenergic system [73]. Consistent with this hypothesis, administration of the glucocorticoid receptor antagonist Mefipristone, also known as RU 486, has been reported to be of benefit in treating severe depression, particularly psychotic depression [74–76]. Although it should be noted that cortisol and other glucocorticoids when given exogenously induce euphoria more commonly than depression [77].

When activated by ligand binding nuclear hormone receptors bind to specific DNA sequences known as hormone response elements and can either stimulate or inhibit expression of downstream target genes. The nuclear hormone receptors have been divided into two groups. Type I receptors (classic steroid receptors) remain in the cytoplasm until they are bound by the appropriate ligand. They then translocate to the nucleus and bind as homodimers to DNA. Type II receptors (vitamin D, thyroid hormone and retinoic acid A receptor) in contrast, are often located in the nucleus even in the absence of ligand binding. Type II receptors usually bind as heterodimers (with retinoic X receptor) to direct gene transcription. However, there is a great deal of variation in this basic scheme. For example naturally-occurring thyroid response elements consist of two or more half-sites containing the sequence [5'-AGGTCA-3']. These half-sites can be arranged as direct repeats, palindromes, or inverted palindromes. The effect of receptor binding on target gene transcription depends in a complex and not fully understood way on

the arrangement of these sites, the state of the hormone receptor (liganded or unliganded) and the presence of other regulatory sites within the promoter of the particular gene (reviewed in [2]). One mechanism, which has been the subject of increasing interest, is the role of co-regulators in the action of nuclear hormone receptors. Just as CREB requires a partner, CREB-binding protein, in order to effect the transcription of its target genes, so too, the action of the nuclear hormone receptors is now believed to involve the activity of a large number of co-activators and co-repressors (reviewed in [71, 78]). Intriguingly some of the same molecules involved in kinase-regulated gene transcription are also involved in regulating the activity of nuclear hormone receptors. For example, CREB-binding protein also binds to the estrogen receptor α .

Kinase signaling cascades can also regulate the activity of these co-regulators and thus modify the influence of hormonal signals. For example, ERK2 can phosphorylate steroid receptor coactivator-1 (SRC-1) [79], and EGF (which activates the MAPK signaling cascade) enhanced the SRC-1/PR-mediated effects on transcription of the target gene. Thus, in this case, activation of a cell-surface receptor by a growth factor leads to an enhanced response to a hormonal signal. In other cases hormonal signals may alter the response to cell-surface receptors. One example of this is the interaction of transforming growth factor- α (TGF- α) and estrogen receptor α signaling. TGF- α normally stimulates proliferation of neural cell precursors. However, in the presence of estrogen receptor α signaling, the mitogenic signal is converted into a differentiation-promoting signal [80]. Thus, cross-talk between the different signaling pathways can produce not just additive, but qualitative changes in the expression of single genes, and in the overall response of the cell.

In general, glucocorticoids act to oppose the inflammatory effects of cytokines such as tumor necrosis factor- α (TNF- α). TNF- α signaling leads to induction of a large number of genes through signaling pathways that involve AP-1 (activator protein 1) as well as Sp1 (signaling protein 1) and NF κ B. Activation of the TNF- α receptor activates I κ BK (inhibitor of κ B kinase). I κ BK phosphorylates I κ B, releasing active NF κ B which then translocates to the nucleus. In several cases activation of gene transcription by NF κ B involves cooperation with the transcription factor Sp1. In a study of the promoter for the monocyte chemoattractant protein 1 gene Boekhoudt et al. [81] showed that Sp1 binding to and histone acetylation of the promoter region was dependent on NF κ B, and conversely Sp1 assembly at the promoter region was required for NF κ B binding. TNF- α signaling leads to the induction of genes involved in promoting inflammation. These actions are opposed by the actions of glucocorticoids, which can be thought of as neuroprotective in that context. However, prolonged exposure to excessive glucocorticoids can have a number of detrimental effects on the brain. As mentioned above, glucocorticoids decrease proliferation of neuronal precursors in the dentate gyrus of the hippocampus and reduce the number and length of apical dendrites in CA3 pyramidal neurons, while antidepressants have the opposite effects. The glucocorticoid hormones, cortisol and corticosterone are secreted by the adrenal gland in response to a variety of stressful stimuli. Secretion of glucocorticoids is regulated by the hypothalamic–pituitary–adrenal axis, with negative feedback at the level of both

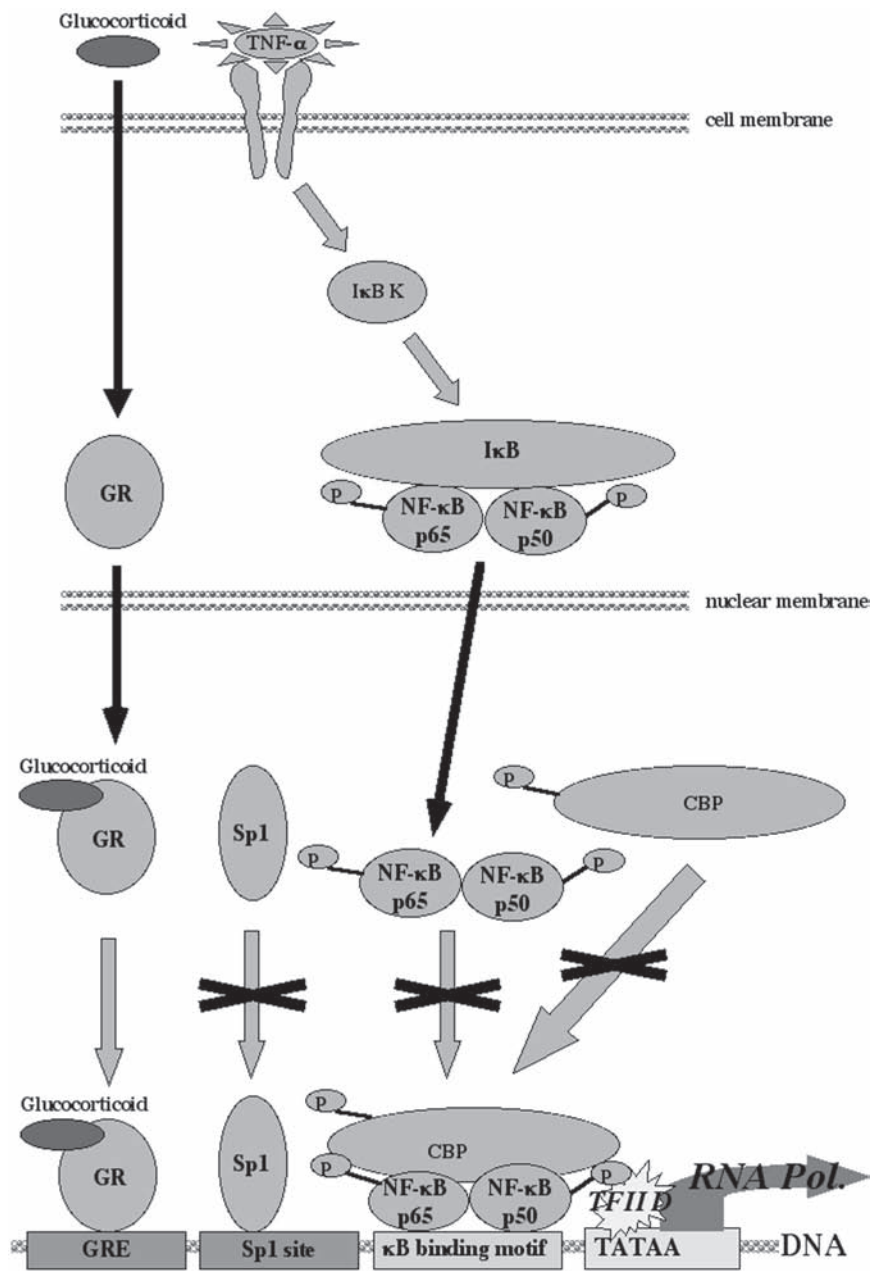


Figure 33.6 Opposing actions of glucocorticoids and TNF α on transcription of the 5-HT $_A$ gene. See text for explanations of specific pathways

the pituitary and hypothalamus. Mineralocorticoid and glucocorticoid receptors mediate the effects of corticosteroids on the brain. Glucocorticoid receptors are more widely expressed, but have a lower affinity for glucocorticoids than do mineralocorticoid receptors. As a result glucocorticoid receptors only become occupied during times of peak glucocorticoid expression, for example during the typical morning circadian peak or in response to stressful stimuli. While glucocorticoid and mineralocorticoid receptors both bind to the same hormone response element sequence, the consequences of binding may be very different. For example, the glucocorticoid receptor, but not the mineralocorticoid receptor has been shown to inhibit AP-1-dependent reporter gene expression [82].

An example of the differing effects of mineralocorticoid and glucocorticoid receptors on gene expression, which may be relevant to the role of stress hormones in depression, is the regulation of the serotonin 5-HT_{1A} receptor gene by glucocorticoids. The 5-HT_{1A} receptor has been shown in knockout mice to be required for some anxiolytic effects of SSRI antidepressants as well as SSRI-induced increases in hippocampal neurogenesis [83], and the 5-HT_{1A}-partial agonist buspirone is used clinically as an anxiolytic and as an adjunct therapy for depression. More recently a polymorphism in the promoter of the 5-HT_{1A} gene has been linked to increased risk for both major depression and suicide [84]. Thus regulation of 5-HT_{1A}-gene transcription may play a role in anxiety-related behaviors. Figure 33.6 illustrates the opposing actions of glucocorticoids and TNF α on the transcription of the 5-HT_{1A} gene. 5-HT_{1A}-gene transcription can be induced by either a synergistic combination of the actions of Sp1 and NF κ B or by NF κ B alone. Both mineralocorticoid and glucocorticoid receptors negatively regulate 5-HT_{1A}-gene transcription, but they do so in slightly different ways. In the presence of corticosterone, glucocorticoid receptors were able to repress transcription mediated by either the synergistic actions of Sp1 and NF κ B or by NF κ B alone. In contrast, mineralocorticoid receptors were able to inhibit the synergistic effects of Sp1 and NF κ B, but had no effect on transcription mediated by NF κ B alone [85]. Low concentrations of glucocorticoids that would activate the mineralocorticoid receptor, but not the glucocorticoid receptor, allow 5-HT_{1A}-gene transcription stimulated by NF κ B, but block the effects of Sp1, while higher concentrations of glucocorticoids released in response to stressful stimuli would block the effects of both Sp1 and NF κ B. Thus, the transcription of the 5-HT_{1A} receptor gene depends on a complex state-dependent interaction among transcriptional activators, steroid hormones and steroid hormone receptors. This complexity may contribute to some of the cell-type and developmental stage specificity of the actions of steroid hormones on gene expression.

33.4

Neuroanatomic Variation: Putting the Message in Context

As described in the preceding sections a great deal is now known about the intracellular signaling pathways activated by different neurotransmitter and steroid

hormone receptors. However, in order for changes in gene expression to result in changes in behavior they must contribute to altered signaling within the brain. Furthermore such changes must be selective with regard to the brain areas and pathways involved. An obvious question is, how can widespread stimuli such as exposure to stress hormones or psychoactive medications result in changes in signaling that are anatomically specific? One answer is that neurotransmitter receptors are expressed in cell type-specific patterns. The existence of different receptors for the same transmitter affords further possibilities for cell type-specific responses. Serotonin, the major target of many clinically used antidepressants, is recognized by a large family of receptors which includes as many as 13 distinct GPCRs and at least one ligand-gated ion channel (reviewed in [86, 87]). Adding to this complexity are processes such as alternate splicing and RNA editing which can produce additional proteins, and post-translational modifications such as oligomerization, and heterodimerization can alter the functions of these receptors. Thus there appears to be an almost endless diversity of functional variants of the different neurotransmitter receptors. These receptors can be coupled to different signaling cascades in a cell type-specific manner such that binding of the same ligand to the same receptor in different areas of the brain produces a unique result.

Cross-talk among the different signaling pathways, as described in the section above can further modulate the results of such signaling such that activation of the same pathway can produce different biochemical or behavioral results depending on the area of the brain in which it is activated. One example of this involves the well-studied signaling molecule CREB. Studies in rodents have shown that chronic, but not acute, treatment with antidepressants leads to up-regulation of both the function and expression of the transcription factor CREB (cyclic AMP response element binding protein) in brain regions implicated in mood disorders, including the hippocampus and the amygdala [19, 88, 89]. Interestingly, exposure to stress leads to CREB activation in many of these same brain areas. For example, exposure to the forced swim test results in a biphasic induction of pCREB (phospho-CREB, the activated form of CREB) in the dentate gyrus of the hippocampus, many sub-regions of cerebral cortex, and the amygdala, with an initial increase between 15 and 30 min after stress exposure and then a return to basal levels, followed by a second sustained peak beginning around 6 h after exposure to the forced swim task and lasting at least 48 h [90]. Forced swim, footshock, restraint, social stress increase, as well as repeated unpredictable stress all increase pCREB immunoreactivity in the nucleus accumbens as well [91, 92]. In addition, Barrot and colleagues have utilized a cyclic AMP response element transgenic reporter mouse to demonstrate that CRE-mediated gene expression is also increased under these conditions [91]. Thus, stress and antidepressant treatment are both capable of increasing the expression and activity of CREB in a variety of brain regions. However, the functional significance of increased CREB in these different brain areas is not always apparent. For example increased pCREB in the hippocampus following stress might be part of the pathological process leading to dendritic shrinkage and decreased proliferation, or it might be part of a compensatory, protective effect. To address the functional consequences of CREB activation in different brain areas in

these behavioral paradigms, investigators have used both inducible transgenic mouse models and direct injection of viral vectors encoding either CREB or dominant-negative inhibitors of CREB. The results have added to our appreciation of the complexity of the role of CREB in both the pathogenesis and treatment of depression. As noted above, expression of CREB [93] or infusion of BDNF into the hippocampus [94] produces an antidepressant-like effect in the learned helplessness and forced swim models of depression. Preliminary studies demonstrate that viral expression of CREB in the amygdala also produces an antidepressant response in the learned helplessness model of depression [95]. However, viral or transgenic expression of CREB in the nucleus accumbens results in a pro-depressive phenotype in both the forced swim and learned helplessness models, while inhibition of CREB in these brain areas has an antidepressant-like effect [92, 96]. Thus, the effect of CREB signaling on behavior depends both on the brain region examined and the context of activation. The fact that CREB is activated in different cellular contexts in different areas of the brain leads to the induction of different target genes in these brain structures. This in turn can lead to diametrically opposed effects on behavior when the same signaling pathway is activated in two different brain areas. In the hippocampus and amygdala one of the targets of CREB is BDNF, which is capable of producing an antidepressant effect [94]. In the nucleus accumbens, one of the key target genes of CREB is prodynorphin, which can produce aversive effects that could contribute to the pro-depressive effects of CREB expression in this region of the brain [92, 96, 97].

33.5

Conclusions

Cell type-specific changes in the concentration and activity of transcription factors allow the expression of different genes to vary in response to developmental programs or changes in the environment. The initiation of transcription is a key event in the organism's response to changes in the outside world and it is the target of many converging signaling pathways. Work in our laboratory and others has identified a number of genes whose expression in the brain changes markedly when animals are treated with different classes of antidepressants. Signaling pathways activated by antidepressants and mood stabilizers include the cyclic AMP/CREB pathway, the MAP kinase pathway, phospholipase C pathway, and the Wnt (wingless-type MMTV integration site family) signaling pathway. Activation of these pathways leads to increased expression of a number of target genes including other transcription factors such as the immediate early genes such as c-jun and c-fos, and neurotrophic factors such as BDNF. Increased expression of neurotrophic factors opposes the deleterious effects of chronic stress, and has antidepressant-like effects in animal models. Interestingly many of the same transcription factors are also increased by stress, although the particular brain areas involved differ from those affected by antidepressants, and the effect of transcription-factor expression is highly dependent on the brain area in which the activation occurs. Brain areas

that are likely to be involved in the neurobiology of depression include the dorsal raphe and locus coeruleus (the major sources of serotonergic and noradrenergic innervation, respectively, for the rest of the brain), subcortical structures including the nucleus accumbens, amygdala, and hypothalamus, as well as the hippocampus and the prefrontal cortex [98]. The major challenge for the future will be the synthesis of existing information regarding intracellular signaling pathways and their effects on gene expression with neuroanatomic information about specific cell populations and connections within the brain that are affected by stress and antidepressant action. Only by synthesizing the information obtained at different levels of analysis will we be able to gain a complete understanding of the role of transcription factors in the biology of depression.

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References

- 1 CASPI, A., SUGDEN, K., MOFFITT, T. E., TAYLOR, A., CRAIG, I. W., HARRINGTON, H., MCCLAY, J., MILL, J., MARTIN, J., BRAITHWAITE, A., POULTON, R., Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **2003**, 301, 386–389.
- 2 BEECH, R. D., Thyroid hormones, affective disorders, and gene-regulation: a re-examination. *Psychiatric Ann.* **1997**, 27, 773–778.
- 3 DUMAN, R. S., HENINGER, G. R., NESTLER, E. J., A molecular and cellular theory of depression. *Arch. Gen. Psychiatry* **1997**, 54, 597–606.
- 4 MANJI, H. K., MOORE, G. J., CHEN, G., Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol. Psychiatry* **2000**, 48, 740–754.
- 5 DUMAN, R. S., Novel therapeutic approaches beyond the serotonin receptor. *Biol. Psychiatry* **1998**, 44, 324–335.
- 6 HUDSON, C. J., YOUNG, L. T., LI, P. P., WARSH, J. J., CNS signal transduction in the pathophysiology and pharmacotherapy of affective disorders and schizophrenia. *Synapse* **1993**, 13, 278–293.
- 7 DREVETS, W. C., PRICE, J. L., SIMPSON JR., J. R., TODD, R. D., REICH, T., VANNIER, M., RAICHEL, M. E., Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **1997**, 386, 824–827.
- 8 DREVETS, W. C., Neuroimaging studies of mood disorders. *Biol. Psychiatry* **2000**, 48, 813–829.
- 9 STOLL, A. L., RENSHAW, P. F., YURGELUN-TODD, D. A., COHEN, B. M., Neuroimaging in bipolar disorder: What have we learned? *Biol. Psychiatry* **2000**, 48, 505–517.
- 10 SHELINE, Y. I., WANG, P. W., GADO, M. H., CSERNANSKY, J. G., VANNIER, M. W., Hippocampal atrophy in recurrent major depression. *Proc. Natl. Acad. Sci. USA* **1996**, 93, 3908–3913.
- 11 SHELINE, Y. I., 3D MRI Studies of Neuroanatomic changes in Unipolar Major Depression: the role of stress and medical co-morbidity. *Biol. Psychiatry* **2000**, 48, 791–800.

- 12 RAJKOWSKA, G., Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol. Psychiatry* **2000**, *48*, 766–777.
- 13 VAWTER, M. P., FREED, W. J., KLEINMAN, J. E., Neuropathology of bipolar disorder. *Biol. Psychiatry* **2000**, *48*, 486–504.
- 14 CZECH, B., MICHAELIS, T., WATANABE, T., FRAHM, J., DE BIURRUN, G., VAN KAMPEN, M., BARTOLOMUCCI, A., FUCHS, E., Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 12796–12801.
- 15 MIGUEL-HIDALGO, J. J., RAJKOWSKA, G., Morphological brain changes in depression: Can antidepressants reverse them? *CNS Drugs* **2002**, *16*, 361–372.
- 16 SHELIN, Y. I., GADO, M. H., KRAEMER, H. C., Untreated depression and hippocampal volume loss. *Am. J. Psychiatry* **2003**, *160*, 1516–1518.
- 17 DUMAN, R. S., MALBERG, J., NAKAGAWA, S., D'SA, C., Neuronal plasticity and survival in mood disorders. *Biol. Psychiatry* **2000**, *48*, 732–739.
- 18 DUMAN, R. S., MALBERG, J., NAKAGAWA, S., Regulation of adult neurogenesis by psychotropic drugs and stress. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 401–407.
- 19 NIBUYA, M., NESTLER, E. J., DUMAN, R. S., Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J. Neurosci.* **1996**, *16*, 2365–2372.
- 20 DAHMEN, N., FEHR, C., REUSS, S., HEIMKE, C., Stimulation of immediate early gene expression by desipramine in rat brain. *Biol. Psychiatry* **1997**, *42*, 317–323.
- 21 TORRES, G., HOROWITZ, J. M., LAFLAMME, N., RIVEST, S., Fluoxetine induces the transcription of genes encoding c-fos, corticotropin-releasing factor and its type 1 receptor in rat brain. *Neuroscience* **1998**, *87*, 463–477.
- 22 TUPLER, R., PERINI, G., GREEN, M. R., Expressing the human genome. *Nature* **2001**, *409*, 832–833.
- 23 BROWN, C. E., LECHNER, T., HOWE, L., WORKMAN, J. L., The many Hats of transcription coactivators. *Trends Biochem. Sci.* **2000**, *25*, 15–19.
- 24 CHEUNG, P., ALLIS, C. D., SASSONE-CORSI, P., Signaling to chromatin through histone modifications. *Cell* **2000**, *103*, 263–271.
- 25 PHIEL, C., ZHANG, F., HUANG, E. Y., GUENTHER, M. G., LAZZAR, M. A., KLEIN, P. S., Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J. Biol. Chem.* **2001**, *276*, 36734–36741.
- 26 ORPHANIDES, G., REINBERG, D., A unified theory of gene expression. *Cell* **2002**, *108*, 439–451.
- 27 SMALE, S. T., Core promoters: active contributors to combinatorial gene regulation. *Genes Dev.* **2001**, *15*, 2503–2508.
- 28 HSU, L.-C., LIU, S., ABEDINPOUR, F., BEECH, R. D., LAHTI, J. M., KIDD, V. J., GREENSPAN, J. A., YEUNG, C.-Y., The murine G + C-rich promoter binding protein mGPBP is required for promoter-specific transcription. *Mol. Cell Biol.* **2003**, *23*, 8773–8785.
- 29 CONKRIGHT, M. D., GUZMAN, E., FLECHNER, L., SU, A. I., HOGENESCH, J. B., MONTMINY, M., Genome-wide analysis of CREB target genes reveals a core promoter requirement for cAMP responsiveness. *Mol. Cell* **2003**, *11*, 1101–1108.
- 30 METZ, R., BANNISTER, A. J., SUTHERLAND, J. A., HAGEMEIER, C., O'ROURKE, E. C., COOK, A., BRAVO, R., KOUZARIDES, T., c-Fos-induced activation of a TATA-box-containing promoter involves direct contact with TATA-box-binding protein. *Mol. Cell Biol.* **1994**, *14*, 6021–6029.
- 31 DUMAN, R. S., Synaptic plasticity and mood disorders. *Mol. Psychiatry* **2002**, *7*, S29–S34.
- 32 KOCH, J. M., KELL, S., HINZE-SELCH, D., ALDENHOFF, J. B., Changes in CREB-phosphorylation during recovery from major depression. *J. Psychiatr. Res.* **2002**, *36*, 369–375.
- 33 ZUBENKO, G. S., HUGH III, H. B., MAHER, B. S., STIFFLER, J. S., ZUBENKO, W., MARAZITA, M. L., Genetic linkage of region containing the CREB1 gene to depressive disorders in women from families with recurrent, early-onset, major depression. *Am. J. Med. Genet.* **2002**, *114*, 980–987.
- 34 DOWLATSHAHI, D., MACQUEEN, G. M., WANG, J. F., YOUNG, L. T., Increased

- temporal cortex CREB concentrations and antidepressant treatment in major depression. *Lancet* **1998**, *352*, 1754–1755.
- 35 LONZE, B. E., GINTY, D. D., Function and regulation of CREB family transcription factors in the nervous system. *Neuron* **2002**, *35*, 605–623.
 - 36 FELINSKI, E. A., QUINN, P. G., The coactivator dTAF_{II}110/hTAF_{II}135 is sufficient to recruit a polymerase complex and activate basal transcription by CREB. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 13078–13083.
 - 37 LAMAS, M., MONACO, L., ZAZOPOULOS, E., LALLI, E., TAMIA, K., PENNA, L., MAZZUCHELLI, C., NANTEL, F., FOULKES, N. S., SASSONE-CORSI, P., CREM: a master-switch in the transcriptional response to cAMP. *Phil. Trans. Royal Soc. Lond. B Biol. Sci.* **1996**, *351*, 561–567.
 - 38 DWIVEDI, Y., RIZAVI, H. S., ROBERTS, R. C., CONLEY, R. C., TAMMINGA, C. A., PANDEY, G. N., Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. *J. Neurochem.* **2001**, *77*, 916–928.
 - 39 D'SA, C., DUMAN, R. S., Antidepressants and neuroplasticity. *Bipolar Disord.* **2002**, *4*, 183–194.
 - 40 SIUCIAK, J. A., LEWIS, D. R., WIEGAND, S. J., LINDSAY, R. M., Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol. Biochem. Behav.* **1997**, *56*, 131–137.
 - 41 SAARELAINE, T., HENDOLIN, P., LUCAS, G., KOPONEN, E., SAIRANEN, M., MACDONALD, E., AGERMAN, K., HAAPASALO, A., NAWA, H., ALOYZ, R., ERNFORS, P., CASTREN, E., Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.* **2003**, *23*, 349–357.
 - 42 CHEN, B., DOWLATSHAHI, D., MACQUEEN, G. M., WANG, J. F., YOUNG, L. T., Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol. Psychiatry* **2001**, *50*, 260–265.
 - 43 KAREGE, F., PERRET, G., BONDOLFI, G., SCHWALD, M., BERTSCHY, G., AUBRY, J. M., Decreased serum brain-derived neurotrophic factor in major depressed patients. *Psychiatry Res.* **2002**, *109*, 143–148.
 - 44 CHAO, M., Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nature Rev. Neurosci.* **2003**, *4*, 299–309.
 - 45 ALI, A., HOEFELICH, K. P., WOODGETT, J. R., Glycogen synthase kinase-3: properties, functions, and regulation. *Chem. Rev.* **2001**, *101*, 2527–2540.
 - 46 HONGISTO, V., SMEDS, N., BRECHT, S., HERDEGEN, T., COURTNEY, M. J., COFFEY, E. T., Lithium blocks the c-Jun stress response and protects neurons via its action on glycogen synthase kinase-3. *Mol. Cell Biol.* **2003**, *23*, 6027–6036.
 - 47 FRODIN, M., GAMMELTOFT, S., Role and regulation of 90-kDa ribosomal S6 kinase (RSK) in signal transduction. *Mol. Cell Endocrinol.* **1999**, *151*, 65–77.
 - 48 HARTWIG, J. H., THELEN, M., ROSEN, A., JANMEY, P. A., NARIN, A. C., ADEREM, A., MARCKS is an actin filament cross-linking protein regulated by protein kinase C and calcium-calmodulin. *Nature* **1992**, *356*, 618–622.
 - 49 STUMPO, D. J., BOCK, C. B., TUTTLE, J. S., BLACKSHEAR, P. J., MARCKS deficiency in mice leads to abnormal brain development and perinatal death. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 944–948.
 - 50 HERDEGEN, T., LEAH, J. D., Inducible and constitutive transcription factors in the mammalian nervous system: control of gene-expression by Jun, Fos, Krox, and CREB/ATF proteins. *Brain Res. Rev.* **1998**, *28*, 370–490.
 - 51 SHAULIAN, E., KARIN, M., AP-1 as a regulator of cell life and death. *Nature Cell Biol.* **2002**, *4*, E131–E136.
 - 52 POPOLI, M., GENNARELLI, M., RACAGNI, G., Modulation of synaptic plasticity by stress and antidepressants. *Bipolar Disord.* **2002**, *4*, 166–182.
 - 53 BERMAN, R. M., CAPPIELLO, A., ANAND, A., OREN, D. A., HENINGER, G. R., CHARNEY, D. S., KRYSTAL, J. H., Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* **2000**, *47*, 351–354.
 - 54 BOYER, P. A., SKOLNICK, P., FOSSUM, F. H., Chronic administration of imipramine and citalopram alters the expression of NMDA receptor subunit mRNAs in mouse brain. A quantitative in

- situ hybridization study. *J. Mol. Neurosci.* **1998**, *10*, 219–233.
- 55 PAUL, I. A., NOWAK, G., LAYER, R. T., POPIK, P., SKOLNICK, P., Adaptation of the N-methyl-D-aspartate receptor complex following chronic antidepressant treatments. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 95–102.
 - 56 WEST, A. E., CHEN, W. G., DALVA, M. B., DOLMETSCH, R. E., KORNHAUSER, J. M., SHAYWITZ, A. J., TAKASU, M. A., TAO, X., GREENBERG, M. E., Calcium regulation of neuronal gene expression. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 11024–11031.
 - 57 WEI, F., QIU, C.-S., LIAUW, J., ROBINSON, D. A., HO, N., CHATILA, T., ZHUO, M., Calcium-calmodulin-dependent protein kinase IV is required for fear memory. *Nature Neurosci.* **2002**, *5*, 573–579.
 - 58 SHEEHAN, T. P., NEVE, R. L., DUMAN, R. S., RUSSELL, D. S., Antidepressant effect of the calcium-activated tyrosine kinase Pyk2 in the lateral septum. *Biol. Psychiatry* **2003**, *54*, 540–551.
 - 59 EASTMAN, Q., GROSSCHEDL, R., Regulation of LEF-1/TCF transcription factors by Wnt and other signals. *Curr. Opin. Cell Biol.* **1999**, *11*, 233–240.
 - 60 SHARPE, C., LAWRENCE, N., MARTINEZ ARIAS, A., Wnt signalling: a theme with nuclear variations. *BioEssays* **2001**, *23*, 311–318.
 - 61 GALCERAN, J., MIYASHITA-LIN, E. M., DEVANEY, E., RUBENSTEIN, J. L. R., GROSSCHEDL, R., Hippocampus development and generation of dentate gyrus granule cells is regulated by LEF1. *Development* **2000**, *127*, 469–482.
 - 62 CHENN, A., WALSH, C. A., Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* **2002**, *297*, 365–369.
 - 63 BOURNAT, J. C., BROWN, A. M. C., SOLER, A. P., Wnt-1 dependent activation of the survival factor NF-kB in PC12 cells. *J. Neurosci. Res.* **2000**, *61*, 21–32.
 - 64 CHEN, G., MASANA, M. I., MANJI, H. K., Lithium regulates PKC-mediated intracellular cross-talk and gene-expression in the CNS *in vivo*. *Bipolar Disord.* **2000**, *2*, 217–236.
 - 65 CHEN, G., RAJKOWSKA, G., DU, F., SERAJI-BOZORGZAD, N., MANJI, H. K., Enhancement of hippocampal neurogenesis by lithium. *J. Neurochem.* **2000**, *74*, 1729–1734.
 - 66 WOOTEN, M. W., Function for NF-kB in neuronal survival: regulation by atypical protein kinase C. *J. Neurosci. Res.* **1999**, *58*, 607–611.
 - 67 ZHONG, H., MAY, M. J., JIMI, E., GHOSH, S., The phosphorylation status of nuclear NF-kappa-B determines its association with CBP/p300 or HDAC1. *Mol. Cell* **2002**, *9*, 625–636.
 - 68 MEFFERT, M. K., CHANG, J. M., WILTGEN, B. J., FANSELOW, M. S., BALTIMORE, D., NF-kB functions in synaptic signaling and behavior. *Nature Neurosci.* **2003**, *6*, 1072–1078.
 - 69 FURUKAWA, K., MATTSON, M. P., The transcription factor NF-kappaB mediates increases in calcium currents and decreases in NMDA- and AMPA/kainate-induced currents induced by tumor necrosis factor-alpha in hippocampal neurons. *J. Neurochem.* **1998**, *70*, 1876–1886.
 - 70 ALBENSI, B. C., MATTSON, M. P., Evidence for the involvement of TNF and NF-kappaB in hippocampal synaptic plasticity. *Synapse* **2000**, *35*, 151–159.
 - 71 MCKENNA, N. J., O'MALLEY, B. W., Combinatorial control of gene expression by nuclear receptors and co-regulators. *Cell* **2002**, *108*, 465–474.
 - 72 THE APA TASK FORCE ON LABORATORY TESTS IN PSYCHIATRY, The dexamethasone test suppression test: an overview of its current status in psychiatry. *Am. J. Psychiatry* **1987**, *144*, 1253–1652.
 - 73 GOLD, P. W., DREVETS, W. C., CHARNEY, D. S., New insights into the role of cortisol and the glucocorticoid receptor in severe depression. *Biol. Psychiatry* **2002**, *52*, 381–385.
 - 74 BELANOFF, J. K., ROTHSCHILD, A. J., CASSIDY, F., DEBATTISTA, C., BAULIEU, E.-E., SCHOLD, C., SCHATZBERG, A. F., An open label trial of C-1073 (Mifepristone) for psychotic major depression. *Biol. Psychiatry* **2002**, *52*, 386–392.
 - 75 BELANOFF, J. K., FLORES, B. H., KALEZHAN, M., SUND, B., SCHATZBERG, A. F., Rapid reversal of psychotic depression using Mifepristone. *J. Clin. Psychopharmacol.* **2001**, *21*, 516–521.
 - 76 MURPHY, B. E. P., FILIPINI, D., GHADIRIAN, A. M., Possible use of

- glucocorticoid receptor antagonists in the treatment of major depression: preliminary results using RU 486. *J. Psychiatr. Neurosci.* **1993**, *18*, 209–213.
- 77 MURPHY, B. E. P., Steroids and depression. *J. Steroid Biochem. Mol. Biol.* **1991**, *38*, 537–558.
 - 78 MEIJER, O. C., Co-regulator proteins and corticosteroid action in the brain. *J. Neuroendocrinol.* **2002**, *14*, 499–505.
 - 79 ROWAN, B. G., WEIGEL, N. L., O'MALLEY, B. W., Phosphorylation of steroid receptor coactivator-1. Identification of the phosphorylation sites and phosphorylation through the mitogen-activated protein kinase pathway. *J. Biol. Chem.* **2000**, *275*, 4475–4483.
 - 80 CIANA, P., GHISLETTI, S., MUSSI, P., EBERINI, I., VEGETO, E., MAGGI, A., Estrogen receptor α , a molecular switch converting transforming growth factor- α -mediated proliferation into differentiation in neuroblastoma cells. *J. Biol. Chem.* **2003**, *278*, 31737–31744.
 - 81 BOEKHOUDT, G. H., GUO, Z., BERESFORD, G. W., BOSS, J. M., Communication between NF-kappa B and Sp1 controls histone acetylation within the proximal promoter of the monocyte chemo-attractant protein 1 gene. *J. Immunol.* **2003**, *170*, 4139–4147.
 - 82 PEARCE, D., YAMAMOTO, K. R., Mineralocorticoid and glucocorticoid receptor activities distinguished by non-receptor factors at a composite regulatory element. *Science* **1993**, *259*, 1161–1165.
 - 83 SANTARELLI, L., SAXE, M., GROSS, C., SURGET, A., BATTAGLIA, F., DULAWA, S., WEISSTAUB, N., LEE, J., DUMAN, R., ARANCIO, O., BELZUNG, C., HEN, R., Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **2003**, *301*, 805–809.
 - 84 LEMONDE, S., TURECKI, G., BAKISH, D., DU, L., HRDINA, P. D., BOWN, C. D., SEQUIERA, A., NEENA, KUSHWAHA, N., MORRIS, S. J., BASAK, A., OU, X.-M., ALBERT, P. R., Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism is associated with major depression and suicide. *J. Neurosci.* **2003**, *23*, 8788–8799.
 - 85 MEIJER, O. C., WILLIAMSON, A., DALLMAN, M. F., PEARCE, D., Transcriptional repression of the 5-HT1A receptor promoter by corticosterone via mineralocorticoid receptors depends on the cellular context. *J. Neuroendocrinol.* **2000**, *12*, 245–254.
 - 86 HOYER, D., HANNON, J. P., MARTIN, G. R., Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol. Biochem. Behav.* **2002**, *71*, 533–554.
 - 87 RAYMOND, J. R., MUKHIN, Y. V., GELASCO, A., TURNER, J., COLLINGSWORTH, G., GETTYS, T. W., GREWAL, J. S., GARNOVSKAYA, M. N., Multiplicity of mechanisms of serotonin receptor signal transduction. *Pharmacol. Ther.* **2001**, *92*, 179–212.
 - 88 FRECHILLA, D., OTANO, A., DEL RIO, J., Effect of chronic antidepressant treatment on transcription factor binding activity in rat hippocampus and frontal cortex. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1998**, *22*, 787–802.
 - 89 THOME, J., SAKAI, N., SHIN, K.-H., STEFFEN, C., ZHANG, Y.-J., IMPEY, S., STORM, D., DUMAN, R. S., cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *J. Neurosci.* **2000**, *20*, 4030–4036.
 - 90 BILANG-BLEUEL, A., RECH, J., DE CARLI, S., HOLSBOER, F., REUL, J. M. H. M., Forced swimming evokes a biphasic response in CREB phosphorylation in extrahypothalamic limbic and neocortical brain structures in the rat. *Eur. J. Neurosci.* **2002**, *15*, 1048–1060.
 - 91 BARROT, M., OLIVIER, J. D. A., PERROTTI, L. I., DI LEONE, R. J., BERTON, O., EISCH, A. J., IMPEY, S., STORM, D. R., NEVE, R. L., YIN, J. C., ZACHARIOU, V., NESTLER, E. J., CREB activity in the nucleus accumbens shell controls gating of behavioral responses to emotional stimuli. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11435–11440.
 - 92 PLIAKAS, A., CARLSON, R. R., NEVE, R. L., KONRADI, C., NESTLER, E. J., CARLEZON, W. A. JR., Altered responsiveness to cocaine and increased immobility in the forced swim test associated with elevated CREB expression in the nucleus accumbens. *J. Neurosci.* **2001**, *21*, 7397–7403.

- 93 CHEN, A. C.-H., SHIRAYAMA, Y., SHIN, K.-H., NEVE, R. L., DUMAN, R. S., Expression of the cAMP response element binding protein (CREB) in hippocampus produces an anti-depressant effect. *Biol. Psychiatry* **2001**, 49, 753–762.
- 94 SHIRAYAMA, Y., CHEN, A. C.-H., NAKAGAWA, S., RUSSELL, D. S., DUMAN, R. S., Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J. Neurosci.* **2002**, 22, 3251–3261.
- 95 WALLACE, T., STELLITANO, K. E., NEVE, R. L., DUMAN, R. S., Effects of CREB expression in the basolateral amygdala on behavioral models of depression and anxiety. *Biol. Psychiatry* **2004**, 56, 151–160.
- 96 NEWTON, S. S., THOME, J., WALLACE, T. L., SHIRAYAMA, Y., SCHLESINGER, L., SAKAI, N., CHEN, J., NEVE, R., NESTLER, E. J., DUMAN, R. S., Inhibition of cAMP response element binding protein or dynorphin in the nucleus accumbens produces an antidepressant-like effect. *J. Neurosci.* **2002**, 22, 10883–10890.
- 97 CARLEZON, W. A. JR., THOME, J., OLSON, V. G., LANE-LADD, S. B., BRODKIN, E. S., HIROI, N., DUMAN, R. S., NEVE, R. L., NESTLER, E. J., Regulation of cocaine reward by CREB. *Science* **1998**, 282, 2272–2275.
- 98 NESTLER, E. J., BARROT, M., DiLEONE, R. J., EISCH, A. J., GOLD, S. J., MONTEGGIA, L. M., Neurobiology of depression. *Neuron* **2002**, 34, 13–25.

34

Pharmacogenetics and Pharmacogenomics of Antidepressant Drug Action

Ma-Li Wong

Abstract

The terms pharmacogenetics and pharmacogenomics are frequently used interchangeably. Pharmacogenetics studies genetically based inter-individual variability in response to drugs and susceptibility to drug-induced side effects. Pharmacogenomics is a new area of medical science that integrates genomics and therapeutics. The human genome sequence has been the starting point of pharmacogenomics, and it leads to a better understanding of interactions between drugs and organisms. Pharmacogenomics utilizes high-throughput technologies, which have been developed to make it possible for researchers to harness the wealth of genomic data toward the goal of improving therapeutics. It involves the systematic identification of all human genes and gene products, the study of human genetic variations, combined with changes in gene and protein expression over time, in health and disease states. This new area of investigation has provoked a paradigm shift in clinical and basic research: the prevalent reductionist approach has been challenged. Currently, studies focusing on one or a couple of genes are giving way to microarray experiments that simultaneously query multiple genes and systems. There has been considerable expectation in the potential impact of pharmacogenomics in the discovery of innovative, effective, and individualized treatments. In this chapter we discuss the complex issues facing pharmacogenomics research and the state of its art.

34.1 Introduction

Issues relevant to the effects of drugs on organisms, or pharmacodynamics and its interface with genetics and genomics, are detailed in this chapter. Pharmacokinetics factors are discussed in Chapter 35. This chapter discusses pharmacogenetics and pharmacogenomics aspects of antidepressant drug action. The former deals with inherited variations in drug effects, and the latter involves the systematic identifi-

cation of all human genes and gene products. First, we detail important aspects in pharmacogenetics/pharmacogenomics research and then we review pathways that have been studied.

The variability in clinical response to the main psychiatric drugs has remained a crucial problem in the management of patients. For antidepressants, the problems are complex and compounded. For instance, in addition to drug-induced adverse effects, symptom amelioration can take several weeks to occur (up to 8–10 weeks) after the initiation of treatment, and a significant proportion of patients continue to have residual symptoms during treatment. Therefore, multiple medication trials may be needed, and during this lengthy time period treated patients may continue to be symptomatic, endure social and employment problems, or attempt suicide.

The identification of predictors of antidepressant drug response would greatly help decrease symptomatic periods and improve treatment compliance in patients who do not respond well to a given initial antidepressant drug. Pharmacogenomics approaches could be useful in raising the efficacy and avoiding adverse effects, by stratifying the eligibility criteria for a given drug according to appropriate genetic markers. The lifetime prevalence of major depression is estimated at 21.3% and 12.7% in women and men, respectively. Taking into consideration the high prevalence of depression and the strong emphasis on its treatment with pharmacological agents, which make antidepressants drugs among the most frequently prescribed pharmacological agents, the ability to predict antidepressant drug response would have a considerable public health impact. But the difficulties in this field have been underscored by the complexity in accounting for variations in biological responses obtained by physiological or biological measures, such as plasma and CSF levels of hormones, neurotransmitters, or their metabolites and brain imaging.

It is likely that a significant proportion of biological variations could result from genetic variations. The scientific and medical communities now have an invaluable and fundamental resource in the 2.9 billion nucleotide base pair sequence of the human genome easily accessible on the Internet [1, 2]. The human genome project has provided the backbone needed for the development of novel molecular genetic approaches for dissecting the heterogeneity of drug responses in at least two different ways – first, by studying genetic polymorphisms, especially single nucleotide polymorphisms (SNPs), in genes/pathways that may influence drug response; and second, by identifying genes or patterns of genes that could be influenced by drug treatment. Those genes/patterns of gene transcription could help us understand the mechanism of action of drugs and also provide novel targets for drug development.

All available human genetic information thus far has enabled the identification of around 22 000 genes that encode protein [3]; this has been the result of a methodical effort to identify previously undiscovered genes of given protein families, which effort continues. It is evident that complete gene lists will enhance the search for medically relevant genes, so that we could list every protein kinase or transcription factor or scrutinize a chromosomal region of interest to distinguish every gene. It is believed that the genome contains over 10 million polymorphic sites in which

the minor allele is present in at least 1% in the human population (these are relatively 'common' polymorphisms). Rare allele variants are thought to be almost unlimited in number [4]. More than seven million variants have been deposited in public databases and mapped to the genome sequence. Single nucleotide polymorphisms, which are differences between individuals in a single base of the genomic sequence, represent the most common genetic variant in humans (<http://www.ncbi.nlm.nih.gov/SNP>). More than 1400 human genes have been associated with diseases in the Online Mendelian Inheritance in Man database (OMIM; <http://www.ncbi.nlm.nih.gov/Entrez>), but in general, these are related to single-gene disorders. Understanding complex disorders and traits, such as antidepressant drug response, will require an in-depth knowledge of physiological functions and of how sets of molecules work together, as well as insights into regulatory sequences and patterns of gene expression related to specific signals. Development of much of this understanding will benefit from the discovery of all the functional information contained in the human genome.

Molecular genetic approaches have noticeable strengths. Those include the notion that the genotype of a specific person is fundamentally invariable; therefore, it could be obtained at any point during a person's lifetime and that genetic information would be valid and unaltered by treatment or environment. Another advantage derives from the tremendous technological advances that have occurred in the last decade, which have refined the accuracy of genotyping techniques: errors have been minimized and they now have virtually no role in these analyses. Technological advances also have played a crucial role in producing the wealth of genomic information provided by the sequencing of the human [5], mouse [6], and rat [7] genomes; as well, advances in bioinformatics tools have made genomic information easily accessible (see Chapter 36). An additional strength is related to the fact that genomic information can be obtained from easily accessible sources, such as peripheral blood samples, buccal swabs, and many other tissues. Recent technological advances have decreased genotyping and sequencing costs, and this trend is expected to continue in the near future, making genetic testing more likely to be considered in the clinical setting.

34.2

Clinical Predictors of Antidepressant Response

Several studies have aimed at identifying predictors of response to antidepressants (for reviews see [8–11]). Biological markers, which include urinary and/or plasma monoamine metabolite levels, neuroendocrine markers (dexamethasone-suppression test), brain-imaging findings (subcortical hyperintensities), EEG findings, and demographic, personality, and clinical characteristics, have been tested as putative markers for antidepressant drug response. However, these studies have not resulted in robust findings that are clinically relevant.

34.3

Phenotype of Antidepressant Treatment

Characterization of phenotype has been a very challenging issue in pharmacogenomics research. The definition of the phenotype under investigation, its reliability and validity, are critical points. There are a minimum of two phenotypes of interest: response and adverse side effects. Both these phenotypes are complex to characterize. It has been recognized that both differences in individual drug response and susceptibility to side effects have a genetic basis [12–14]. Such differences represent particularly difficult problems for researchers, as those phenotypes seem to emerge from gene–environment interactions.

34.3.1

Phenotype: Treatment Response

Most studies rely on data obtained during short-term drug trials in which efficacy is monitored by standardized rating scales. Pharmacological and pharmacogenomics studies in depression have used the Hamilton Depression Rating Scale as their primary outcome measure. Assessment of drug response is complex, as investigators have to take into account placebo response, but most pharmacogenomics/pharmacogenetic studies do not include a placebo group, primarily because ethical considerations prevent investigators from withholding effective treatments from patients. Placebo response rates may approach 30%–40%, whereas antidepressant treatment response rates are around 60%–70% [15, 16]. The ratio of placebo to active treatment is high, suggesting that 50% or more of drug responders are actually displaying a placebo response, which significantly decreases the power of phenotypic discrimination. Studies with a placebo lead-in period can minimize this problem, but this type of design has been considered largely impractical for large studies. A further complication arises from what we know about the natural history of major depression. This disease has been characterized as a recurrent one; therefore, a proportion of patients may improve with time – they have symptomatic episodes and periods of recovery.

34.3.2

Phenotype: Susceptibility to Adverse Side Effects

The phenotype of drug-induced side effects also seem to be complex, especially when drug–drug interactions need to be considered or when comorbid disorders are present. Patients may be taking multiple medications or dietary supplements that can interfere with the pharmacokinetics (see Chapter 35) or pharmacodynamics of the antidepressant drug in use. A list including the possible side effects for tricyclics (TCA), monoamine oxidase inhibitors (MAOI), and newer, more specific antidepressants (such as SSRIs, SNRIs) is very long. Side effect profiles for these classes of drugs are extensively detailed in Chapters 6 (Monoaminergic-based Pharmacotherapy) and 16 (Clinical Pharmacology of New Classes of Antidepressant Drugs).

Here is a brief summary of common side effects of antidepressants:

- TCAs: dry mouth, blurred vision, sedation, dizziness, constipation, urinary hesitancy, orthostatic hypotension, weight gain, tremors.
- MAOIs: postural hypotension, insomnia, agitation, sedation. Strict dietary regimen that excludes foods and beverages having a high content of dietary amines (such as cheeses, yogurt, fermented or dry meats, wine, beer, etc.) is recommended to minimize the risk of hypertensive crisis.
- Newer antidepressant drugs: nausea, anxiety, agitation, insomnia, headache, diarrhea, sexual dysfunction. Newer antidepressant drugs in general have a better side effect profile than the older drugs.

Exacerbation of some symptoms within the spectrum of major depressive disorder (such as suicidality) during antidepressant treatment has been long noted, and experienced clinicians know that is prudent to closely monitor patients during initiation or change of medication. In fact, perceived increased suicidality has recently been fueling the controversy on the use of antidepressant medication in children.

34.4

Drug Response and Genes

Findings suggesting that genetic factors play a role in antidepressant drug response first emerged 40 years ago. Observational studies reported a high level of concordance of a given class of antidepressant (TCA or MAOI) treatment effect within first-degree relatives [17–19]. It has also been noted that a subset of patients respond (or do not respond) to a drug of the same class in a subsequent major depressive episode [20]. Even in the absence of family and twin studies, recent pharmacogenetic studies have benefited from these insights.

34.4.1

Studies on Candidate Genes for Antidepressant Response

Neither the neurobiology of mood disorders nor the mechanisms of action of antidepressants are completely known to date, even if knowledge is progressively accumulating [21]. Therefore, major difficulties in studies on relevant genes include the choice of the appropriate genetic polymorphisms to associate with the drug response, the need to assess multiple variables that are probably partially related to one another. Those variables contribute only small effects in sample sizes that are highly costly to generate and even so are not as large as desired.

34.4.2

Haplotypes

Pharmacogenetic studies have been faced with multiple challenges (Table 34.1) in making successful use of genetic and genomics information to determine bio-

medically relevant genetic variants for each phenotype. One of the most severe challenges concerns the problem of multiple testing. The wealth of SNP data in multiple candidate genes can increase to hundreds or thousands the number of SNPs one could test. Haplotypes are common patterns of DNA variations in the human genome sequence. Alleles comprising blocks of such SNPs in close physical proximity are often correlated, result in reduced genetic variability, and define a limited number of haplotype-tag SNPs. The identification of haplotypes within the human genome is one of the goals of the international HapMap project [22]. An international consortium which is developing a map of these patterns across the genome by determining the genotypes of one million or more sequence variants, their frequencies, and their degree of association, in DNA samples from populations across the globe – from Africa, Asia, and Europe. It is expected that the HapMap project will greatly facilitate the discovery of sequence variants that affect common diseases, which should also aid the development of diagnostic tools and enhance our ability to choose new targets for therapeutic intervention [22].

Table 34.1 Key issues in the pharmacogenetics of antidepressants, from reference [21]

Clinical

Retrospective vs. prospective studies
Sample size
Confidentiality
Individual and family informed consent
Genetic background
Ethnic stratification
Community consultation
Continuous vs. categorical outcome measures
Correctly assigning phenotypes
Choice of drug and treatment strategy
Treatment compliance
Placebo responses
Environmental contributions to treatment outcome
Shared environment
Replication of results across centers and populations

Molecular Genetics

Genome-wide SNP mapping
Candidate genes
Allele frequencies
Antidepressant-related gene discovery
SNP discovery
Functional characterization of polymorphisms
Examination of many SNPs in a few genes
Examination of a few SNPs in many genes
Coding vs. noncoding polymorphisms
Functional vs. nonfunctional polymorphisms
Consideration of haplotypes
Statistical approaches to multiple comparisons
Determining small effects in the context of multiple comparisons

34.4.3

Genetic Stratification

Pharmacogenetic studies have often used case-control design; such designs have the potential for problems due to undetected ethnic stratification between study groups [23, 24]. Family-based approaches have been suggested as an alternative strategy. In these studies, DNA is collected from parents and siblings of probands. Although family-based studies circumvent ethnic stratification, this design can present other problems, because they are less feasible and less powerful and their results might not always be generalizable [25]. Methods to help account for genetic stratification have been under development. Such techniques of genomic control for association studies are based on the assumption that study groups can be tested for the presence of stratification by assessing allele markers that are not associated with the phenotype of interest. In theory, about 40 unlinked markers need to be tested to achieve a 95% probability of detecting stratification in study groups larger than 200 individuals [26]. Correction factors or subject removal can be used to resolve stratification between groups [27, 28].

34.4.4

Pharmacogenetic Studies

Serretti's group published the first study providing evidence that genetic variation in the upstream regulatory region of a gene involved in the pharmacodynamics of antidepressant drugs can affect antidepressant drug response [29]. That work showed that patients having the *long* isoform of the serotonin transporter promoter had a better response to fluvoxamine than those with the *short* isoform ($p = 0.017$).

An overview of the literature on pharmacogenetic studies of antidepressant response is provided in Table 34.2. We reviewed studies on antidepressant drugs in mood disorders and verified that a number of studies have consistently confirmed the association of the 5-HTT *short* variant with worse response in Caucasians. Additional studies have included the tryptophan hydroxylase gene (TPH), the G-protein $\beta 3$ -subunit (G $\beta 3$) C825T, and the serotonin receptor 2A. Two important candidate systems for pharmacogenetic studies are discussed in the following sections.

Table 34.2 Studies on the pharmacogenetics of antidepressant response (modified from [88])

Authors	Reference	Patient Ethnicity (Number)	Design of the Clinical Trial	Gene Polymorphism	Findings
Smeraldi et al. (1998)	29	Italian (102) DSM-IV MD Delusional	Double blind 6 wk fluvoxamine 300 mg d ⁻¹ + pindolol 2.5 mg d ⁻¹ vs. fluvoxamine 300 mg d ⁻¹ + placebo	5-HTT 5-HTTLPR (promoter)	<i>l-l</i> homozygotes and <i>l-s</i> heterozygotes: better response to fluvoxamine than <i>s-s</i> homozygotes with addition of pindolol (no difference between the genotypes)
Benedetti et al. (1999)	89	Italian (68) DSM-IV BP1 depressed, nonpsychotic	Total sleep deprivation, 1 night	5-HTT 5-HTTLPR (promoter)	Better response in 5-HTTLPR <i>l-l</i> homozygotes
Kim et al. (2000)	33	Korean (120) DSM-III-R MD	Prospective, random assignment, 6 wk fluoxetine 20–50 mg d ⁻¹ or paroxetine 20–60 mg d ⁻¹	5-HTT 5-HTTLPR (promoter) VNTR (intron 2)	<i>s-s</i> 5-HTTLPR homozygotes: better response than <i>l-l</i> or <i>l-s</i> genotypes; <i>l-l</i> intron-2 homozygotes: better response than other genotypes
Yoshida et al. (2002)	34	Japanese (66) DSM-IV MD	Prospective, 6 wk fluvoxamine b.i.d., initial dose of 50 mg d ⁻¹ , increased to 100 mg d ⁻¹ after a week and then to 200 mg d ⁻¹ after another week	5-HTT 5-HTTLPR (promoter)	<i>s-s</i> 5-HTTLPR homozygotes: better response than <i>l-l</i> or <i>l-s</i> genotypes
Pollock et al. (2000)	90	Not specified (57 completed trial) DSM-IV MD nonpsychotic, nonbipolar	Double blind 12 wk paroxetine 20–30 mg d ⁻¹ vs. nortriptyline from 25 mg d ⁻¹ (per blood level, 50–150 ng mL ⁻¹)	5-HTT 5-HTTLPR (promoter)	Faster response to paroxetine in <i>l-l</i> homozygotes than <i>l-s</i> heterozygotes or <i>s-s</i> homozygotes; no difference among genotypes in response to nortriptyline
Zanardi et al. (2000)	91	Italian (60) DSM-IV MD nonpsychotic	Single-blind placebo run-in, 4 wk paroxetine 40 mg d ⁻¹	5-HTT 5-HTTLPR (promoter)	Presence of 1 copy of 5-HTTLPR associated with better and faster response to paroxetine <i>l-l</i> genotypes, better response than <i>l-s</i> ; <i>l-s</i> genotypes better than <i>s-s</i>

Table 34.2 (continued)

Authors	Reference	Patient Ethnicity (Number) Diagnosis	Design of the Clinical Trial	Gene Polymorphism	Findings
Mundo et al. (2001)	92	Not specified (63) BP I or II	Retrospective patients with history of antidepressant-induced mania (IM+) compared to patients with no history (IM-)	5-HTT 5-HTTLPR (promoter) VNTR (intron 2)	Excess frequency of 5-HTTLPR <i>s</i> allele and <i>s-s</i> homozygotes in IM+ group; no difference in VNTR allele or genotype frequency
Serretti et al. (2001a) Zanardi et al. (2001)	35 93	Italian (217) 144 (71 delusional) (40 delusional) Subset of 155 patients from [35] reanalyzed by Zanardi et al. [93]	Double blind 6 wk fluvoxamine 300 mg d ⁻¹ + pindolol 2.5 mg d ⁻¹ vs. fluvoxamine 300 mg d ⁻¹ + placebo (includes the sample reported by Smeraldi et al. [29])	Tryptophan hydroxylase TPH A218C 5-HTT 5-HTTLPR	TPH* <i>A/A</i> variant associated with slower response to fluvoxamine; 5-HTTLPR <i>l-l</i> and <i>l-s</i> associated with faster response to fluvoxamine; no interaction between TPH and 5-HTTLPR; no relationship of 5-HTTLPR association to diagnosis (UP/BP), delusions, or severity of depression [93]
Serretti et al. (2001b)	94	Italian (99)	Double blind 6 wk paroxetine 20–40 mg d ⁻¹ (overlaps with samples reported by Zanardi et al. [91] and Serretti et al. [95]) Pindolol 2.5 mg t.i.d. blindly added to 42 patients	Tryptophan hydroxylase TPH A ₂₁₈ C	TPH* <i>A/A</i> and TPH* <i>A/C</i> variants associated with poorer response to fluvoxamine but not to fluvoxamine + pindolol
Cusin et al. (2002)	37	Italian (443) 258 BP 195	Prospective, 6 wk fluvoxamine 300 mg d ⁻¹ (<i>n</i> = 307); paroxetine 20–40 mg d ⁻¹ (<i>n</i> = 136); pindolol 2.5 mg t.i.d. blindly added to 149–443 patients (overlaps with samples reported by Smeraldi et al. [29] and Serretti et al. [95])	5-HT-2A receptor 5-HT-2A–T ₁₀₂ C 5-HT2A–C ₁₄₂₀ T MAOA MAOA 30-bp repeat	5-HT-2A–C ₁₄₂₀ T associated with higher levels of HAMD at baseline and worse response but not significant using random regression model; 5-HT-2A–T102C and MAOA–30-bp repeat not associated with response

Table 34.2 (continued)

Authors	Reference	Patient Ethnicity (Number)	Design of the Clinical Trial	Gene Polymorphism	Findings
Takahashi et al. (2002)	96	Japanese (66) DSM-IV MD	Prospective, 6 wk fluvoxamine b.i.d., initial dose of 50 mg d ⁻¹ , increased to 100 mg d ⁻¹ after a week and then to 200 mg d ⁻¹ after another week	5-HTT 5-HTTLPR (promoter) VNTR (intron 2) TPH-A218C	These three polymorphisms did not affect the development of fluvoxamine-induced nausea; the incidence of nausea did not predict treatment response to fluvoxamine
Murphy et al. (2003)	97	American (264) DSM IV MD	Multicenter study (18 outpatient clinics); 8-wk double-blind randomized trial: paroxetine (<i>n</i> = 124) and mirtazepine (<i>n</i> = 122) in geriatric depression (all patients > 65 years of age (mean age 72±5))	5-HT2AR: T102C CYP2D6	5-HT2AR C/C genotype associated with discontinuations due to side effects and with side-effect severity in paroxetine-treated patients; 5-HT2AR genotype did not predict treatment outcome for either medication; T/C genotype had no effect on mirtazepine side effects
Serretti et al. (2001)	95	Italian (364) DSM-IV MD 197 BP 167	Prospective, 6 wk fluvoxamine 300 mg d ⁻¹ ; paroxetine 20–40 mg d ⁻¹ ; pindolol 2.5 mg t.i.d. blindly added to 130 patients (overlaps with samples reported by Smeraldi et al. [29], Zanardi et al. [91], and Serretti et al. [94])	Dopamine 2 receptor DRD2 Ser311Cys311, VNTR Dopamine D4 receptor DRD4 exon 3, 48-bp repeat	No association of either polymorphism with response (response for fluvoxamine and paroxetine analyzed together)
Zill et al. (2000)	98	German (76) DSM-IV MD 78 BP 10	Retrospective? Patients received a variety of treatments, including TCA (32%), noradrenalin and specific (27%), SSRI (10%), serotonin and noradrenalin uptake inhibitor (7%), ECT (10%), TMS (7%), combinations (7%)	G protein β3 subunit C ₈₅ T	TT homozygosity associated with better response to antidepressant treatment (all types)

Table 34.2 (continued)

Authors	Reference	Patient Ethnicity (Number) Diagnosis	Design of the Clinical Trial	Gene Polymorphism	Findings
Baghai et al. (2001)	99	German (121) 87 BP 34 DSM-IV MD	Retrospective, patients received a variety of treatments, including TCA ($n = 23$), mirtazapine ($n = 43$), SSRI ($n = 12$), venlafaxine ($n = 10$), ECT ($n = 17$), or rTMS ($n = 23$); 29 patients received combinations of treatments	Angiotensin-converting enzyme ACE <i>I/D</i>	<i>D</i> allele carriers had better response to treatments (lower HAM-D scores and more frequent remissions) and shorter duration of hospitalization; <i>I-I</i> homozygotes had higher number of treatments
Roberts et al. (2002)	100	New Zealand (160) DSMIII-R MD	Prospective, 6 wk randomized to fluoxetine ($n = 82$) or nortriptyline ($n = 78$); 72 completed an adequate trial of fluoxetine, and 54 completed an adequate trial of nortriptyline; recruited from a long-term clinical trial	<i>ABCB1</i> (or <i>MDR1</i>) gene C3435T	Homozygosity for 3435T alleles of <i>ABCB1</i> : a risk for nortriptyline-induced postural hypotension
Licinio et al. (2004)	53	Mexican Americans in Los Angeles (80) DSM IV MD	Prospective, randomized placebo lead-in, double-blind 8 wk treatment with fluoxetine or desipramine	CRHR1 rs1876828 rs242939 rs242941	Association between <i>GAG</i> haplotype and greater reduction in depression and anxiety scores in high-anxiety group only

34.5

Serotonin System

34.5.1

Serotonin Transporter (5-HTT)

5-HTT is the primary site for the action of SSRIs and other antidepressants that block the uptake of serotonin. It is located on presynaptic serotonergic nerve terminals. The two polymorphisms that have been studied in *SLC6A4*, the gene that encodes 5-HTT, are: (1) *5-HTTLPR* (5-HTT-linked polymorphic region), which has been extensively studied, and (2) a variable tandem repeat (VNTR) in the second intron, which has three alleles (*STin2*9*, *STin2*10*, and *STin2*12*).

Subsequent to the studies of O'Reilly et al. [30] assessing responses to the MAOI tranilcipromine in a two-generation family, Dr. Serretti's group reported evidence for preferential transmission of fluvoxamine response in nuclear families [19]. Following a report of the possible association of *5-HTTLPR* polymorphism with affective disorders [31], *5-HTTLPR* was studied in association with SSRI response. Because SSRIs act directly on the serotonin system, differences at this locus could result in differences in therapeutic response [32]. Consistent with this hypothesis, several studies found an association of the short (s) allele in the *5-HTTLPR* site with a poor response to antidepressant treatment. It is noteworthy that ethnicity may influence this association. In Korean and Japanese patients, Kim et al. [33] and Yoshida et al. [34], respectively, reported an association of the *short* variant of 5-HTT with better treatment response. Kim et al. [33] also found an association with the intron-2 VNTR.

34.5.2

Tryptophan Hydroxylase

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of serotonin. The *TPH*A/A* variant was associated with a slower response to fluvoxamine ($p = 0.01$; [35]). Variants *TPH*A/A* and *TPH*A/C* were associated with poorer response to paroxetine [36].

34.5.3

Serotonin 2A Receptor Gene

Two intronic polymorphisms in the serotonin 2A receptor gene *5-HT-2A* have been studied (T102C and C1420T). C1420T was associated with more severe depressive symptoms, as assessed by HAMD scale scores at baseline, but neither of these two polymorphisms affected antidepressant drug response [37].

34.6

Neuroendocrine System

Evidence supporting the disruption of hypothalamic–pituitary–adrenal (HPA) axis function in depression has accumulated and includes the following important clinical findings in chronological order: (1) increased 24-h cortisol production [38], (2) lack of suppression of plasma cortisol levels during the dexamethasone-suppression test [39], (3) increased cerebrospinal fluid CRH levels [40], (4) dysregulation of HPA responses during exogenous CRH administration [41–43], and (5) loss of the negative correlation between plasma cortisol and serial CSF CRH [44]. Studies have also demonstrated that several antidepressants of different classes suppress CRH gene expression [45–47] in rodents and in depressed [48] and healthy humans [49]. Suppression of CRH activity could therefore be a common final effect of antidepressant treatment. Corticotropin-releasing hormone receptor type 1 (CRHR1) seems a logical candidate gene for antidepressant-mediated responses [50–52].

Recently, we reported an association of CRHR1 genotypes with the phenotype of antidepressant treatment response in 80 depressed Mexican Americans who completed a randomized placebo lead-in, double-blind, 8-week treatment with fluoxetine or desipramine [53]. Patients were classified into a high-anxiety group [Hamilton rating scales for anxiety (HAM-A) of 18 or higher] and a low-anxiety group (HAM-A lower than 18). Haplotypic association between CRHR1, tested using the haplotype-tag single nucleotide polymorphisms (htSNPs) rs1876828, rs242939, and rs242941, revealed that in the high-anxiety group there was a relative greater reduction in HAM-A and HAM-D scores in patients homozygous for the GAG haplotype than in heterozygotes. Those associations were not found in the low-anxiety group. These findings suggest that variations in the CRHR1 gene may affect response to drugs that target CRHR1.

34.7

Microarray Studies

Major gaps in the understanding of the pathophysiology of major depression have hampered our ability to improve treatment. In a recent perspective article, Mirnics and Pevsner [54] provided an overview of the potential, findings, challenges, and directions of the use of microarray technology to study the biology of CNS disease. High-throughput large-scale gene-expression analysis is expected to help fill essential gaps in our understanding of the relationship between genotype and phenotype, as well as to help in the search for the etiology of complex multifaceted disorders. This task is particularly challenging for psychiatry, because it has to rely on the limited availability of postmortem brain tissue, which has presented multiple challenges, presented below.

34.7.1

CNS Tissue Heterogeneity

Several subpopulations of cells with large phenotypic diversity are present in brain samples; therefore, it is expected that even large changes in gene-transcription levels in a small subpopulation of cells may be hard to detect, because these changes would be masked by other changes in gene-transcription levels in the whole tissue sample. This is reflected in the relative changes in the expression levels, which generally do not reach a two-fold difference when experimental and control brain samples are compared [54, 55]. These small relative changes result in substantial overlap between real differences in expression and noise. Because of the cellular heterogeneity of brain tissue, careful experimental design, combined with extensive data verification and conservative interpretation of data, are requisites for studies of postmortem brain tissue.

34.7.2

CNS Tissue Complexity

Transcripts are most abundant in the neuron soma, but the corresponding proteins are often localized in axonal projections or nerve terminals, which are generally located far away from the cell soma. These facts have to be taken into account during data interpretation [56], because gene expression changes and protein changes may occur in different brain compartments. Moreover, the concentrations of some proteins are not transcriptionally regulated; therefore, transcription and protein levels might be regulated in the opposite direction.

34.7.3

CNS Nosological Classification of Diseases

The broad clinical phenotypes of brain disease need to be taken into account. Even single-gene disorders (such as adrenoleukodystrophy) can display a broad range of clinical presentations. Diseases can also have a continuum of clinical phenotypes [57].

34.7.4

Gene–Environment Interactions

The genetic makeup and lifestyle of individual subjects are diverse and can be reflected in their transcription profiles. Other medical conditions such as age, gender, ethnicity, postmortem interval, drug treatment, and use of illicit substances, to mention the most important ones, may also be reflected in individual transcriptomes. Data obtained from animal models of chronic drug treatment, especially data acquired from studies of nonhuman primates, can be helpful [58].

34.7.5

Sample Integrity

It is an essential aspect of any microarray experiment that RNA needs to be of high integrity. Brain pH seems to best predict whether RNA will be recovered intact; samples with a pH less than 6.25 rarely contain intact RNA. Postmortem interval alone seems to be a poor predictor of sample integrity [59]; agonal factors have a major impact on gene-expression profiles [60]. Systematic changes in gene expression associated with brain tissue pH were recently reported [61].

34.7.6

Postmortem Microarray Studies

Findings in postmortem brain tissue of individuals have been reported:

- Alzheimer's disease – studies report decreased expression of nerve terminal proteins (synaptophysin, synapsin, synaptotagmin) [62–66]. Changes in 89 genes have correlated with premortem mental status and neurofibrillary tangle index [67] in the hippocampal CA1 region.
- Cocaine overdose – up-regulation of glutamate receptors in the ventral tegmental area was reported [68].
- Ethanol abuse – myelination, cell-cycle transcripts, and cAMP-related transcripts may be implicated in this condition [55, 69].
- Multiple sclerosis – studies implicate genes involved in inflammation/immune responses and myelination processes [70–72].
- Rett syndrome – increased levels of glial transcripts and decreased expression of GABA and glutamate receptors have been reported [73].
- Schizophrenia – presynaptic release, metabolic pathways, GABA-glutamate transcripts, and glial function may be implicated in this disease [56, 74–79]. Microarray studies have also implicated the *RGS4* gene [80] in schizophrenia.

Microarrays studies have yet to address postmortem changes in individuals having major depression or bipolar disorder.

34.7.7

Patterns of Gene Transcription Induced by Antidepressant Drug Treatment

Data from microarray studies focused on antidepressant effects in animal models have started to accumulate. Studies using whole brain tissues were not able to find transcription changes in *CREB* and *CRH* [81, 82], but such changes were found by Drigues et al. [83] in the rat hippocampus. Landgrebe et al. [82] described a predominant down-regulation of gene transcription in whole brain after treatment with mirtazapine and paroxetine, which was also found in the hypothalamus [84]. The synaptic machinery has been implicated in the responses to antidepressant treatment that occur in the rat frontal cortex (vesicle-associated membrane protein-2/

synaptobrevin-2) [85], hippocampus (synaptophysin) [83], hypothalamus (SC2 synaptic glycoprotein, syntaxin 2, vesicle-associated membrane protein-1) [84] or after electroconvulsive seizure therapy (ECS) [85]. ECS changed the regulation of several genes in the hippocampus that are involved in the mediation of neurogenesis and cell proliferation and in angiogenic–endothelial signaling, such as genes encoding neuritin, nerve growth factor, stem cell factor, vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and basic fibroblast growth factor (FGF-2) [86]. Cellular functions in the hypothalamus have also been implicated in antidepressant effects, including protein synthesis, scaffolding/intracellular transport, and mitochondrial function [84]. Antidepressants interfere with an array of genes involved in signaling, survival, and protein metabolism in the fronto-temporal cortices [87].

34.8

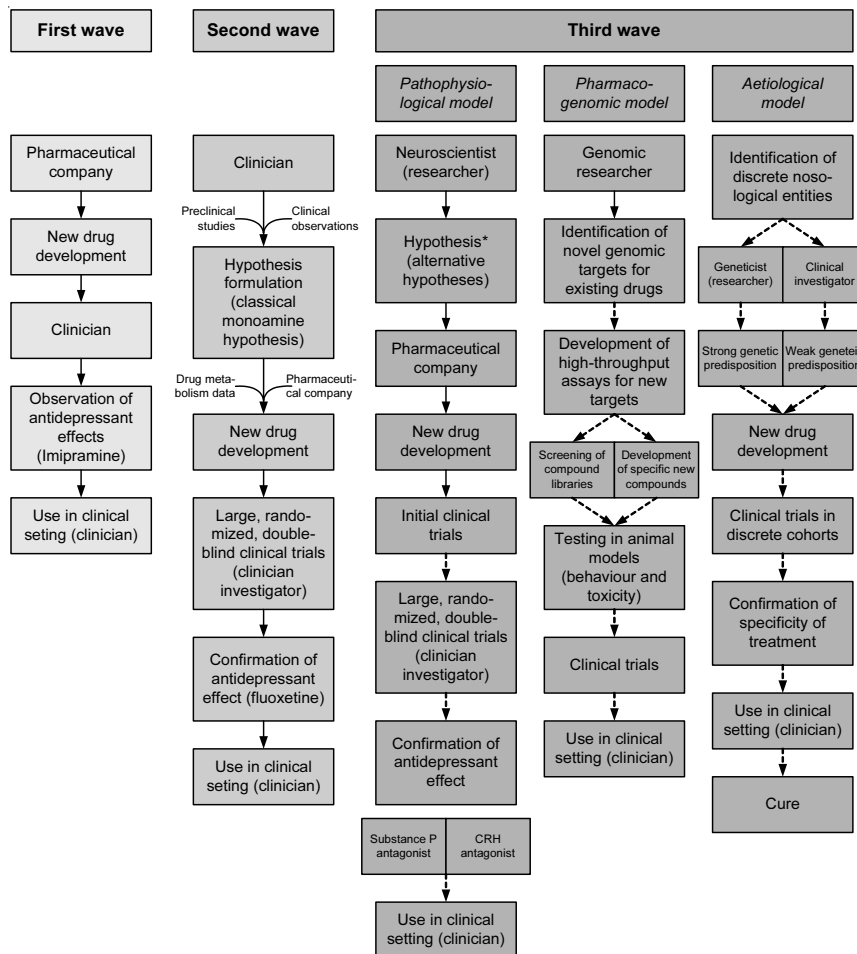
Conclusions

At present there are no accepted predictors of clinical response to specific antidepressants. The choice of medication is arbitrary and largely based on their side-effect profiles. Each drug trial can last 6–8 weeks; if patients do not respond to one drug, another one is tried. After each failure, the likelihood that patients will become noncompliant increases.

Much continues to be unknown about the biology of major depression; thus, pharmacogenetic and pharmacogenomics perspectives may fulfill the promise for the development of customized treatments, and they also represent good starting points for understanding the pathophysiological mechanisms underlying mood disorders. All pharmacogenetic studies performed to date have been inspired by the theories arising from neurobiological research on the pathogenesis of these disorders. We recently reviewed the progression of antidepressant drug production and proposed that the newer recent antidepressant have set on course a paradigm shift in the strategies for drug discovery in depression [88]. In fact, we hypothesize that the pharmacogenomic model for drug discovery will play a significant role in the present (third) wave of antidepressant production (Figure 34.1).

Figure 34.1 Strategies for antidepressant drug discovery, showing the progression from drug production to marketing in each ‘wave’ of antidepressant drug development. In the first wave, new compounds were produced by pharmaceutical companies and made available for clinicians to test. Observations of antidepressant effects were collected by chance for iproniazid and based on a hunch for imipramine. We selected imipramine as the prototypical drug of the first wave because it continues to be used today. Clinical observations of drug effects and preclinical studies

were the driving forces for the second wave of drug development. During the second wave, the regulation of clinical trials developed at a fast pace and clinician investigators had to take into account several regulatory and ethical issues. All drugs that entered the U.S. market showed clear superiority to placebo in large randomized double-blind trials. During the second wave, all compounds were developed under the classical monoamine hypothesis; we selected fluoxetine as a prototypical drug of this wave, as it was one of the first drugs to be developed and became extremely popular.



The third wave of antidepressant drug development has branched into parallel and complementary processes that can be generalized into three hypothetical strategies on the basis of pathophysiological models, pharmacogenomic models, and etiological models. In these models, solid lines represent processes that have already occurred and broken lines represent hypothetical processes that are in development or that we predict will occur in the future. In the pathophysiological model, we use two examples of drugs (antagonists of substance P and antagonists of corticotropin-releasing hormone) that represent proof-of-concept for translational research in depression. In the pharmacogenomic and etiological models, it is likely that large randomized trials

may not be relevant, because discrete populations could possess specific pharmacogenetic targets/polymorphisms or defined nosological entities, respectively. The driving forces of the third wave are the researchers who have formulated or will formulate pathophysiological, pharmacological, and etiological models. It will only be appropriate to define a cure once there is a defined etiological cause. In this context, 'cure' is defined as a specific treatment that restores the physiological function(s) of an identifiable genetic or environmental variation, and prevention will ideally be achieved with minimal adverse drug reactions.

* Alternative working hypotheses include neuroendocrine, neuroimmune, neuroprotection, and neurogenesis (from reference [88]).

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References

- 1 WEINSHILBOUM, R., Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase. *Drug Metab. Dispos.* **2001**, 29, 601–605.
- 2 DREWS, J., Drug discovery: a historical perspective. *Science* **2000**, 287, 1960–1964.
- 3 BENTLEY, D. R., Genomes for medicine. *Nature* **2004**, 429, 440–445.
- 4 KRUGLYAK, L., NICKERSON, D. A., Variation is the spice of life. *Nat. Genet.* **2001**, 27, 234–236.
- 5 LANDER, E. S., LINTON, L. M., BIRREN, B., NUSBAUM, C., ZODY, M. C., BALDWIN, J., et al., Initial sequencing and analysis of the human genome. *Nature* **2001**, 409, 860–921.
- 6 WATERSTON, R. H., LINDBLAD-TOH, K., BIRNEY, E., ROGERS, J., ABRIL, J. F., AGARWAL, P., et al., Initial sequencing and comparative analysis of the mouse genome. *Nature* **2002**, 420, 520–562.
- 7 GIBBS, R. A., WEINSTOCK, G. M., METZKER, M. L., MUZNY, D. M., SODERGREN, E. J., SCHERER, S., et al., Genome sequence of the brown Norway rat yields insights into mammalian evolution. *Nature* **2004**, 428, 493–521.
- 8 BIELSKI, R. J., FRIEDEL, R. O., Prediction of tricyclic antidepressant response: a critical review. *Arch. Gen. Psychiatry* **1976**, 33, 1479–1489.
- 9 GOODWIN, F. K., Predictors of antidepressant response. *Bull. Menninger Clin.* **1993**, 57, 146–160.
- 10 JOYCE, P. R., PAYKEL, E. S., Predictors of drug response in depression. *Arch. Gen. Psychiatry* **1989**, 46, 89–99.
- 11 SCHATZBERG, A. F., Noradrenergic versus serotonergic antidepressants: predictors of treatment response. *J. Clin. Psychiatry* **1998**, 59 (Suppl. 14), 15–18.
- 12 GARROD, A. E., *Inborn Errors of Metabolism*. Oxford: Oxford University Press, **1909**.
- 13 GARROD, A. E., The incidence of alcaptonuria. *Lancet* **1902**, 2, 1616–1620.
- 14 MOTULSKY, A. G., Drug reactions, enzymes, and biochemical genetics. *J. Am. Med. Assoc.* **1957**, 165, 835–837.
- 15 BERRETTINI, W., Psychiatric pharmacogenetics: a developing science. *Neuropsychopharmacology* **2002**, 26, 128–129.
- 16 MALHOTRA, A. K., MURPHY JR., G. M., KENNEDY, J. L., Pharmacogenetics of psychotropic drug response. *Am. J. Psychiatry* **2004**, 161, 780–796.
- 17 PARE, C. M., REES, L., SAINSBURY, M. J., Differentiation of two genetically specific types of depression by the response to antidepressants. *Lancet* **1962**, 2, 1340–1343.
- 18 ANGST, J., A clinical analysis of the effects of tofranil in depression: longitudinal and follow-up studies. Treatment of blood-relations. *Psychopharmacologia* **1961**, 2, 381–407.
- 19 FRANCHINI, L., SERRETTI, A., GASPERINI, M., SMERALDI, E., Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. *J. Psychiatr. Res.* **1998**, 32, 255–259.
- 20 PARE, C. M., MACK, J. W., Differentiation of two genetically specific types of depression by the response to antidepressant drugs. *J. Med. Genet.* **1971**, 8, 306–309.
- 21 WONG M.-L., LICINIO, J., Research and treatment approaches to depression. *Nature Rev. Neurosci.* **2001**, 2, 343–351.
- 22 The International HapMap Project. *Nature* **2003**, 426, 789–796.
- 23 MALHOTRA, A. K., GOLDMAN, D., Benefits and pitfalls encountered in psychiatric genetic association studies. *Biol. Psychiatry* **1999**, 45, 544–550.
- 24 PATERSON, A. D., Case-control association studies in complex traits: the end of an era? *Mol. Psychiatry* **1997**, 2, 277–278.
- 25 BRUNN, T. G., EWALD, H., Selection bias of susceptibility genes possible when

- using parent-offspring trios in genetic association studies. *Mol. Psychiatry* **1999**, *4*, 415–416.
- 26 PRITCHARD, J. K., ROSENBERG, N. A., Use of unlinked genetic markers to detect population stratification in association studies. *Am. J. Hum. Genet.* **1999**, *65*, 220–228.
 - 27 DEVLIN, B., ROEDER, K., WASSERMAN, L., Genomic control for association studies: a semiparametric test to detect excess-haplotype sharing. *Biostatistics* **2000**, *1*, 369–387.
 - 28 XU, K., LIU, X. H., NAGARAJAN, S., GU, X. Y., GOLDMAN, D., Relationship of the delta-opioid receptor gene to heroin abuse in a large Chinese case/control sample. *Am. J. Med. Genet.* **2002**, *110*, 45–50.
 - 29 SMERALDI, E., ZANARDI, R., BENEDETTI, F., DI BELLA, D., PEREZ, J., CATALANO, M., Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Mol. Psychiatry* **1998**, *3*, 508–511.
 - 30 O'REILLY, R. L., BOGUE, L., SINGH, S. M., Pharmacogenetic response to antidepressants in a multicas family with affective disorder. *Biol. Psychiatry* **1994**, *36*, 467–471.
 - 31 COLLIER, D. A., STOBBER, G., LI, T., HEILS, A., CATALANO, M., DI BELLA, D., et al., A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol. Psychiatry* **1996**, *1*, 453–460.
 - 32 LESCH, K. P., Serotonergic gene expression and depression: implications for developing novel antidepressants. *J. Affect Disord.* **2001**, *62*, 57–76.
 - 33 KIM, D. K., LIM, S. W., LEE, S., SOHN, S. E., KIM, S., HAHN, C. G., et al., Serotonin transporter gene polymorphism and antidepressant response. *Neuroreport* **2000**, *11*, 215–219.
 - 34 YOSHIDA, K., ITO, K., SATO, K., TAKAHASHI, H., KAMATA, M., HIGUCHI, H., et al., Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, *26*, 383–386.
 - 35 SERRETTI, A., ZANARDI, R., ROSSINI, D., CUSIN, C., LILLI, R., SMERALDI, E., Influence of tryptophan hydroxylase and serotonin transporter genes on fluvoxamine antidepressant activity. *Mol. Psychiatry* **2001**, *6*, 586–592.
 - 36 SERRETTI, A., ZANARDI, R., CUSIN, C., ROSSINI, D., LORENZI, C., SMERALDI, E., Tryptophan hydroxylase gene associated with paroxetine antidepressant activity. *Eur. Neuropsychopharmacol.* **2001**, *11*, 375–380.
 - 37 CUSIN, C., SERRETTI, A., ZANARDI, R., LATTUADA, E., ROSSINI, D., LILLI, R., et al., Influence of monoamine oxidase A and serotonin receptor 2A polymorphisms in SSRI antidepressant activity. *Int. J. Neuropsychopharmacol.* **2002**, *5*, 27–35.
 - 38 SACHAR, E. J., HELLMAN, L., FUKUSHIMA, D. K., GALLAGHER, T. F., Cortisol production in depressive illness: a clinical and biochemical clarification. *Arch. Gen. Psychiatry* **1970**, *23*, 289–298.
 - 39 CARROLL, B. J., FEINBERG, M., GREDEN, J. F., A specific laboratory test for the diagnosis of melancholia. *Arch. Gen. Psychiatry* **1981**, *38*, 15–22.
 - 40 NEMEROFF, C. B., WILDERLOV, E., BISETTE, G., WALLEUS, H., KARLSSON, I., EKLUND, K., et al., Elevated concentrations of CSF corticotropin-releasing-factor-like immunoreactivity in depressed patients. *Science* **1984**, *226*, 1342–1344.
 - 41 GOLD, P. W., CHROUSOS, G., KELLNER, C., POST, R., ROY, A., AUGERINOS, P., et al., Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am. J. Psychiatry* **1984**, *141*, 619–627.
 - 42 HOLSBOER, F., GIRKEN, A., STALIA, G. K., MULLER, O. A., Blunted corticotropin and normal cortisol response to human corticotropin-releasing factor in depression. *New Engl. J. of Med.* **1984**, *311*, 1127.
 - 43 GOLD, P. W., LORIAUX, D. L., ROY, A., KLING, M. A., CALABRESE, J. R., KELLNER, C. H., et al., Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. *N. Engl. J. Med.* **1986**, *314*, 1329–1335.
 - 44 WONG, M. L., KLING, M. A., MUNSON, P. J., LISTWAK, S., LICINIO, J., PROLO, P.,

- et al., Pronounced and sustained central hypnoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl. Acad. Sci. USA* **2000**, 97, 325–330.
- 45 BRADY, L. S., WHITFIELD JR., H. J., FOX, R. J., GOLD, P. W., HERKENHAM, M., Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain. Therapeutic implications. *J. Clin. Invest.* **1991**, 87, 831–837.
 - 46 BRADY, L. S., GOLD, P. W., HERKENHAM, M., LYNN, A. B., WHITFIELD JR., H. J., The antidepressants fluoxetine, idazoxan and phenelzine alter corticotropin-releasing hormone and tyrosine hydroxylase mRNA levels in rat brain: therapeutic implications. *Brain Res.* **1992**, 572, 117–125.
 - 47 REUL, J. M., STEC, I., SODER, M., HOLLSBOER, F., Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic–pituitary–adrenocortical system. *Endocrinology* **1993**, 133, 312–320.
 - 48 GOLD, P. W., CHROUSOS, G. P., Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs. low CRH/NE states. *Mol. Psychiatry* **2002**, 7, 254–275.
 - 49 MICHELSON, D., GALLIVEN, E., HILL, L., DEMITRACK, M., CHROUSOS, G., GOLD, P., Chronic imipramine is associated with diminished hypothalamic–pituitary–adrenal axis responsivity in healthy humans. *J. Clin. Endocrinol. Metab.* **1997**, 82, 2601–2606.
 - 50 PERRIN, M. H., DONALDSON, C. J., RUOPING, C., LEWIS, K. A., VALE, W. W., Cloning and functional expression of a rat brain corticotropin releasing factor (CRF) receptor. *Endocrinology* **1993**, 133, 3058–3061.
 - 51 WONG, M. L., LICINIO, J., PASTERNAK, K. I., GOLD, P. W., Localization of corticotropin-releasing hormone (CRH) receptor mRNA in adult rat brain by in situ hybridization histochemistry. *Endocrinology* **1994**, 135, 2275–2278.
 - 52 POTTER, E., SUTTON, S., DONALDSON, C., CHEN, R., PERRIN, M., LEWIS, K., et al., Distribution of corticotropin-releasing factor receptor mRNA expression in the rat brain and pituitary. *Proc. Natl. Acad. Sci. USA* **1994**, 8777–8781.
 - 53 LICINIO, J., O’KIRWAN, F., IRIZARRY, K., MERRIMAN, B., THAKUR, S., JEPSON, R., et al., Association of a corticotropin-releasing hormone receptor 1 haplotype and antidepressant treatment response in Mexican-Americans. *Mol. Psychiatry* **2004**, 9, 237–251.
 - 54 MIRNICS, K., PEVSNER, J., Progress in the use of microarray technology to study the neurobiology of disease. *Nat. Neurosci.* **2004**, 7, 434–439.
 - 55 LEWOHL, J. M., WANG, L., MILES, M. F., ZHANG, L., DODD, P. R., HARRIS, R. A., Gene expression in human alcoholism: microarray analysis of frontal cortex. *Alcohol Clin. Exp. Res.* **2000**, 24, 1873–1882.
 - 56 PONGRAC, J., MIDDLETON, F. A., LEWIS, D. A., LEVITT, P., MIRNICS, K., Gene expression profiling with DNA microarrays: advancing our understanding of psychiatric disorders. *Neurochem. Res.* **2002**, 27, 1049–1063.
 - 57 LEWIS, D. A., LEVITT, P., Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci* **2002**, 25, 409–432.
 - 58 PIERRI, J. N., CHAUDRY, A. S., WOO, T. U., LEWIS, D. A., Alterations in chandelier neuron axon terminals in the prefrontal cortex of schizophrenic subjects. *Am. J. Psychiatry* **1999**, 156, 1709–1719.
 - 59 HARRISON, P. J., HEATH, P. R., EASTWOOD, S. L., BURNET, P. W., McDONALD, B., PEARSON, R. C., The relative importance of premortem acidosis and postmortem interval for human brain gene expression studies: selective mRNA vulnerability and comparison with their encoded proteins. *Neurosci. Lett.* **1995**, 200, 151–154.
 - 60 TOMITA, H., VAWTER, M. P., WALSH, D. M., EVANS, S. J., CHOUDARY, P. V., LI, J., et al., Effect of agonal and post-mortem factors on gene expression profile: quality control in microarray analyses of postmortem human brain. *Biol. Psychiatry* **2004**, 55, 346–352.
 - 61 LI, J. Z., VAWTER, M. P., WALSH, D. M., TOMITA, H., EVANS, S. J., CHOUDARY, P. V., et al., Systematic changes in gene expression in postmortem human brains

- associated with tissue pH and terminal medical conditions. *Hum. Mol. Genet.* **2004**, *13*, 609–616.
- 62 COLANGELO, V., SCHURR, J., BALL, M. J., PELAEZ, R. P., BAZAN, N. G., LUKIW, W. J., Gene expression profiling of 12633 genes in Alzheimer hippocampal CA1: transcription and neurotrophic factor down-regulation and up-regulation of apoptotic and pro-inflammatory signaling. *J. Neurosci. Res.* **2002**, *70*, 462–473.
 - 63 LORING, J. F., WEN, X., LEE, J. M., SEILHAMER, J., SOMOGYI, R., A gene expression profile of Alzheimer's disease. *DNA Cell Biol.* **2001**, *20*, 683–695.
 - 64 MUFSON, E. J., COUNTS, S. E., GINSBERG, S. D., Gene expression profiles of cholinergic nucleus basalis neurons in Alzheimer's disease. *Neurochem. Res.* **2002**, *27*, 1035–1048.
 - 65 YAO, P. J., ZHU, M., PYUN, E. I., BROOKS, A. I., THERIANOS, S., MEYERS, V. E., et al., Defects in expression of genes related to synaptic vesicle trafficking in frontal cortex of Alzheimer's disease. *Neurobiol. Dis.* **2003**, *12*, 97–109.
 - 66 PASINETTI, G. M., Use of cDNA microarray in the search for molecular markers involved in the onset of Alzheimer's disease dementia. *J. Neurosci. Res.* **2001**, *65*, 471–476.
 - 67 BLALOCK, E. M., GEDDES, J. W., CHEN, K. C., PORTER, N. M., MARKESBERY, W. R., LANDFIELD, P. W., Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 2173–2178.
 - 68 ALBERTSON, D. N., PRUETZ, B., SCHMIDT, C. J., KUHN, D. M., KAPATOS, G., BANNON, M. J., Gene expression profile of the nucleus accumbens of human cocaine abusers, evidence for dysregulation of myelin. *J. Neurochem.* **2004**, *88*, 1211–1219.
 - 69 LEWOHL, J. M., DODD, P. R., MAYFIELD, R. D., HARRIS, R. A., Application of DNA microarrays to study human alcoholism. *J. Biomed. Sci.* **2001**, *8*, 28–36.
 - 70 MYCKO, M. P., PAPOIAN, R., BOSCHERT, U., RAINE, C. S., SELMAJ, K. W., cDNA microarray analysis in multiple sclerosis lesions: detection of genes associated with disease activity. *Brain* **2003**, *126*, 1048–1057.
 - 71 WHITNEY, L. W., LUDWIN, S. K., MCFARLAND, H. F., BIDDISON, W. E., Microarray analysis of gene expression in multiple sclerosis and EAE identifies 5-lipoxygenase as a component of inflammatory lesions. *J. Neuroimmunol.* **2001**, *121*, 40–48.
 - 72 LOCK, C., HERMANS, G., PEDOTTI, R., BRENDOLAN, A., SCHADT, E., GARREN, H., et al., Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat. Med.* **2002**, *8*, 500–508.
 - 73 COLANTUONI, C., JEON, O. H., HYDER, K., CHENCHIK, A., KHAMANI, A. H., NARAYANAN, V., et al., Gene expression profiling in postmortem Rett syndrome brain: differential gene expression and patient classification. *Neurobiol. Dis.* **2001**, *8*, 847–865.
 - 74 MIRNICS, K., MIDDLETON, F. A., MARQUEZ, A., LEWIS, D. A., LEVITT, P., Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. *Neuron* **2000**, *28*, 53–67.
 - 75 HEMBY, S. E., GINSBERG, S. D., BRUNK, B., ARNOLD, S. E., TROJANOWSKI, J. Q., EBERWINE, J. H., Gene expression profile for schizophrenia: discrete neuron transcription patterns in the entorhinal cortex. *Arch. Gen. Psychiatry* **2002**, *59*, 631–640.
 - 76 VAWTER, M. P., CROOK, J. M., HYDE, T. M., KLEINMAN, J. E., WEINBERGER, D. R., BECKER, K. G., et al., Microarray analysis of gene expression in the prefrontal cortex in schizophrenia: a preliminary study. *Schizophr. Res.* **2002**, *58*, 11–20.
 - 77 TKACHEV, D., MIMMACK, M. L., RYAN, M. M., WAYLAND, M., FREEMAN, T., JONES, P. B., et al., Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* **2003**, *362*, 798–805.
 - 78 MIMMACK, M. L., RYAN, M., BABA, H., NAVARRO-RUIZ, J., IRITANI, S., FAULL, R. L., et al., Gene expression analysis in schizophrenia: reproducible up-regulation of several members of the apolipoprotein L family located in a high-susceptibility locus for schizophrenia on chromosome 22. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4680–4685.

- 79 HAKAK, Y., WALKER, J. R., LI, C., WONG, W. H., DAVIS, K. L., BUXBAUM, J. D., et al., Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc. Natl. Acad. Sci. USA* **2001**, 98, 4746–4751.
- 80 MIRNICS, K., MIDDLETON, F. A., STANWOOD, G. D., LEWIS, D. A., LEVITT, P., Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. *Mol. Psychiatry* **2001**, 6, 293–301.
- 81 RAUSCH, J. L., GILLESPIE, C. F., FEI, Y., HOBBS, H. M., STOMING, T., GANAPATHY, V., et al., Antidepressant effects on kinase gene expression patterns in rat brain. *Neurosci. Lett.* **2002**, 334, 91–94.
- 82 LANDGREBE, J., WELZL, G., METZ, T., VAN GALEN, M. M., ROPERS, H., WURST, W., et al., Molecular characterisation of antidepressant effects in the mouse brain using gene expression profiling. *J. Psychiatr. Res.* **2002**, 36, 119–129.
- 83 DRIGUES, N., POLTYREV, T., BEJAR, C., WEINSTOCK, M., YAUDIM, M. B., cDNA gene expression profile of rat hippocampus after chronic treatment with antidepressant drugs. *J. Neural. Transm.* **2003**, 110, 1413–1436.
- 84 WONG, M. L., O'KIRWAN, F., HANNESTAD, J. P., IRIZARRY, K. J., ELASHOFF, D., LICINIO, J., St John's wort and imipramine-induced gene expression profiles identify cellular functions relevant to antidepressant action and novel pharmacogenetic candidates for the phenotype of antidepressant treatment response. *Mol. Psychiatry* **2004**, 9, 237–251.
- 85 YAMADA, M., TAKAHASHI, K., TSUNODA, M., NISHIOKA, G., KUDO, K., OHATA, H., et al., Differential expression of VAMP2/synaptobrevin-2 after antidepressant and electroconvulsive treatment in rat frontal cortex. *Pharmacogenomics J.* **2002**, 2, 377–382.
- 86 NEWTON, S. S., COLLIER, E. F., HUNSBERGER, J., ADAMS, D., TERWILLIGER, R., SELVANAYAGAM, E., et al., Gene profile of electroconvulsive seizures: induction of neurotrophic and angiogenic factors. *J. Neurosci.* **2003**, 23, 10841–10851.
- 87 PALOTS, M., PALOTS, A., PUSKS, L. G., KITAJKA, K., PKSKI, M., JANKA, Z., et al., Gene expression profile analysis of the rat cortex following treatment with imipramine and citalopram. *Int. J. Neuropsychopharmacol.* **2004**, 1–13.
- 88 WONG, M. L., LICINIO, J., From monoamines to genomic targets: a paradigm shift for drug discovery in depression. *Nat. Rev. Drug Discov.* **2004**, 3, 136–151.
- 89 BENEDETTI, F., SERRETTI, A., COLOMBO, C., CAMPORI, E., BARBINI, B., DI BELLA, D., et al., Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *Am. J. Psychiatry* **1999**, 156, 1450–1452.
- 90 POLLOCK, B. G., FERRELL, R. E., MULSANT, B. H., MAZUMDAR, S., MILLER, M., SWEET, R. A., et al., Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. *Neuropsychopharmacology* **2000**, 23, 587–590.
- 91 ZANARDI, R., BENEDETTI, F., DI BELLA, D., CATALANO, M., SMERALDI, E., Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *J. Clin. Psychopharmacol.* **2000**, 20, 105–107.
- 92 MUNDO, E., WALKER, M., CATE, T., MACCIARDI, F., KENNEDY, J. L., The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder: preliminary findings. *Arch. Gen. Psychiatry* **2001**, 58, 539–544.
- 93 ZANARDI, R., SERRETTI, A., ROSSINI, D., FRANCHINI, L., CUSIN, C., LATTUADA, E., et al., Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression. *Biol. Psychiatry* **2001**, 50, 323–330.
- 94 SERRETTI, A., MACCIARDI, F., VERGA, M., CUSIN, C., PEDRINI, S., SMERALDI, E., Tyrosine hydroxylase gene associated with depressive symptomatology in mood disorder. *Am. J. Med. Genet.* **1998**, 81, 127–130.
- 95 SERRETTI, A., ZANARDI, R., CUSIN, C., ROSSINI, D., LILLI, R., LORENZI, C., et al., No association between dopamine D(2) and D(4) receptor gene variants and antidepressant activity of two selective

- serotonin reuptake inhibitors. *Psychiatry Res.* **2001**, 104, 195–203.
- 96 TAKAHASHI, H., YOSHIDA, K., ITO, K., SATO, K., KAMATA, M., HIGUCHI, H., et al., No association between the serotonergic polymorphisms and incidence of nausea induced by fluvoxamine treatment. *Eur. Neuropsychopharmacol.* **2002**, 12, 477–481.
 - 97 MURPHY JR., G. M., KREMER, C., RODRIGUES, H. E., SCHATZBERG, A. F., Pharmacogenetics of antidepressant medication intolerance. *Am. J. Psychiatry* **2003**, 160, 1830–1835.
 - 98 ZILL, P., BAGHAI, T. C., ZWANZGER, P., SCHULE, C., MINOV, C., RIEDEL, M., et al., Evidence for an association between a G-protein beta3-gene variant with depression and response to antidepressant treatment. *Neuroreport* **2000**, 11, 1893–1897.
 - 99 BAGHAI, T. C., SCHULE, C., ZWANZGER, P., MINOV, C., SCHWARZ, M. J., DE JONGE, S., et al., Possible influence of the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene on therapeutic outcome in affective disorders. *Mol. Psychiatry* **2001**, 6, 258–259.
 - 100 ROBERTS, R. L., JOYCE, P. R., MULDER, R. T., BEGG, E. J., KENNEDY, M. A., A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. *Pharmacogenomics J.* **2002**, 2, 191–196.

35

Pharmacogenetics of Antidepressant Drug Metabolism and Its Clinical Implications*Adrián LLerena***Abstract**

It is frequently observed in clinical practice that there is a certain variability in clinical efficacy and in the occurrence of side effects in patients treated with the same dose of a drug. This inter-individual variability also in the response to antidepressant drugs can be partly attributed to differences in plasma concentrations of the drug and/or its metabolites. One of the major factors influencing drug elimination and, thus, plasma concentration is the activity of the cytochrome P450 (CYP) enzymes. Every CYP enzyme is encoded by a separate gene; thus, each represents a monogenetic trait. A large number of these enzymes have been described and classified into 18 families. At present, CYP2D6, CYP2C19, CYP2C9, CYP1A2, and CYP3A4 have been shown to be the most important enzymes in psychopharmacology because of their implication in the metabolism of several psychotropic drugs, including antidepressants. Individuals with low enzyme activity are referred as slow or poor metabolizers, while the others are rapid or extensive metabolizers.

Besides the genetic determination, environmental factors and concomitant treatment also may modify the activity of these enzymes. Another aspect is the ability of certain antidepressant drugs to inhibit the activity of specific CYP enzymes. The clinical relevance of this fact is that this inhibition may lead to higher than expected plasma concentrations of the drug and also to drug interaction with other medications metabolized by the same specific enzyme.

In this review the present knowledge on the CYP enzyme-mediated metabolism of the specific antidepressant drugs and the possible clinical implications are summed up. The knowledge of the possible influence of CYP enzymes on the therapeutic efficacy of antidepressant drugs has grown remarkably recently, and in clinical practice if unexpected side effects occur or therapeutic failure is observed during antidepressant drug treatment, the possible involvement of pharmacogenetic factors should be considered and the appropriate examinations be carried out.

35.1

Inter-individual Variability in Drug Response

Drug efficacy in general, and antidepressant effects particularly, are frequently associated with great inter- and intra-individual differences in therapeutic response. This variability may result in increased incidence of adverse drug reactions (side effects) or, conversely, in diminished clinical response. Following administration, the drug evokes, modifies, or inhibits the targeted physiological processes – the study of these processes belongs to the discipline of pharmacodynamics (the effects of drugs on the organism). On the other hand, pharmacokinetics can be conceptualized as the effects of the human body on the administered compound (Rowland and Tozer, 1995). The pharmacokinetic processes (absorption, distribution, metabolism, and elimination) need to maintain the desired concentration at the drug's site of action (i.e., at the receptor level) for a sufficient period of time. Thus, the variability of drug responses might be due to changes in drug pharmacodynamics or pharmacokinetics (plasma concentration).

At present, our knowledge of the role of pharmacodynamic factors in the inter-individual variability of drug response is still fairly limited. This is largely due to methodological and ethical problems, since it is difficult to study pharmacodynamic processes *in vivo* at the receptor level, especially in psychopharmacology. However, sophisticated brain imaging methods, such as functional magnetic resonance imaging (fMRI), or positron emission tomography (PET), and their uses in dynamic and activation studies have opened a completely new field in the investigation of drug effects at the receptor level in the human brain.

The goal of pharmacological therapy is to achieve an optimal drug concentration at the site of the drug's action, normally at the receptor level. The role of pharmacokinetic factors in drug treatment has been a field of thorough investigation for the past several decades. Differences in plasma levels between individuals after the same dose of a drug may be attributed to factors influencing drug absorption, distribution, or elimination; however, the majority of inter-individual differences are related to differences in drug metabolism (Vesell, 1977). Drugs that are mainly excreted unchanged do not exhibit such a pronounced variability in their disposition kinetics; therefore, drug metabolism is thought to be the source of the variability. With a few exceptions (such as lithium), drugs used in the treatment of psychiatric disorders are highly lipophilic and thus subject to extensive metabolic biotransformation in the body. This transformation yields more-polar metabolites, which are more easily excreted in the urine or bile. Thus, metabolism is an important cause of variability in psychotropic drug plasma concentrations and response.

35.2

Inter-individual Differences in Drug Metabolism

Inter-individual differences in drug metabolism may be determined by environmental or genetic factors (Kalow, 1990; Meyer, 1990). Pharmacogenetics is a new

discipline, which deals with the study of genetically determined variations in drug metabolism and response. The term 'pharmacogenetics' was coined by Vogel et al. (1959), and since that time our knowledge of the importance of genetic factors in drug metabolism has grown remarkably (LLerena et al., 1996).

After the development of the human genome knowledge, the term 'pharmacogenomics' was introduced, and it is defined as the utilization of genetic information to predict the outcome of drug treatment (therapeutic and side effects) (Pickar and Rubinow, 2001). The pharmacogenomic strategy aims to identify genes that influence clinical responses to drug treatment (Catalano, 1999). Although this strategy traditionally has focused on metabolism genes that influence drug disposition, the broader appeal of pharmacogenomics is the possibility of predicting drug response (efficacy) or limiting side-effect profiles. The ability to predict drug response would allow individualized pharmacotherapy, which could maximize the chance of finding an optimal drug and dose for each patient. Consequently, this personalization could optimize the drug efficacy/side effects ratio, offering savings in both time and cost of care and substantially improving the patient's long-term prognosis.

Besides genetic factors, drug disposition and thus therapeutic efficacy and/or side effects can be modified by various other nongenetic factors, such as physiology (age, gender, pregnancy, exercise, etc.), pathology (fever, diseases, infections, etc.) or environment (diet, tobacco smoking, alcohol intake, xenobiotics) (Pelkonen and Sotaniemi, 1987; LLerena et al., 1996).

Drug-metabolizing enzymes are present abundantly in the human body. Lipophilic substances – and most psychotropic drugs belong to this class – are usually metabolized in the liver. The first step of this process – which can be oxidation, reduction, dealkylation, desulfation, or deamination – is usually referred to as a Phase I reaction. Oxidation is catalyzed mainly by the cytochrome P450 enzyme family, which is the most important group of enzymes in drug disposition. The members of the cytochrome P450 enzyme family have the following common features: they contain a heme group, are situated in the endoplasmic reticulum of the liver, and utilize NADPH and oxygen.

The Phase II reactions are catalyzed by transferases, which transfer an active moiety such as glucuronic acid, sulfate, or glutathione to the compound, usually after they have been metabolized in Phase I reactions. These reactions serve to transform the hydrophobic compound into a form that is more water-soluble and can be easily eliminated through the urine or bile.

Although the genetic polymorphism of several drug-metabolizing enzymes (acetylcholinesterases, glucoronidization enzymes, etc.) has been described, the oxidative processes mediated by cytochrome P450 enzymes seem to be the most important metabolic step for very many clinically relevant drugs. This is because the genetic polymorphism of cytochrome P450 enzymes has been extensively studied in recent decades.

35.3

Genetic Polymorphism of Cytochrome P450 Enzymes

Every P450 enzyme is encoded by a separate gene; thus each represents a monogenetic trait. A large number of these enzymes have been described (currently more than 50 human enzymes) and classified into 18 families. The classification is based on sequence homology (Nelson et al., 1996). Genes that have 40% or greater homology are classified in the same family and are named with the root CYP (derived from cytochrome P450) followed by an Arabic number, which refers to the family. Genes within an enzyme family with greater than 55% homology are classified in the same subfamily indicated by uppercase Latin letters (A, B, C, D, etc.). Genes within the same subfamily are designated by Arabic numbers (1, 2, 3, 4, etc.). Drug-metabolizing enzymes are known in the first, second, and third CYP enzyme families.

The genetic variability of drug-metabolizing enzymes can exist as polymorphism or as a rare trait. By definition, polymorphism is a Mendelian or monogenic trait that exists in the population in at least two phenotypes (and presumably at least two genotypes), neither of which occurs with a frequency less than 1%. If the frequency is lower than this, it is called a rare trait (Bertilsson, 1995). The allelic variant that is responsible for the genetic determinant of the isoenzyme can be determined (Gonzalez and Idle, 1994). The polymorphic or mutant alleles that are different from the most common allele (i.e., the wild type = wt) are designated by an asterisk followed by an Arabic number. The wt allele is always the *1 allele, for example, *CYP2D6.1* is the wild-type allele.

The catalytic activity of a cytochrome enzyme can be determined by the test of phenotyping. In this test the drug-metabolizing capacity is measured by a test drug specifically metabolized by the CYP enzyme in question. After a single dose of the test drug, the concentrations of the drug and its metabolite (in urine, blood) are determined over a period of time, and the metabolic ratio (MR) is calculated: $MR = (\text{amount of drug as unchanged}) / (\text{amount of drug as metabolite})$. The metabolic ratio reflects the actual activity of the specific enzyme. Jackson et al. (1986) demonstrated that this index is adequate for evaluating the drug-metabolizing capacity of an enzyme.

The activity of polymorphic CYP enzymes (in terms of MR) is bimodally distributed in the population. People with decreased or absent activity of the enzyme have high MRs, and the rest have normal. On the basis of population studies, a cutoff point to distinguish subjects with high or low MR can be defined. This point can be calculated from the bimodal distribution and is called the antimode (Evans et al., 1980, 1983). This value makes it possible to define separate phenotypes. Individuals with low enzyme activity are referred as slow or poor metabolizers (PM), and the others are rapid or extensive metabolizers (EM) with respect to that enzyme. The different phenotypes are determined by the genotypes of the CYP enzymes (Gonzalez and Idle, 1994; Meyer and Zanger, 1997).

Different isoenzymes involved in the metabolism of several clinically important drugs, including antidepressants, have been described in humans. At present,

CYP2D6, CYP2C19, CYP2C9, CYP1A2 and CYP3A4 have been shown to be the most important enzymes in psychopharmacology because of their implication in psychotropic drug biotransformation, although the role of other CYP isoenzymes cannot be ruled out.

35.3.1

CYP2D6

The debrisoquine hydroxylase polymorphism is by far the most thoroughly studied genetic polymorphism of the drug-metabolizing enzymes. The polymorphism of this enzyme was discovered independently by two different groups in the late 1970s. Mahgoub et al. (1977) studied the metabolism of debrisoquine, a post-ganglionic adrenergic blocking hypotensive drug, while Eichelbaum et al. (1979) investigated that of sparteine, an alkaloid anti-arrhythmic oxytocic drug. Both groups found that polymorphism existed in the metabolism of these drugs, which occurred at a 4-hydroxylation enzymatic step in debrisoquine and an N1 oxidation in sparteine metabolism. Autosomal recessive inheritance was established by family studies (Evans et al., 1980). Later it was proved that these two drug polymorphisms were based on a common genetic defect in the debrisoquine hydroxylase enzyme in the Caucasian population (Eichelbaum et al., 1982).

The distribution of debrisoquine metabolic ratio in Caucasian populations is characterized by bimodality. Around 7% of Caucasians have high debrisoquine MR values (PMs), i.e., excretion of the unchanged drug is the major route of elimination, and the amount of excreted metabolite is extremely low or negligible.

The incidence of the debrisoquine PM phenotype has been studied in different populations. In European, American, and Australian Caucasian populations the frequency of PM phenotype is 5%–10%. In Caucasian populations the frequency of PMs of debrisoquine type and also the distribution of the enzyme activity seem to be homogenous. On the basis of 8764 MR determinations, Alván et al. (1990) calculated that the overall frequency of PM phenotype in European Caucasian populations is 7.4%. In a Spanish population, among 925 healthy volunteers the rate of poor metabolizers was 4.9% (LLerena et al., 1993a).

Inter-ethnic differences in the activity of CYP2D6 enzyme in various populations are shown in Table 35.1.

CYP2D6 genotype: The bimodal distribution of the debrisoquine hydroxylase activity suggests a possible monogenic inheritance of the trait. Theoretically, the distribution of phenotypes for a monogenic recessive trait should be trimodal (homozygote-recessive, heterozygote, and homozygote-dominant), with three peaks. The reason for the bimodality here is that the heterozygotes and recessive homozygotes cannot be functionally separated by phenotyping methods, i.e., the distribution curves overlap.

Eichelbaum et al. (1987) in a linkage study mapped the gene for debrisoquine hydroxylase to the long arm of chromosome 22 in linkage with the blood factor P1. Independently, another group (Gonzalez et al., 1988a) using a CYP2D6 cDNA probe and mouse-human and hamster-human somatic hybrid cells also mapped the

Table 35.1 CYP2D6 enzyme activity in different population studies among healthy volunteers

Country	Population	Number of Individuals	Test Drug	PMs (%)	Reference
Europe					
Denmark	Caucasian	301	sparteine	7.3	Brøsen et al. 1985
Finland	Caucasian	211	debrisoquine	5.2	Arvela et al. 1988
Hungary	Caucasian	100	debrisoquine	10	Gachályi et al. 1986
Spain	Caucasian	925	debrisoquine	4.9	LLerena et al. 1993a
Sweden	Caucasian	1011	debrisoquine	6.9	Bertilsson et al. 1992
Asia					
Japan	Asian	295	metoprolol	0.7	Sohn et al. 1991
China	Asian	695	debrisoquine	1.0	Bertilsson et al. 1992
Korea	Asian	218	metoprolol	0.5	Sohn et al. 1991
Africa					
Egypt	Arab	72	debrisoquine	1.4	Mahgoub et al. 1979
Nigeria	African	138	debrisoquine	0.75	Iyun et al. 1986 Simoooya et al. 1993
America					
USA	Caucasian	480	dextromethorphan	7.7	Relling et al. 1991
USA	Afro-American	106	dextromethorphan	1.9	Relling et al. 1991
Panama	Indian	51	sparteine	0	Arias et al. 1988
Australia					
Australia	Caucasian	100	debrisoquine	6	Peart et al. 1986

CYP2D6 locus to the long arm of chromosome 22. In the liver of PM individuals some variants of CYP2D6 mRNA with different lengths were found (Gonzalez et al., 1988b). After cloning and sequencing the *CYP2D6* gene (Kimura et al., 1989), it became possible to search for mutations in PM individuals and to develop allele-specific polymerase chain reaction (PCR) tests (Heim and Meyer, 1990).

In Caucasian populations the most frequent mutations are *CYP2D6*4* (21% of Caucasians), which leads to a substitution, and, consequently, to defective splicing (Kagimoto et al., 1990); *CYP2D6*5*, which leads to complete gene deletion (Gaedigk et al., 1991); and *CYP2D6*3*, which contains a frame-shift mutation due to a deletion (Kagimoto et al., 1990).

The differences of CYP2D6 activity observed in Asian populations could be attributed to genetic factors. In a Chinese population Johansson et al. (1994) described the existence of two mutations, *CYP2D6*10* and *CYP2D6*36*, which have high allele frequency (51% and 37%, respectively) and lead to instability of the enzyme. This in turn causes diminished catalytic activity and thus provides a firm explanation for the higher MRs observed in the Chinese population.

Bertilsson et al. (1993) investigated the genetic basis of ultra-rapid metabolism in healthy individuals (UM). In these individuals there is an extra *CYP2D6* gene (*CYP2D6*1*), i.e., two active *CYP2D6* genes are present and expressed, and this

Table 35.2 The frequency of some *CYP2D6* alleles in a Caucasian population (Marez et al., 1997; Sachse et al., 1997)

<i>Allele</i>	<i>Frequency (%)</i>	<i>Nucleotide Change</i>	<i>Enzyme Activity</i>
*1	32–36	wild type	normal
*1 _{xn}	0.5	multiplication	increased
*2	25–32	substitution	decreased/normal
*2 _{xn}	1.4	multiplication	increased
*3	2.0	deletion + frameshift	absent
*4	16–20	substitution splicing defect	absent
*4 _{xn}	≤ 0.1	multiplication	absent
*5			
*6	0.9–1.1	deletion + frameshift	absent
*7	≤ 0.1	substitution	absent
*8	≤ 0.1	substitution	absent
*9	1.8–2.7	deletion	decreased
*10	1.5	substitution	decreased
*11	≤ 0.1	substitution splicing defect	absent
*12	≤ 0.1	substitution	absent
*13	≤ 0.1	deletion + insertion	absent
*14	≤ 0.1	substitution	absent
*15	≤ 0.1	insertion	absent
*16	≤ 0.1	deletion + insertion	absent
*17	≤ 0.1	substitution	decreased

leads to a higher metabolic activity. The duplicated allele is not a rare mutation; the overall frequency of the duplicated/amplified *CYP2D6* allele is about 1% in a Swedish population (Dahl et al., 1995). Also, alleles carrying two or three extra *CYP2D6**1 or *2 genes, yielding in a total of three or four active *CYP2D6* genes, have been described. The frequency of different *CYP2D6* alleles is shown in Table 35.2.

35.3.2 **CYP2C19**

CYP2C19 is the source of *S*-mephenytoin oxidation polymorphism, which is bimodally distributed in the population (De Morais et al., 1994a). In EM individuals the *S* enantiomer of mephenytoin is rapidly hydroxylated to its metabolite, but the *R* enantiomer is slowly *N*-demethylated. In PM individuals, the rate of *S*-mephenytoin hydroxylation is lower, due to the altered enzyme activity, and therefore the amount of *S*-mephenytoin is higher; the rate of *N*-demethylation is the same in the two phenotypes. The mephenytoin *S/R* enantiomer ratio determined from the urine collected during the 8-h period following the ingestion of the racemate is used for phenotyping. In EM persons the *S/R* ratio is always < 0.9, and in PMs it is around 1.0. Omeprazole is reported to have certain advantages over mephenytoin as a probe drug for CYP2C19, because of the lower incidence of side effects (Chang et al., 1995). CYP2C19 is not inducible by xenobiotics.

The prevalence of PMs of *S*-mephenytoin was 1.34% in 373 unrelated healthy Spanish Caucasian individuals (Reviriego et al., 1993). Combined data from the 22 homogeneous studies show that the frequency of poor metabolizers in healthy unrelated Caucasians as determined by phenotyping is 2.8%, but in Orientals (Japanese, Chinese, Koreans) the incidence is about 14%–20% (Nakamura et al., 1985; Xie et al., 1999; Xie, 2000). Among 103 black Zimbabweans 4% were poor metabolizers (Masimirembwa et al., 1995).

The impaired activity of the enzyme is inherited as an autosomal-recessive trait (Inaba et al., 1986; Ward et al. 1987). The family members of CYP2C19 PM persons are also slow metabolizers (LLerena et al., 1993b). The two most common defects are two null alleles: the first is a mutation in exon 5 (*CYP2C19**2), and the second is a single-base transition in exon 4 (*CYP2C19**3). These two defects account for > 99% of the defective alleles in Oriental populations but only for ~ 87% of the defective alleles in Caucasians (De Morais et al., 1994a, 1994b; Brøsen et al., 1995). Three different point mutations have also been reported that result in single amino-acid substitutions: *CYP2C19**4, which accounts for an additional 3% of the defective alleles in Caucasians, and the rare mutations (~1.5% of Caucasian PM alleles) *CYP2C19**5 and *CYP2C19**6 (Ferguson et al., 1998; Ibeanu et al., 1998a, 1998b). Two additional alleles of the poor-metabolizer phenotype for *S*-mephenytoin 4-hydroxylation in Caucasians (*CYP2C19**7, *8) have been described (Ibeanu et al., 1999).

The *CYP2C19* polymorphism is of clinical importance because CYP2C19 catalyses the metabolism of several pharmacologically important drugs, including amitriptyline, clomipramine, imipramine, and also diazepam, citalopram, and moclobemide (Bertilsson et al., 1995). However, no inhibitory effect of antidepressants or neuroleptics on the activity of CYP2C19 enzyme has been demonstrated in psychiatric patients (LLerena et al., 1993c).

35.3.3

CYP2C9

CYP2C9 is another clinically relevant enzyme. We studied the impact of the *CYP2C9* genotype on phenotyping in a Spanish population (Dorado et al., 2003a). Diclofenac hydroxylation capacity was studied as a marker of CYP2C9 activity in a population of 102 healthy volunteers. After a single oral dose, the urinary concentrations of diclofenac and its metabolite 4'-hydroxydiclofenac were analyzed (Dorado et al., 2003b). We showed the functional implication of genotypes and proved that the allele *CYP2C9**3 seems to decrease the enzyme activity. The diclofenac/4'-OH-diclofenac ratio was significantly higher among subjects with *CYP2C9**1/*3 and *CYP2C9**2/*3 genotypes than in those with *CYP2C9**1/*1. The ratio was approximately threefold higher in the only subject homozygous for the *CYP2C9**3 variant (Dorado et al., 2003b). Carriers of alleles *CYP2C9**2 and *3 have lower enzyme activity than carriers of the wild-type allele, as do carriers of rare alleles (*CYP2C9**4, *CYP2C9**5, and *CYP2C9**6). Some people with complete lack of enzyme activity have been described (Lee et al., 2002).

The allele frequencies of *CYP2C9* vary between different populations. We reported that the frequencies of the *CYP2C9**1, *2, and *3 alleles in the Spanish population were similar to those found in previously studied white European populations. *CYP2C9**2 and *3 allele frequencies are about 12% and 8% in Caucasians (Dorado et al., 2003a).

A relationship between *CYP2C9* and the risk of depression has also been described. In patients suffering from major depression, the *CYP2C9**3 allele frequency was higher than in populations of schizophrenic patients and of healthy volunteers (LLerena et al., 2003). This study suggested that *CYP2C9* genetic polymorphism may be related to major depressive disorder owing to an alteration in serotonin or arachidonic acid metabolism.

As described later, the contribution of *CYP2C9* to antidepressant metabolism has been studied with amitriptyline (Ghahramani et al., 1997), doxepin (Kirchheiner et al., 2002), trimipramine (Kirchheiner et al., 2003a), and fluoxetine (LLerena et al., 2004).

35.3.4 **CYP1A2**

CYP1A2 is one of the major CYP enzymes, accounting for 15% of the total P450 content in the human liver (Shimada et al., 1994). There is broad inter-individual variability with respect to *CYP1A2* activity among humans (Kalow and Tang, 1991). The variation may be due to the enzyme's induction and inhibition by other drugs or by environmental exposures. Tobacco smoking and coffee and alcohol consumption make a substantial contribution to the variability. To measure the metabolic activity of *CYP1A2*, caffeine has been suggested for use as a phenotyping probe in vivo (Fuhr et al., 1996). Although the metabolism of caffeine is complex, the major metabolic steps to forming metabolites such as 1,7-dimethylxanthine and 1-methylxanthine are catalyzed by *CYP1A2*, and the measurement of urinary metabolites after caffeine ingestion can be used to calculate metabolic ratios. However, in psychiatric patients phenotyping may be cumbersome, because the incidence of heavy smoking and coffee consumption is particularly high (Kellermann et al., 2000), and these interfere with the procedure.

There is little information on inter-ethnic differences in the enzyme activity (Butler et al., 1992; Bartoli et al., 1996). No genetic polymorphism resulting in an altered protein sequence for *CYP1A2* had been described until a rare mutation (*CYP1A2**2) was reported in a Chinese sample (Huang et al., 1999). The enzyme is well known for its role in the metabolic activation of environmental and food-borne carcinogens, including arylamines and heterocyclic amines (Eaton et al., 1995).

CYP1A2 is involved in the metabolism of a large number of drugs, including antidepressant drugs like imipramine, mianserin, and nortriptyline (Bertilsson et al., 1994; Koyama et al., 1996a, 1996b, 1997; Ring et al., 1996; Benoit et al., 1997; Olesen and Linnet, 1997).

35.3.5

CYP3A4

The CYP3A enzyme subfamily is the most abundant cytochrome in the liver, accounting for up to 30% of the total cytochrome P450 content of the adult human liver (Shimada et al., 1994). The two most important enzymes are CYP3A3 and CYP3A4, which have a 98% amino acid similarity and oxidize the same drugs. It is currently an unsettled question whether they are encoded by different genes or represent allelic variants of the same genetic locus. There is marked inter-individual heterogeneity in the expression of *CYP3A* genes. Phenotyping of this enzyme is difficult, because the CYP3A enzyme is abundantly present in the small intestine, and thus any oral test designed for the evaluation of liver metabolism is influenced by the activity of the CYP3A enzyme in the intestines. The most widely accepted and tested CYP3A probes are erythromycin and midazolam. However, none of the current phenotyping procedures are ideal (Streetman et al., 2000).

The initial studies of in-vivo nifedipine oxidation (marker drug for CYP3A4 activity) showed an apparent polymorphism among a set of 53 healthy individuals (Kleinbloesem et al., 1984), but subsequent pharmacokinetic studies with a larger group could not confirm this result (Schellens et al., 1988). An intriguing observation of dramatic ethnic differences in nifedipine oxidation was made in a study comparing South Asians and Caucasians (Ahsan et al., 1991), and also both in-vitro and in-vivo differences between Caucasians and Japanese were found with regard to CYP3A4 activity (Shimada et al., 1994). To date, there are no reports in humans of a definitive evidence for a *CYP3A4* genetic polymorphism related to the catalytic activity (Horsmans et al., 1992). An in-vitro study has revealed polymorphic alleles (*CYP3A4**2, *3) encoding enzymes with altered catalytic activity (Sata et al., 2000).

As with CYP1A2, the CYP3A4 enzyme is highly inducible by a number of drugs and affected by diet; therefore, it is difficult to find the exact role that genetic factors may have in its activity. CYP3A4 plays a significant role in the metabolism of approximately half of the drugs in use today (Guengerich, 1999). Several psychotropic drugs, including carbamazepine, midazolam, triazolam, diazepam, clomipramine, and imipramine, are also metabolized by the CYP3A4 enzyme (Michalets, 1998).

35.4

Pharmacogenetics of Antidepressant Drugs

Prescribing antidepressant drugs is a substantial part of the present strategy for treatment of depression. However, there is variability in the response and in side effects to antidepressant drugs. Failure to respond to antidepressant drug therapy, as well as the presence of intolerable side effects, is an important issue affecting compliance. At present, there is no possibility of reliably predicting an individual's response probability before onset of a certain drug treatment; however, some factors for predicting plasma levels of certain antidepressant drugs are already known.

Among the cytochrome P450s described, CYP2D6 plays the most important role in the metabolism of antidepressant drugs. As stated previously, CYP2D6 shows high variability in enzyme activity due to genetic polymorphism. Both poor and ultra-rapid metabolizers have been described.

35.4.1

Pharmacogenetics of Tricyclic Antidepressants

It was already observed in the late 1960s that the same dose of a tricyclic antidepressant may result in a 50-fold difference in the plasma concentration of the drug and thus may substantially influence the clinical effect and the appearance of adverse effects. Soon after, in twin studies, the genetic influence on the equilibrium steady-state plasma concentrations of nortriptyline was demonstrated. After the same dose of nortriptyline, the plasma concentrations were similar in monozygotes but showed inter-individual differences in dizygotes (Alexanderson et al., 1969).

The influence of polymorphism in *CYP2D6* on the metabolism of tricyclic antidepressants has been extensively described. In the 1980s it was demonstrated that poor metabolizers (using a phenotyping test drug, i.e., debrisoquine or sparteine) have lower clearance than extensive metabolizers. Later, in the 1990s when CYP2D6 methods became available, a decrease in plasma clearance was also shown among individuals carrying two deficient alleles of *CYP2D6* (genotypically poor metabolizers) compared to EMs or UMs. To best of our knowledge so far, this effect has been described for the metabolism of amitriptyline (Mellstrom et al., 1983, 1986) nortriptyline (Bertilsson et al. 1980; Mellstrom et al., 1981; Dahl et al., 1996), clomipramine (Nielsen et al., 1992), desipramine (Bertilsson et al., 1983; Spina et al., 1987, 1997), imipramine (Brosen et al., 1986a, 1986b), doxepine (Kirchheiner et al., 2002), and trimipramine (Kirchheiner et al., 2003a).

CYP2C19 is another important polymorphic enzyme for the metabolism of tricyclic antidepressants. Different studies using mephenytoin a test drug and using genotyping have shown that CYP2C19 seems to be involved in the metabolism of amitriptyline (Jiang et al., 2002; Shimoda et al., 2002), clomipramine (Nielsen et al., 1994; Yokono et al., 2001), doxepine (Kirchheiner et al., 2002), imipramine (Skjelbo et al., 1991; Morinobu et al., 1997), and trimipramine (Kirchheiner et al., 2003a).

It has also been demonstrated that CYP2C19 PMs had higher AUCs than EM individuals during treatment with the antidepressant drugs imipramine and desipramine (Koyama et al., 1996a).

There is not much information about the influence of CYP2C9 on the metabolism of tricyclic antidepressants. The influence of various *CYP2C9* allelic variants seems not to be relevant for the kinetics of trimipramine (Kirchheiner et al., 2003a) or doxepin (Kirchheiner et al., 2002).

35.4.2

Pharmacogenetics of Selective Serotonin-reuptake Inhibitors

Similar to the situation with tricyclic antidepressants, CYP2D6 polymorphism has a relevant role during treatment with selective serotonin-reuptake inhibitors (SSRIs). Some of them are potent inhibitors of the enzyme activity, including fluoxetine, fluvoxamine, and paroxetine (Laine et al., 2001). Therefore, the metabolism of the drugs is inhibited after multiple dosing, which may be why differences in AUCs were described after single doses of fluvoxamine, whereas multiple doses result in similar AUCs in PMs compared to EMs, indicating a phenotype conversion from EM to PM (Carrillo et al., 1996; Spigset et al., 1997, 1998). Fluvoxamine has been also shown to be mainly metabolized by CYP2D6 and CYP1A2 among healthy volunteers (Spigset et al., 2001).

We have recently shown the combined effects of the *CYP2D6* and *CYP2C9* genotypes on the ratio of the plasma concentrations of fluoxetine to its active metabolite norfluoxetine in psychiatric patients during steady-state conditions (Table 35.3) (LLerena et al., 2004).

The influence of the *CYP2D6* phenotype and genotype on paroxetine plasma concentration has also been described: AUCs were twice as high among PMs than EMs (Sindrup et al., 1992).

So far, no influences of *CYP2D6* polymorphism on the metabolism of sertraline and citalopram have been described. However, sertraline has a modest inhibitory effect on *CYP2D6* in vitro (Crewe et al., 1992), and the metabolite of citalopram, demethylcitalopram, has a modest inhibitory effect on *CYP2D6* (Gram et al., 1993).

CYP2C19 seems to be relevant to the metabolism of sertraline (Wang et al., 2001) and citalopram (Sindrup et al., 1993). Among *CYP2C19* PMs, AUCs were higher than EMs.

Fluvoxamine is a unique SSRI since it is also a strong inhibitor of *CYP1A2* both in vitro and in vivo (Brosen et al., 1993; Jeppesen et al., 1996).

Table 35.3 The dose-corrected (C/D) plasma concentrations ($\text{nmol L}^{-1} \text{mg}^{-1}$, mean \pm S.D.) of fluoxetine, norfluoxetine, active moiety (fluoxetine plus norfluoxetine), and fluoxetine/norfluoxetine ratio among *CYP2D6* EM homozygote patients ($n = 38$) with different *CYP2C9* genotype groups

<i>CYP2C9</i> genotypes	*1/*1 ($n = 19$)	*1/*2 ($n = 11$)	*1/*3 ($n = 8$)
C/D of fluoxetine [†]	9.9 \pm 4.8	15.1 \pm 9.3 [#]	16.3 \pm 9.8 [‡]
C/D of norfluoxetine [†]	15.8 \pm 7.0	20.4 \pm 10.5	22.3 \pm 12.4 [#]
C/D of active component [†] (fluoxetine+norfluoxetine)	25.1 \pm 10.1	35.5 \pm 18.5 [#]	38.6 \pm 22.1 [‡]
fluoxetine/norfluoxetine ratio	0.73 \pm 0.41	0.74 \pm 0.34	0.72 \pm 0.14

[†] (Kruskal–Wallis test, overall $p < 0.05$).

[#] Significantly different ($p < 0.05$) from the wild-type (*1/*1) group by Dunn's post test.

[‡] Significantly different ($p < 0.01$) from the wild-type (*1/*1) group by Dunn's post test.

35.4.3

Pharmacogenetics of Other Antidepressants

The influence of *CYP2D6* polymorphism on venlafaxine metabolism has been described. Venlafaxine enantiomers are transformed to the equipotent *O*-demethylvenlafaxine (Otton, et al., 1996; Fukuda et al., 2000; Veefkind et al., 2000). *CYP2D6* is involved in the *O*-demethylation metabolic pathway of venlafaxine in humans: although *CYP2D6* catalyses the *O*-demethylation of both enantiomers of venlafaxine, it displays a marked stereoselectivity towards the R enantiomer (Eap et al., 2003). Healthy volunteers carrying defective alleles of *CYP2C19* or *CYP2D6* showed a higher concentration of venlafaxine; thus, these alleles are the most likely genetic factors for inter-individual differences in the pharmacokinetics of venlafaxine.

Firkusny and Gleiter (1994) found an influence of *CYP2D6* polymorphism on the plasma concentration of maprotiline in healthy volunteers; however, these data were contradictory to those found for patients treated under monotherapy (Baumann et al., 1988).

Moclobemide seems to be both a substrate and an inhibitor of *CYP2C19* (Gram et al., 1995). It has been shown that AUCs were higher among *CYP2C19* PMs than in EMs. However, *CYP2D6* seems not to be involved in moclobemide metabolism (Schoerlin et al., 1990). Concurrent administration of moclobemide markedly reduced the *O*-demethylation of dextromethorphan, which indicates that moclobemide can affect the pharmacokinetics of drugs that are mainly metabolized by *CYP2D6* (Hartter et al., 1998).

Bupropion seems to be a substrate of *CYP2B6* (Faucette et al., 2000; Kirchheiner et al., 2003b), but apparently its metabolism is not influenced by *CYP2D6* (Pollock et al., 1996).

The enantioselective hydroxylation of the mianserin to *S*-mianserin seems to be mediated by *CYP2D6* in patients (Mihara et al., 1997a).

CYP2D6 seems not to be implicated in the metabolism of nefazodone (Barbhaiya et al., 1996), reboxetine (Dostert et al., 1997), or trazodone (Mihara et al., 1997b).

Mirtazapine 8-hydroxylation is mainly mediated by *CYP2D6* at low mirtazapine concentrations (Dodd et al., 2001), but recombinant enzymes indicated an increasing contribution of *CYP1A2* with increasing mirtazapine concentration. Mirtazapine does not substantially inhibit *CYP1A2*, *CYP2C9*, *CYP2C19*, or *CYP2D6* activity and has a modest degree of inhibition of *CYP3A* activity (Störmer et al., 2000).

The metabolism of nefazodone and its metabolite, hydroxynefazodone, to each of their active metabolites is catalyzed mainly by *CYP3A4*, a finding that is in agreement with clinical reports of drug–drug interactions of nefazodone with substrates and inhibitors of *CYP3A4* (Rotzinger and Baker, 2002). In healthy volunteers, the plasma results of a single dose showed no significant differences in pharmacokinetic parameters for nefazodone and hydroxynefazodone in *CYP2D6* EM compared with PM subjects. For another nefazodone metabolite, *m*-chlorophenylpiperazine (mCPP), the AUC was almost fourfold higher in PM than EM subjects, and the mCPP elimination half-life doubled, which indicate that the

conversion of mCPP to *p*-hydroxy-mCPP is attributable to metabolism by CYP2D6 (Barbhaiya et al., 1996).

A principal role of CYP3A in the formation of *O*-deethylreboxetine from (*S,S*)-reboxetine and (*R,R*)-reboxetine was reported. In addition, (*S,S*)-reboxetine and (*R,R*)-reboxetine were found to be competitive inhibitors of CYP2D6 and CYP3A4 (Wienkers et al., 1999). Reboxetine is unlikely to cause clinically significant interactions with substrates of CYP2D6 in healthy volunteers (Avenoso et al., 1999). In another study, 11 healthy volunteers received reboxetine and ketoconazole (a known potent CYP3A4 inhibitor) (Herman et al., 1999). Ketoconazole significantly increased the mean area under the plasma concentration–time curves (AUC) for (*R,R*)-reboxetine and (*S,S*)-reboxetine. The results suggest that CYP3A4 is an important enzyme of reboxetine metabolism in healthy volunteers.

35.5 Clinical Implications

35.5.1

Potential Risk of Drug Interactions and Side Effects

Genotypically, PM subjects might be prone to higher than expected drug plasma concentrations when treated at regular doses. Thus, undesirable side effects might occur, such as the higher risk of arrhythmia reported in four CYP2D6 PM patients during treatment with venlafaxine (Lessard et al., 1999).

On the other hand, among genotypically ultra-rapid patients a lack of therapeutic effect may occur, as recently demonstrated in a Mexican-American depressive patient treated with desipramine (Flores et al., 2004).

Cytochrome P450 activity can be inhibited by several drugs, including some antipsychotic drugs (Otani and Aoshima, 2000). Thus, coadministration of antipsychotic drugs inhibits the metabolism of the antidepressants metabolized by the same enzyme, which may result in clinically relevant drug interactions. It has been reported that fluvoxamine interferes with the metabolism of thioridazine in schizophrenic patients under steady-state conditions. Coadministration of fluvoxamine increases the plasma concentration of thioridazine (Carrillo et al., 1999). Later, it was shown that CYP2D6 and the increase in thioridazine plasma concentration are related to QTc interval lengthening and to Torsade de Pointes type arrhythmias (Berez et al., 2003; Llerena et al., 2002).

Yasui et al. (1997) reported that coadministration of thioridazine increased the steady-state plasma concentration of *S*-mianserin but not that of *R*-mianserin. Conversely, paroxetine is a potent inhibitor of CYP2D6 (Bertilsson et al., 2002) and inhibits the metabolism of other substrates for CYP2D6. Ozdemir et al. (1997) reported that paroxetine inhibited the metabolism of perphenazine and increased its plasma concentration.

The importance of pharmacokinetic drug interactions that involve cytochrome enzymes has been increasingly emphasized, since CYP2D6 plays an important

role in the metabolism of several important psychotropic agents and other drugs (e.g., beta blockers, antidepressants) (LLerena et al., 1996). Thus, clinicians should be aware that metabolic interactions can occur and that, consequently, potentially severe side effects or an unexpected decrease in clinical efficacy (due to the plasma concentration changes of the drug and/or its metabolites) should be reckoned when new medications (CYP2D6 inhibitors) are introduced during treatment with a drug metabolized by CYP2D6.

35.5.2

Clinical Use of Pharmacogenetic Data

The results of the research work in pharmacogenetics have confirmed the importance of genetic and environmental factors in the metabolism of several drugs, including antidepressants, and thus in the therapeutic outcome and the risk of side effects. In clinical practice, the influence of CYP enzyme activity can be determined by genotyping or phenotyping, and the overall influence is reflected by the plasma concentrations of the administered drugs and their metabolites.

In view of the current data, assessment of CYP2D6 (and other important CYPs) status might be a useful aid for clinicians to predict inter-individual variability in the plasma concentration of antipsychotic drugs and to tailor therapeutic regimens to individual patients. The cost/benefit ratio of monitoring the plasma levels of antidepressant and antipsychotic drugs and CYP enzyme phenotyping and genotyping is the focus of thorough research at present.

The current data also suggest that genetically inherited activity is modified by drug inhibition during concomitant drug treatment. Thus, phenotyping procedures may be a valuable aid to the physician for evaluating possible pharmacokinetic interactions or unpredictable adverse effects when doses are changed or a new drug is added to the therapeutic regimen of a patient.

35.6

Conclusions

The present review shows the importance of cytochrome enzymes in the metabolism of antidepressant drugs. Several cytochromes P450 (CYP2D6, CYP2C9, CYP2C19) have been shown to be implicated in the metabolism of widely used antidepressant drugs. Polymorphism of genes for these enzymes may be at least partly responsible for the inter-individual variability observed in plasma levels and therapeutic responses.

The drugs are not only metabolized by the enzymes, but they also inhibit the activity of the enzymes (i.e., CYP2D6). The inhibition may carry clinical consequences, such as drug interactions and/or side effects (e.g., cardiotoxicity).

Therefore, CYP phenotyping and/or genotyping should be a very useful tool for improving the clinical use of antidepressant drugs. At present in clinical practice if unexpected side effects occur or therapeutic failure is observed with antidepressant

drugs, the possible involvement of pharmacogenetic factors should also be considered and adequate examinations be carried out.

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References

- AHSAN, C. H., RENWICK, A. G., MACKLIN, B., CHALLENGER, V. F., WALLER, D. G., GEORGE, C. F., Ethnic differences in the pharmacokinetics of oral nifedipine. *Br. J. Clin. Pharmacol.* **1991**, *31*, 399–403.
- ALEXANDERSON, B., EVANS, D. A., SJOQVIST, F., Steady-state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. *Br. Med. J.* **1969**, *2*, 764–768.
- ALVAN, G., BECHTEL, P., ISELIUS, L., GUNDERT-REMY, U., Hydroxylation polymorphisms of debrisoquine and mephenytoin in European populations. *Eur. J. Clin. Pharmacol.* **1990**, *39*, 533–537.
- ARIAS, T. D., JORGE, L. F., LEE, D., BARRANTES, R., INABA, T., The oxidative metabolism of sparteine in the Cuna Amerindians of Panama: absence of evidence for deficient metabolizers. *Clin. Pharmacol. Ther.* **1988**, *43*, 456–465.
- ARVELA, P., KIRJARINTA, M., KIRJARINTA, M., KARKI, N., PELKONEN, O., Polymorphism of debrisoquine hydroxylation among Finns and Lapps. *Br. J. Clin. Pharmacol.* **1988**, *26*, 601–603.
- AVENOSO, A., FACCIOLO, G., SCORDO, M. G., SPINA, E., No effect of the new antidepressant reboxetine on CYP2D6 activity in healthy volunteers. *Ther. Drug Monit.* **1999**, *21*, 577–579.
- BARBHAIYA, R. H., BUCH, A. B., GREENE, D. S., Single and multiple dose pharmacokinetics of nefazodone in subjects classified as extensive and poor metabolizers of dextromethorphan. *Br. J. Clin. Pharmacol.* **1996**, *42*, 573–581.
- BARTOLI, A., XIAODONG, S., GATTI, G., CIPOLLA, G., MARCHISELLI, R., PERUCCA, E., The influence of ethnic factors and gender on CYP1A2-mediated drug disposition: a comparative study in Caucasian and Chinese subjects using phenacetin as a marker substrate. *Ther. Drug Monit.* **1996**, *18*, 586–591.
- BAUMANN, P., BOSSHART, P., GABRIS, G., GASTPAR, M., KOEB, L., WOGGON, B., Acetylation of maprotiline and desmethylmaprotiline in depressive patients phenotyped with sulfamidine, debrisoquine, and mephenytoin. *Arzneimittelforschung* **1988**, *38*, 292–296.
- BENOIT, G. G., NAUD, C. F., SIMARD, M. A., ASTIER, A. L., Noninterference of cytochrome P-4501A2 in the cytotoxicity of tacrine by genetically engineered V79 Chinese hamster cells for stable expression of the human or rat isoform and two human hepatocyte cell lines. *Biochem. Pharmacol.* **1997**, *53*, 423–427.
- BERECZ, R., DE LA RUBIA, A., DORADO, P., FERNANDEZ-SALGUERO, P., DAHL, M. L., LLERENA, A., Thioridazine steady-state plasma concentrations are influenced by tobacco smoking and CYP2D6, but not by the CYP2C9 genotype. *Eur. J. Clin. Pharmacol.* **2000**, *59*, 45–50.
- BERTILSSON, L., Geographical/interracial differences in polymorphic drug oxidation: current state of knowledge of cytochromes P450 (CYP) 2D6 and 2C19. *Clin. Pharmacokinet.* **1995**, *29*, 192–207.
- BERTILSSON, L., ABERG-WISTEDT, A., The debrisoquine hydroxylation test predicts

- steady-state plasma levels of desipramine. *Br. J. Clin. Pharmacol.* **1983**, *15*, 388–390.
- BERTILSSON, L., EICHELBAUM, M., MELLSTROM, B., SAWE, J., SCHULZ, H. U., SJOQVIST, F., Nortriptyline and antipyrine clearance in relation to debrisoquine hydroxylation in man. *Life Sci.* **1980**, *27*, 1673–1677.
- BERTILSSON, L., LOU, Y. Q., DU, Y. L., LIU, Y., KUANG, T. Y., LIAO, X. M., WANG, K. Y., REVIRIEGO, J., ISELIUS, L., Sjöqvist, F., Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquin and S-mephenytoin. *Clin. Pharmacol. Ther.* **1992**, *51*, 388–397.
- BERTILSSON, L., DAHL, M. L., Sjöqvist, F., ABERG-WISTEDT, A., HUMBLE, M., JOHANSSON, I., LUNDQVIST, E., INGELMAN-SUNDBERG, M., Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. *Lancet* **1993**, *341*, 63.
- BERTILSSON, L., CARRILLO, J. A., DAHL, M. L., LLERENA, A., ALM, C., BONDESSON, U., LINDSTRÖM, L., RODRIGUEZ DE LA RUBIA, I., RAMOS, S., BENÍTEZ, J., Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br. J. Clin. Pharmacol.* **1994**, *38*, 471–473.
- BERTILSSON, L., DAHL, M. L., DALEN, P., AL-SHURBAJI, A., Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Br. J. Clin. Pharmacol.* **2002**, *53*, 111–122.
- BROSEN, K., OTTON, S. V., GRAM, L. F., Sparteine oxidation polymorphism in Denmark. *Acta Pharmacol. Toxicol. (Copenhagen)* **1985**, *57*, 357–360.
- BROSEN, K., GRAM, L. F., KLYSNER, R., BECH, P., Steady-state levels of imipramine and its metabolites: significance of dose-dependent kinetics. *Eur. J. Clin. Pharmacol.* **1986a**, *30*, 43–49.
- BROSEN, K., KLYSNER, R., GRAM, L. F., OTTON, S. V., BECH, P., BERTILSSON, L., Steady-state concentrations of imipramine and its metabolites in relation to the sparteine/debrisoquine polymorphism. *Eur. J. Clin. Pharmacol.* **1986b**, *30*, 679–684.
- BROSEN, K., SKJELBO, E., RASMUSSEN, B. B., POULSEN, H. E., LOFT, S., Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem. Pharmacol.* **1993**, *45*, 1211–1214.
- BROSEN, K., DE MORAIS, S. M., MEYER, U. A., GOLDSTEIN, J. A., A multifamily study on the relationship between CYP2C19 genotype and S-mephenytoin oxidation phenotype. *Pharmacogenetics* **1995**, *5*, 312–317.
- BUTLER, M. A., LANG, N. P., YOUNG, J. F., CAPORASO, N. E., VINEIS, P., HAYES, R. B., TEITEL, C. H., MASSENGILL, J. P., LAWSEN, M. F., KADLUBAR, F. F., Determination of CYP1A2 and NAT2 phenotypes in human populations by analysis of caffeine urinary metabolites. *Pharmacogenetics* **1992**, *2*, 116–127.
- CARRILLO, J. A., DAHL, M. L., SVENSSON, J. O., ALM, C., RODRIGUEZ, I., BERTILSSON, L., Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. *Clin. Pharmacol. Ther.* **1996**, *60*, 183–190.
- CARRILLO, J. A., RAMOS, S. I., HERRAIZ, A. G., LLERENA, A., AGUNDEZ, J. A., BEREZ, R., DURAN, M., BENITEZ, J., Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients. *J. Clin. Psychopharmacol.* **1999**, *19*, 494–499.
- CATALANO, M., The challenges of psychopharmacogenetics. *Am. J. Hum. Genet.* **1999**, *65*, 606–610.
- CHANG, M., DAHL, M. L., TYBRING, G., GOTHARSON, E., BERTILSSON, L., Use of omeprazole as a probe drug for CYP2C19 phenotype in Swedish Caucasians: comparison with S-mephenytoin hydroxylation phenotype and CYP2C19 genotype. *Pharmacogenetics* **1995**, *5*, 358–363.
- CREWE, H. K., LENNARD, M. S., TUCKER, G. T., WOODS, F. R., HADDOCK, R. E., The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br. J. Clin. Pharmacol.* **1992**, *34*, 262–265.
- DAHL, M. L., JOHANSSON, I., BERTILSSON, L., INGELMAN-SUNDBERG, M., Sjöqvist, F., Ultrarapid hydroxylation of debrisoquine in a Swedish population: analysis of the molecular genetic basis. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 516–520.
- DAHL, M. L., BERTILSSON, L., NORDIN, C., Steady-state plasma levels of nortriptyline and its 10-hydroxy metabolite: relationship to the CYP2D6 genotype. *Psychopharmacology (Berl.)* **1996**, *123*, 315–319.

- DE MORAIS, S. M., WILKINSON, G. R., BLAISDELL, J., NAKAMURA, K., MEYER, U. A., GOLDSTEIN, J. A., The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. *J. Biol. Chem.* **1994a**, 269, 15419–15422.
- DE MORAIS, S. M., WILKINSON, G. R., BLAISDELL, J., MEYER, U. A., NAKAMURA, K., GOLDSTEIN, J. A., Identification of a new genetic defect responsible for the polymorphism of S-mephenytoin metabolism in Japanese. *Mol. Pharmacol.* **1994b**, 46, 594–598.
- DODD, S., BOULTON, D. W., BURROWS, G. D., DE VANE, C. L., NORMAN, T. R., In vitro metabolism of mirtazapine enantiomers by human cytochrome P450 enzymes. *Hum. Psychopharmacol.* **2001**, 16, 541–544.
- DORADO, P., BEREZ, R., NORBERTO, M. J., YASAR, U., DAHL, M. L., LLERENA, A., CYP2C9 genotypes and diclofenac metabolism in Spanish healthy volunteers. *Eur. J. Clin. Pharmacol.* **2003a**, 59, 221–225.
- DORADO, P., BEREZ, R., CACERES, M. C., LLERENA, A., Analysis of diclofenac and its metabolites by high-performance liquid chromatography: relevance of CYP2C9 genotypes in diclofenac urinary metabolic ratios. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2003b**, 789, 437–442.
- DOSTERT, P., BENEDETTI, M. S., POGGESI, I., Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur. Neuropsychopharmacol.* **1997**, 7, Suppl. 1, S23–35.
- EAP, C. B., LESSARD, E., BAUMANN, P., BRAWAND-AMEY, M., YESSINE, M. A., O'HARA, G., TURGEON, J., Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. *Pharmacogenetics* **2003**, 13, 39–47.
- EATON, D. L., GALLAGHER, E. P., BAMMLER, T. K., KUNZE, K. L., Role of cytochrome P4501A2 in chemical carcinogenesis: implications for human variability in expression and enzyme activity. *Pharmacogenetics* **1995**, 5, 259–274.
- EICHELBAUM, M., SPANNBRUCKER, N., STEINCKE, B., DENGLE, H. J., Defective N-oxidation of sparteine in man: a new pharmacogenetic defect. *Eur. J. Clin. Pharmacol.* **1979**, 16, 183–187.
- EICHELBAUM, M., BERTILSSON, L., SAWE, J., ZEKORN, C., Polymorphic oxidation of sparteine and debrisoquine: related pharmacogenetic entities. *Clin. Pharmacol. Ther.* **1982**, 31, 184–186.
- EICHELBAUM, M., BAUR, M. P., DENGLE, H. J., OSIKOWSKA-EVERS, B. O., TIEVES, G., ZEKORN, C., RITTNER, C., Chromosomal assignment of human cytochrome P-450 (debrisoquine/sparteine type) to chromosome 22. *Br. J. Clin. Pharmacol.* **1987**, 23, 455–458.
- EVANS, D. A., MAHGOUB, A., SLOAN, T. P., IDLE, J. R., SMITH, R. L., A family and population study of the genetic polymorphism of debrisoquine oxidation in a white British population. *J. Med. Gen.* **1980**, 17, 102–105.
- EVANS, D. A., HARMER, D., DOWNHAM, D. Y., WHIBLEY, E. J., IDLE, J. R., RITCHIE, J., SMITH, R. L., The genetic control of sparteine and debrisoquine metabolism in man with new methods of analysing bimodal distributions. *J. Med. Genet.* **1983**, 20, 321–329.
- FAUCETTE, S. R., HAWKE, R. L., LECLUYSE, E. L., SHORD, S. S., YAN, B., LAETHEM, R. M., LINDLEY, C. M., Validation of bupropion hydroxylation as a selective marker of human cytochrome P450 2B6 catalytic activity. *Drug Metab. Dispos.* **2000**, 28, 1222–1230.
- FERGUSON, R. J., DE MORAIS, S. M., BENHAMOU, S., BOUCHARDY, C., BLAISDELL, J., IBEANU, G., WILKINSON, G. R., SARICH, T. C., WRIGHT, J. M., DAYER, P., GOLDSTEIN, J. A., A new genetic defect in human CYP2C19: mutation of the initiation codon is responsible for poor metabolism of S-mephenytoin. *J. Pharmacol. Exp. Ther.* **1998**, 284, 356–361.
- FIRKUSNY, L., GLEITER, C. H., Maprotiline metabolism appears to co-segregate with the genetically determined CYP2D6 polymorphic hydroxylation of debrisoquine. *Br. J. Clin. Pharmacol.* **1994**, 37, 383–388.
- FLORES, D. L., ALVARADO, I., WONG, M. L., LICINIO, J., FLOCKHART, D., Clinical implications of genetic polymorphism of CYP2D6 in Mexican Americans. *Ann. Intern. Med.* **2004**, 1, 140.
- FUHR, U., ROST, K. L., ENGELHARDT, R., SACHS, M., LIERMANN, D., BELLOC, C.,

- BEAUNE, P., JANEZIC, S., GRANT, D., MEYER, U. A., STAIB, A. H., Evaluation of caffeine as a test drug for CYP1A2, NAT2 and CYP2E1 phenotyping in man by in vivo versus in vitro correlations. *Pharmacogenetics* **1996**, 6, 159–176.
- FUKUDA, T., NISHIDA, Y., ZHOU, Q., YAMAMOTO, I., KONDO, S., AZUMA, J., The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. *Eur. J. Clin. Pharmacol.* **2000**, 56, 175–180.
- GACHÁLYI, B., RÓNA, K., VAS, A., KÁLDOR, A., A debrisoquin hydroxiláció polimorfizmusának vizsgálata. *Orv. Hetil.* **1986**, 127, 2299–2301.
- GAEDIGK, A., BLUM, M., GAEDIGK, R., EICHELBAUM, M., MEYER, U. A., Deletion of the entire cytochrome P450 CYP2D6 gene as a cause of impaired drug metabolism in poor metabolizers of the debrisoquine/sparteine polymorphism. *Am. J. Hum. Genet.* **1991**, 48, 943–950.
- GHARAMANI, P., ELLIS, S. W., LENNARD, M. S., RAMSAY, L. E., TUCKER, G. T., Cytochromes mediating the N-demethylation of amitriptyline. *J. Clin. Pharmacol.* **1997**, 43, 137–144.
- GONZALEZ, F. J., IDLE, J. R., Pharmacogenetic phenotyping and genotyping: present status and future potential. *Clin. Pharmacokinet.* **1994**, 26, 59–70.
- GONZALEZ, F. J., VILBOIS, F., HARDWICK, J. P., MCBRIDE, O. W., NEBERT, D. W., GELBOIN, H. V., MEYER, U. A., Human debrisoquine 4-hydroxylase (P450IID1): cDNA and deduced amino acid sequence and assignment of the CYP2D locus to chromosome 22. *Genomics* **1988a**, 2, 174–179.
- GONZALEZ, F. J., SKODA, R. C., KIMURA, S., UMENO, M., ZANGER, U. M., NEBERT, D. W., GELBOIN, H. V., HARDWICK, J. P., MEYER, U. A., Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature* **1988b**, 331, 442–446.
- GRAM, L. F., HANSEN, M. G., SINDRUP, S. H., BROSEN, K., POULSEN, J. H., AAES-JORGENSEN, T., OVERO, K. F., Citalopram: interaction studies with levomepromazine, imipramine, and lithium. *Ther. Drug Monit.* **1993**, 15, 18–24.
- GRAM, L. F., GUENTERT, T. W., GRANGE, S., VISTISEN, K., BROSEN, K., Moclobemide, a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. *Clin. Pharmacol. Ther.* **1995**, 57, 670–677.
- GUENGERICH, F. P., Cytochrome P-450 3A4: regulation and role in drug metabolism. *Annu. Rev. Pharmacol. Toxicol.* **1999**, 39, 1–17.
- HARTTER, S., DINGEMANSE, J., BAIER, D., ZIEGLER, G., HIEMKE, C., Inhibition of dextromethorphan metabolism by moclobemide. *Psychopharmacology (Berlin)* **1998**, 135, 22–26.
- HEIM, M., MEYER, U. A., Genotyping of poor metabolisers of debrisoquine by allele-specific PCR amplification. *Lancet* **1990**, 336, 529–532.
- HERMAN, B. D., FLEISHAKER, J. C., BROWN, M. T., Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin. Pharmacol. Ther.* **1999**, 66, 374–379.
- HORMANS, Y., DESAGER, J. P., HARVENGT, C., Absence of CYP3A genetic polymorphism assessed by urinary excretion of 6 beta-hydroxycortisol in 102 healthy subjects on rifampicin. *Pharmacol. Toxicol.* **1992**, 71, 258–261.
- HUANG, J. D., GUO, W. C., LAI, M. D., GUO, Y. L., Lambert GH Detection of a novel cytochrome P-450 1A2 polymorphism (F21L) in Chinese. *Drug Metab. Dispos.* **1999**, 27, 98–101.
- IBEANU, G. C., BLAISDELL, J., GHANAYEM, B. I., BEYELER, C., BENHAMOU, S., BOUCHARDY, C., WILKINSON, G. R., DAYER, P., DALY, A. K., GOLDSTEIN, J. A., An additional defective allele, CYP2C19*5, contributes to the S-mephenytoin poor metabolizer phenotype in Caucasians. *Pharmacogenetics* **1998a**, 8, 129–135.
- IBEANU, G. C., GOLDSTEIN, J. A., MEYER, U., BENHAMOU, S., BOUCHARDY, C., DAYER, P., GHANAYEM, B. I., BLAISDELL, J., Identification of new human CYP2C19 alleles (CYP2C19*6 and CYP2C19*2B) in a Caucasian poor metabolizer of mephenytoin. *J. Pharmacol. Exp. Ther.* **1998b**, 286, 1490–1495.
- IBEANU, G. C., BLAISDELL, J., FERGUSON, R. J., GHANAYEM, B. I., BROSEN, K., BENHAMOU,

- S., BOUCHARDY, C., WILKINSON, G. R., DAYER, P., GOLDSTEIN, J. A., A novel transversion in the intron 5 donor splice junction of *CYP2C19* and a sequence polymorphism in exon 3 contribute to the poor metabolizer phenotype for the anticonvulsant drug *S*-mephenytoin. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 635–640.
- INABA, T., JURIMA, M., KALOW, W., Family studies of mephenytoin hydroxylation deficiency. *Am. J. Hum. Genet.* **1986**, *38*, 768–772.
- IYUN, A. O., LENNARD, M. S., TUCKER, G. T., WOODS, H. F., Metoprolol and debrisoquin metabolism in Nigerians: lack of evidence for polymorphic oxidation. *Clin. Pharmacol. Ther.* **1986**, *40*, 387–394.
- JACKSON, P. R., TUCKER, G. T., LENNARD, M. S., WOODS, H. F., Polymorphic drug oxidation: pharmacokinetic basis and comparison of experimental indices. *Br. J. Clin. Pharmacol.* **1986**, *22*, 541–550.
- JEPPSEN, U., GRAM, L. F., VISTISEN, K., LOFT, S., POULSEN, H. E., BROSEN, K., Dose-dependent inhibition of *CYP1A2*, *CYP2C19* and *CYP2D6* by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur. J. Clin. Pharmacol.* **1996**, *51*, 73–78.
- JIANG, Z. P., SHU, Y., CHEN, X. P., HUANG, S. L., ZHU, R. H., WANG, W., HE, N., ZHOU, H. H., The role of *CYP2C19* in amitriptyline *N*-demethylation in Chinese subjects. *Eur. J. Clin. Pharmacol.* **2002**, *58*, 109–113.
- JOHANSSON, I., OSCARSON, M., YUE, Q.-Y., BERTILSSON, L., SJÖQVIST, F., INGELMAN-SUNDBERG, M., Genetic analysis of the Chinese *P4502D* locus: characterization of variant *CYP2D6* genes present in subjects with diminished capacity for debrisoquine hydroxylation. *Mol. Pharmacol.* **1994**, *46*, 452–459.
- KAGIMOTO, M., HEIM M., KAGIMOTO, K., ZEUGIN, T., MEYER, U. A., Multiple mutations of the human cytochrome *P450IID6* gene (*CYP2D6*) in poor metabolizers of debrisoquine: study of the functional significance of individual mutations by expression of chimeric genes. *J. Biol. Chem.* **1990**, *265*, 17209–17214.
- KALOW, W., Pharmacogenetics: past and future. *Life Sci.* **1990**, *47*, 1385–1397.
- KALOW, W., TANG, B. K., Use of caffeine metabolite ratios to explore *CYP1A2* and xanthine oxidase activities. *Clin. Pharmacol. Ther.* **1991**, *50*, 508–519.
- KELLERMANN, M., REDONDO, M., BEREZ, R., PIÑAS, B., LLERENA, A., DEGRELL, I., The epidemiology and risk factors of schizophrenia in two regions of Spain and Hungary. Abstract for the 10th European Symposium on Psychiatry, Psychiatric Epidemiology and Social Psychiatry, April 6–8, **2000**, Budapest, Hungary.
- KIMURA, S., UMEMO, M., SKODA, R. C., MEYER, U. A., GONZALEZ, F. J., The human debrisoquine 4-hydroxylase (*CYP2D*) locus: sequence and identification of the polymorphic *CYP2D6* gene, a related gene, and a pseudogene. *Am. J. Hum. Genet.* **1989**, *45*, 889–904.
- KIRCHHEINER, J., MEINEKE, I., MULLER, G., ROOTS, I., BROCKMOLLER, J., Contributions of *CYP2D6*, *CYP2C9* and *CYP2C19* to the biotransformation of *E*- and *Z*-doxepin in healthy volunteers. *Pharmacogenetics* **2002**, *12*, 571–580.
- KIRCHHEINER, J., MULLER, G., MEINEKE, I., WERNECKE, K. D., ROOTS, I., BROCKMOLLER, J., Effects of polymorphisms in *CYP2D6*, *CYP2C9*, and *CYP2C19* on trimipramine pharmacokinetics. *J. Clin. Psychopharmacol.* **2003a**, *23*, 459–466.
- KIRCHHEINER, J., KLEIN, C., MEINEKE, I., SASSE, J., ZANGER, U. M., MURDTER, T. E., ROOTS, I., BROCKMOLLER, J., Bupropion and 4-OH-bupropion pharmacokinetics in relation to genetic polymorphisms in *CYP2B6*. *Pharmacogenetics* **2003b**, *13*, 619–626.
- KLEINBLOESEM, C. H., VAN BRUMMELEN, P., FABER, H., DANHOF, M., VERMEULEN, N. P., BREIMER, D. D., Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. *Biochem. Pharmacol.* **1984**, *33*, 3721–3724.
- KOYAMA, E., TANAKA, T., CHIBA, K., KAWAKATSU, S., MORINOBU, S., TOTSUKA, S., ISHIZAKI, T., Steady-state plasma concentrations of imipramine and desipramine in relation to *S*-mephenytoin 4'-hydroxylation status in Japanese depressive patients. *J. Clin. Psychopharmacol.* **1996a**, *16*, 286–293.
- KOYAMA, E., CHIBA, K., TANI, M., ISHIZAKI, T., Identification of human cytochrome

- P450 isoforms involved in the stereoselective metabolism of mianserin enantiomers. *J. Pharmacol. Exp. Ther.* **1996b**, 278, 21–30.
- KOYAMA, E., CHIBA, K., TANI, M., ISHIZAKI, T., Reappraisal of human CYP isoforms involved in imipramine N-demethylation and 2-hydroxylation: a study with microsomes obtained from putative extensive and poor metabolizers of S-mephenytoin and eleven recombinant human CYPs. *J. Pharmacol. Exp. Ther.* **1997**, 281, 1199–1210.
- LAINÉ, K., TYBRING, G., HARITTER, S., ANDERSSON, K., SVENSSON, J. O., WIDEN, J., BERTILSSON, L., Inhibition of cytochrome P4502D6 activity with paroxetine normalizes the ultrarapid metabolizer phenotype as measured by nortriptyline pharmacokinetics and the debrisoquin test. *Clin. Pharmacol. Ther.* **2001**, 70, 327–335.
- LEE, C. R., GOLDSTEIN, J. A., PIEPER, J. A., Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics* **2002**, 12, 251–263.
- LESSARD, E., YESSINE, M. A., HAMELIN, B. A., O'HARA, G., LEBLANC, J., TURGEON, J., Influence of CYP2D6 activity on the disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. *Pharmacogenetics* **1999**, 9, 435–443.
- LLERENA, A., EDMAN, G., COBALEDA, J., BENÍTEZ, J., SCHALLING, D., BERTILSSON, L., Relationship between personality and debrisoquine hydroxylation capacity: suggestion of an endogenous neuroactive substrate or product of the cytochrome P4502D6. *Acta Psychiatr Scand.* **1993a**, 87, 23–28.
- LLERENA, A., VALDIVIELSO, M. J., BENÍTEZ, J., BERTILSSON, L., Reproducibility over time of mephenytoin and debrisoquine hydroxylation phenotypes. *Pharmacol. Toxicol.* **1993b**, 73, 46–48.
- LLERENA, A., HERRAIZ, A. G., COBALEDA, J., JOHANSSON, I., DAHL, M.-L., Debrisoquin and mephenytoin hydroxylation phenotypes and CYP2D6 genotype in patients treated with neuroleptic and antidepressant agents. *Clin. Pharmacol. Ther.* **1993c**, 54, 606–611.
- LLERENA, A., COBALEDA, J., MARTÍNEZ, C., BENÍTEZ, J., Interethnic differences in drug metabolism: influence of genetic and environmental factors on debrisoquine hydroxylation phenotype. *Eur. J. Drug Metab. Pharmacokinet.* **1996**, 21, 129–138.
- LLERENA, A., BEREZ, R., DE LA RUBIA, A., DORADO, P., QTc interval lengthening is related to CYP2D6 hydroxylation capacity and plasma concentration of thioridazine in patients. *J. Psychopharmacol.* **2002**, 16, 361–364.
- LLERENA, A., BEREZ, R., DORADO, P., GONZALEZ, A. P., PENAS-LLEDO, E. M., DE LA RUBIA, A., CYP2C9 gene and susceptibility to major depressive disorder. *Pharmacogenomics J.* **2003**, 3, 300–302.
- LLERENA, A., DORADO, P., BEREZ, R., GONZALEZ, A. P., PENAS-LLEDO, E. M., Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. *Eur. J. Clin. Pharmacol.* **2004**, 59, 869–873.
- MAHGOUB, A., IDLE, J. R., DRING, L. G., LANCASTER, R., SMITH, R. L., Polymorphic hydroxylation of debrisoquine in man. *Lancet* **1977**, 2, 584–586.
- MAHGOUB, A., IDLE, J. R., SMITH, R. L., A population and familial study of the defective alicyclic hydroxylation of debrisoquine among Egyptians. *Xenobiotica* **1979**, 9, 51–56.
- MAREZ, D., LEGRAND, M., SABBAGH, N., GUIDICE, J. M., SPIRE, C., LAFITTE, J. J., MEYER, U. A., BROLY, F., Polymorphism of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. *Pharmacogenetics* **1997**, 7, 193–202.
- MASIMIREMBWA, C., BERTILSSON, L., JOHANSSON, I., HASLER, J. A., INGELMAN-SUNDBERG, M., Phenotyping and genotyping of S-mephenytoin hydroxylase (cytochrome P450 2C19) in a Shona population of Zimbabwe. *Clin. Pharmacol. Ther.* **1995**, 57, 656–661.
- MELLSTROM, B., BERTILSSON, L., SAWE, J., SCHULZ, H. U., SJOQVIST, F., E- and Z-10-hydroxylation of nortriptyline: relationship to polymorphic debrisoquine

- hydroxylation. *Clin. Pharmacol. Ther.* **1981**, *30*, 189–193.
- MELLSTROM, B., BERTILSSON, L., LOU, Y. C., SAWE, J., SJOQVIST, F., Amitriptyline metabolism: relationship to polymorphic debrisoquine hydroxylation. *Clin. Pharmacol. Ther.* **1983**, *34*, 516–520.
- MELLSTROM, B., SAWE, J., BERTILSSON, L., SJOQVIST, F., Amitriptyline metabolism: association with debrisoquin hydroxylation in nonsmokers. *Clin. Pharmacol. Ther.* **1986**, *39*, 369–371.
- MEYER, U. A., Genetic polymorphism of drug metabolism. *Fundam. Clin. Pharmacol.* **1990**, *4*, 595–615.
- MEYER, U. A., ZANGER, U. M., Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 269–296.
- MICHALETS, E. L., Update: clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* **1998**, *18*, 84–112.
- MIHARA, K., OTANI, K., TYBRING, G., DAHL, M. L., BERTILSSON, L., KANEKO, S., The CYP2D6 genotype and plasma concentrations of mianserin enantiomers in relation to therapeutic response to mianserin in depressed Japanese patients. *J. Clin. Psychopharmacol.* **1997a**, *17*, 467–471.
- MIHARA, K., OTANI, K., SUZUKI, A., YASUI, N., NAKANO, H., MENG, X., OHKUBO, T., NAGASAKI, T., KANEKO, S., TSUCHIDA, S., SUGAWARA, K., GONZALEZ, F. J., Relationship between the CYP2D6 genotype and the steady-state plasma concentrations of trazodone and its active metabolite *m*-chlorophenylpiperazine. *Psychopharmacology (Berl.)* **1997b**, *133*, 95–98.
- MORINOBU, S., TANAKA, T., KAWAKATSU, S., TOTSUKA, S., KOYAMA, E., CHIBA, K., ISHIZAKI, T., KUBOTA, T., Effects of genetic defects in the CYP2C19 gene on the N-demethylation of imipramine, and clinical outcome of imipramine therapy. *Psychiatry Clin. Neurosci.* **1997**, *51*, 253–257.
- NAKAMURA, K., GOTO, F., RAY, W. A., McALLISTER, C. B., JACQZ, E., WILKINSON, G. R., BRANCH, R. A., Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. *Clin. Pharmacol. Ther.* **1985**, *38*, 402–408.
- NELSON, D. R., KOYMANS, L., KAMATAKI, T., STEGEMAN, J. J., FEYEREISEN, R., WAXMAN, D. J., WATERMAN, M. R., GOTOH, O., COON, M. J., ESTABROOK, R. W., GUNSALUS, I. C., NEBERT, D. W., P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. *Pharmacogenetics* **1996**, *6*, 1–42.
- NIELSEN, K. K., BROSEN, K., GRAM, L. F., Steady-state plasma levels of clomipramine and its metabolites: impact of the sparteine/debrisoquine oxidation polymorphism. Danish University Antidepressant Group. *Eur. J. Clin. Pharmacol.* **1992**, *43*, 405–411.
- NIELSEN, K. K., BROSEN, K., HANSEN, M. G., GRAM, L. F., Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. *Clin. Pharmacol. Ther.* **1994**, *55*, 518–527.
- OLESEN, O. V., LINNET, K., Hydroxylation and demethylation of the tricyclic antidepressant nortriptyline by cDNA-expressed human cytochrome P-450 isozymes. *Drug Metab. Dispos.* **1997**, *25*, 740–744.
- OTANI, K., AOSHIMA, T., Pharmacogenetics of classical and new antipsychotic drugs. *Ther. Drug Monit.* **2000**, *22*, 118–121.
- OTTON, S. V., BALL, S. E., CHEUNG, S. W., INABA, T., RUDOLPH, R. L., SELLERS, E. M., Venlafaxine oxidation in vitro is catalysed by CYP2D6. *Br. J. Clin. Pharmacol.* **1996**, *41*, 149–156.
- OZDEMIR, V., NARANJO, C. A., HERRMANN, N., REED, K., SELLERS, E. M., KALOW, W., Paroxetine potentiates the central nervous system side effects of perphenazine: contribution of cytochrome P4502D6 inhibition in vivo. *Clin. Pharmacol. Ther.* **1997**, *62*, 334–347.
- PEART, G. F., BOUTAGY, J., SHENFIELD, G. M., Debrisoquine oxidation in an Australian population. *Br. J. Clin. Pharmacol.* **1986**, *21*, 465–471.
- PELKONEN, O., SOTANIEMI, E. A., Environmental factors of enzyme induction and inhibition. *Pharmacol. Ther.* **1987**, *33*, 115–120.
- PICKAR, D., RUBINOW, K., Pharmacogenomics of psychiatric disorders. *Trends Pharmacol. Sci.* **2001**, *22*, 75–83.

- POLLOCK, B. G., SWEET, R. A., KIRSHNER, M., Reynolds CF Bupropion plasma levels and CYP2D6 phenotype. *Ther. Drug Monit.* **1996**, *18*, 581–585.
- RELLING, M. V., CHERRIE, J., SCHELL, M. J., PETROS, W. P., MEYER, W. H., EVANS, W. E., Lower prevalence of the debrisoquin oxidative poor metabolizer phenotype in American black versus white subjects. *Clin. Pharmacol. Ther.* **1991**, *50*, 308–313.
- REVIRIEGO, J., BERTILSSON, L., CARRILLO, J. A., LLERENA, A., VALDIVIELSO, M. J., BENÍTEZ, J., Frequency of S-mephenytoin hydroxylation deficiency in 373 Spanish subjects compared to other Caucasian populations. *Eur. J. Clin. Pharmacol.* **1993**, *44*, 593–595.
- RING, B. J., CATLOW, J., LINDSAY, T. J., GILLESPIE, T., ROSKOS, L. K., CERIMELE, B. J., SWANSON, S. P., HAMMAN, M. A., WRIGHTON, S. A., Identification of the human cytochromes P450 responsible for the in vitro formation of the major oxidative metabolites of the antipsychotic agent olanzapine. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 658–666.
- ROTZINGER, S., BAKER, G. B., Human CYP3A4 and the metabolism of nefazodone and hydroxynefazodone by human liver microsomes and heterologously expressed enzymes. *Eur. Neuropsychopharmacol.* **2002**, *12*, 91–100.
- ROWLAND, M., TOZER, T. N., Clinical Pharmacokinetics: Concepts and Applications, 3rd ed. Williams & Wilkins, Philadelphia, **1995**.
- SACHSE, C., BROCKMOLLER, J., BAUER, S., ROOTS, I., Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am. J. Hum. Genet.* **1997**, *60*, 284–295.
- SATA, F., SAPONE, A., ELIZONDO, G., STOCKER, P., MILLER, V. P., ZHENG, W., RAUNIO, H., CRESPI, C. L., GONZALEZ, F. J., CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: evidence for an allelic variant with altered catalytic activity. *Clin. Pharmacol. Ther.* **2000**, *67*, 48–56.
- SCHELLENS, J. H., SOONS, P. A., BREIMER, D. D., Lack of bimodality in nifedipine plasma kinetics in a large population of healthy subjects. *Biochem. Pharmacol.* **1988**, *37*, 2507–2510.
- SCHOERLIN, M. P., BLOUIN, R. A., PFEFFEN, J. P., GUENTERT, T. W., Comparison of the pharmacokinetics of moclobemide in poor and efficient metabolizers of debrisoquine. *Acta Psychiatr. Scand. Suppl.* **1990**, *360*, 98–100.
- SHIMADA, T., YAMAZAKI, H., MIMURA, M., INUI, Y., GUENGERICH, F. P., Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 414–423.
- SHIMODA, K., SOMEYA, T., YOKONO, A., MORITA, S., HIROKANE, G., TAKAHASHI, S., OKAWA, M., The impact of CYP2C19 and CYP2D6 genotypes on metabolism of amitriptyline in Japanese psychiatric patients. *J. Clin. Psychopharmacol.* **2002**, *22*, 371–378.
- SIMOONYA, O. O., NJUNJU, E., HODJEGAN, A. R., LENNARD, M. S., TUCKER, G. T., Debrisoquine and metoprolol oxidation in Zambians: a population study. *Pharmacogenetics* **1993**, *3*, 205–208.
- SINDRUP, S. H., BROSEN, K., GRAM, L. F., HALLAS, J., SKJELBO, E., ALLEN, A., ALLEN, G. D., COOPER, S. M., MELLOWS, G., TASKER, T. C., The relationship between paroxetine and the sparteine oxidation polymorphism. *Clin. Pharmacol. Ther.* **1992**, *51*, 278–287.
- SINDRUP, S. H., BROSEN, K., HANSEN, M. G., AAES-JORGENSEN, T., OVERO, K. F., GRAM, L. F., Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. *Ther. Drug Monit.* **1993**, *15*, 11–17.
- SKJELBO, E., BROSEN, K., HALLAS, J., GRAM, L. F., The mephenytoin oxidation polymorphism is partially responsible for the N-demethylation of imipramine. *Clin. Pharmacol. Ther.* **1991**, *49*, 18–23.
- SOHN, D. R., SHIN, S. G., PARK, C. W., KUSAKA, M., CHIBA, K., ISHIZAKI, T., Metoprolol oxidation polymorphism in a Korean population: comparison with native Japanese and Chinese populations. *Br. J. Clin. Pharmacol.* **1991**, *32*, 504–507.
- SPIGSET, O., GRANBERG, K., HAGG, S., NORSTROM, A., DAHLQVIST, R., Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19

- phenotype polymorphisms. *Eur. J. Clin. Pharmacol.* **1997**, 52, 129–133.
- SPIGSET, O., GRANBERG, K., HAGG, S., SODERSTROM, E., DAHLQVIST, R., Non-linear fluvoxamine disposition. *Br. J. Clin. Pharmacol.* **1998**, 45, 257–263.
- SPIGSET, O., AXELSSON, S., NORSTROM, A., HAGG, S., DAHLQVIST, R., The major fluvoxamine metabolite in urine is formed by CYP2D6. *Eur. J. Clin. Pharmacol.* **2001**, 57, 653–658.
- SPINA, E., ARENA, A., PISANI, F., Urinary desipramine hydroxylation index and steady-state plasma concentrations of imipramine and desipramine. *Ther. Drug Monit.* **1987**, 9, 129–133.
- SPINA, E., AVENOSO, A., CAMPO, G. M., SCORDO, M. G., CAPUTI, A. P., PERUCCA, E., Effect of ketoconazole on the pharmacokinetics of imipramine and desipramine in healthy subjects. *Br. J. Clin. Pharmacol.* **1997**, 43, 315–318.
- STORMER, E., VON MOLTKE, L. L., SHADER, R. I., GREENBLATT, D. J., Metabolism of the antidepressant mirtazapine in vitro: contribution of cytochromes P-450 1A2, 2D6, and 3A4. *Drug Metab. Dispos.* **2000**, 28, 1168–1175.
- STREETMAN, D. S., BERTINO JS JR, NAFZIGER, A. N., Phenotyping of drug-metabolizing enzymes in adults: a review of in-vivo cytochrome P450 phenotyping probes. *Pharmacogenetics* **2000**, 10, 187–216.
- VEEFKIND, A. H., HAFFMANS, P. M., HOENCAMP, E., Venlafaxine serum levels and CYP2D6 genotype. *Ther. Drug Monit.* **2000**, 22, 202–208.
- VESELL, E. S., Genetical and environmental factors affecting drug disposition in man. *Clin. Pharmacol. Ther.* **1977**, 22, 659–679.
- VOGEL, F., Moderne Probleme der Human-genetik. *Ergeb. Inn. Med. Kinderheilk.* **1959**, 12, 52–125.
- WANG, J. H., LIU, Z. Q., WANG, W., CHEN, X. P., SHU, Y., HE, N., ZHOU, H. H., Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin. Pharmacol. Ther.* **2001**, 70, 42–47.
- WARD, S. A., GOTO, F., NAKAMURA, K., JACQZ, E., WILKINSON, G. R., BRANCH, R. A., S-mephenytoin 4-hydroxylase is inherited as an autosomal-recessive trait in Japanese families. *Clin. Pharmacol. Ther.* **1987**, 42, 96–99.
- WIENKERS, L. C., ALLIEVI, C., HAUER, M. J., WYNALDA, M. A., Cytochrome P-450-mediated metabolism of the individual enantiomers of the antidepressant agent reboxetine in human liver microsomes. *Drug Metab. Dispos.* **1999**, 27, 1334–1340.
- XIE, H. G., Genetic variations of S-mephenytoin 4'-hydroxylase (CYP2C19) in the Chinese population. *Life Sci.* **2000**, 66, 175–181.
- XIE, H. G., STEIN, C. M., KIM, R. B., WILKINSON, G. R., FLOCKHART, D. A., WOOD, A. J., Allelic, genotypic and phenotypic distributions of S-mephenytoin 4'-hydroxylase (CYP2C19) in healthy Caucasian populations of European descent throughout the world. *Pharmacogenetics* **1999**, 9, 539–549.
- YASUI, N., TYBRING, G., OTANI, K., MIHARA, K., SUZUKI, A., SVENSSON, J. O., KANEKO, S., Effects of thioridazine, an inhibitor of CYP2D6, on the steady-state plasma concentrations of the enantiomers of mianserin and its active metabolite, desmethylmianserin, in depressed Japanese patients. *Pharmacogenetics* **1997**, 7, 369–374.
- YOKONO, A., MORITA, S., SOMEYA, T., HIROKANE, G., OKAWA, M., SHIMODA, K., The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. *J. Clin. Psychopharmacol.* **2001**, 21, 549–555.

36

Bioinformatics Approaches for Identifying Allelic Variants in Candidate Pathways underlying Major Depression and Antidepressant Treatment Response

Kristopher J. L. Irizarry

Abstract

Bioinformatics methods have been rapidly advancing and, although many detailed aspects of bioinformatics seem deeply rooted in complex mathematics and sophisticated computational algorithms, the core of bioinformatics is focused on integrating biological knowledge in ways that facilitate genomic discoveries. This chapter provides a detailed view of some of the current methods available for assembling and analyzing combinations of single nucleotide polymorphisms (SNPs) in the context of depression and antidepressant treatment. The chapter begins with the assembly of a large candidate gene set based on the current knowledge of genes and pathways underlying this disorder. Afterwards, methods of selecting and identifying functional and haplotype informative SNPs are discussed, as are methods for analyzing the resulting genotyping data.

In an effort to provide workable and useful bioinformatics knowledge, the chapter offers a number of detailed explanations and descriptions of currently available resources which can be immediately applied to the genetics of depression. Throughout the chapter, the focus is placed on concepts and ideas rather than equations and algorithms. This chapter should be of use to any investigator interested in applying state-of-the-art bioinformatics approaches to the generation and analysis of genetic data relevant to investigations of depression and response to antidepressant treatment.

36.1

Overview of the Genetic Basis of Depression

Although the precise biochemical, molecular, and neurological circuits underlying the pathophysiology of depression have not been completely elucidated [1], a considerable amount of progress has been made. The emerging picture, based on numerous pieces of evidence, has centered the focus upon the monoamines, specifically, the serotonergic and noradrenergic transmitter systems [2–4]. However,

the fact that these neurotransmitter systems are effectively modulated within minutes after exposure to antidepressants [5], while the antidepressant effects of the medications require multiple weeks of chronic use [6], underscores the fact that the molecular and genetic basis of depression remains unknown.

The results of numerous PET and fMRI imaging studies have identified regions of the prefrontal cortex, anterior thalamus, anterior cingulate, subgenual cingulate, orbital frontal cortex, hippocampus, and medial frontal cortex that are likely to be involved in depression [7]. Within these regions, it has become apparent that activity of monoaminergic signaling is reduced or otherwise impaired in unipolar depression. However, systems as diverse as the cholinergic system, the glutaminergic system, the GABergic system, and even the corticotropin releasing hormone (CRH) and hypothalamic–pituitary–adrenal (HPA) axis have been previously implicated in depression as well (for a review, see [8]).

With such a diverse variety of brain regions and signaling systems associated, it is clear that unipolar major depression represents a very complex disorder that occurs as a result of many different genes interacting with each other and the environment. As if the many genes underlying these signaling systems weren't enough, it appears that clinical evidence derived from measurements of hippocampal regions suggests that there is a reduction in its volume in depressed patients [9].

Such results imply that dendritic sprouting, axonal guidance, neurogenesis, as well as other cellular processes involved in neuronal plasticity, might be substantially down-regulated in response to severe chronic stressors preceding the emergence of depression [10]. In fact, the downstream targets of chronic antidepressant treatment appear to include neurotrophic factors such as BDNF [11]. Moreover, the BDNF receptor, *trkB*, has been shown to be induced by antidepressant treatment and is also required for the antidepressant effects to occur [12].

The downstream signaling components of monoamine receptors include cAMP, protein kinase A, phosphodiesterases, and CREB [13], and the downstream signaling components of the growth factor receptors include the MAP kinases [14], STATs [15], and the forkhead transcription factor FKHRL1 [16]. Additionally, there is increasing evidence that inflammation and related immune responses might precipitate depression via the action of specific cytokines [17].

Attempts to integrate this diverse body of data implicating almost every possible regulatory system in the functioning brain as a participant in the etiology of depression makes the search for genetic correlates daunting.

36.2

Understanding Limits of the Current Models

The current models of depression suggest that stress-induced neuronal changes negatively affect region-specific neuronal connectivity and plasticity and that these changes strongly correlate with the onset and progression of depression [18]. Because each of these processes, the perception of cellular stress and the rate and

extent of neuronal plasticity, are ultimately controlled by genes, the models suggest, at least in part, a genetic basis for susceptibility to depression.

However, the lack of detailed knowledge surrounding the molecular events controlling human neuronal signal transduction, neural development, and plasticity severely affects any candidate-based genetic approach one hopes will identify the contributing genes, and more importantly, the alleles responsible for such phenotypic variation.

Furthermore, the very large set of genes involved significantly reduces the statistical power of most traditional genetic studies. This is because traditional genetic association studies rely on the fact that the genes of interest each contribute at least a 1.5 to 2 fold increase in relative risk for a disorder when the associated allele is present [19]. Therefore, to have a 2-fold increase for each associated allele, there can be at most 4–6 genes with such major effect, assuming that one considers alleles or haplotypes present at 5% or greater frequency in the population. This is because, to a rough approximation, the allele frequency in the affected group should be 1.5 to 2 times the frequency in the unaffected group in order to be associated with 1.5 to 2 times the relative risk.

However, when facing such numerous genomic targets, it may be that only in very few instances are there a small handful of genes that are responsible for the majority of inter-individual phenotypic variations in neuronal signaling, growth, and plasticity. More likely, however, is the possibility that hundreds of genes are responsible and that each gene individually contributes very little to the observable phenotypic variation. In such a scenario, traditional genetics approaches are unable to detect any associated alleles. Therefore, the use of bioinformatics in the context of such complexity can prove to be a substantial asset in the quest for the genetic basis of depression and antidepressant treatment response.

36.3

Bioinformatics in the Post-genomic Era

Bioinformatics has dramatically transformed the field of biology over the last 20 years. From its origins in sequence alignment [20] and homology detection [21] to its role in assembling shotgun-sequenced genomes [22], bioinformatics has evolved hand in hand with the growth and complexity of biological datasets. Although the widespread publicity of the completed human genome has made the field of bioinformatics well known, the diverse subdisciplines of bioinformatics exhibit a rapidly accelerating rate of development.

Within the broad domain of bioinformatics, some researchers are developing methods for improving the signal-to-noise ratio in microarray hybridization detection [23], as others are incorporating methods of mining text-based databases such as PubMed to identify novel anti-tumor drugs [24]. Some informatics groups are optimizing graph theory algorithms for querying complex multiple sequence alignments [25], in contrast to others who are building controlled vocabularies to use in annotation ontologies [26]. Still, while some bioinformaticians are building

comprehensive tools for viewing and searching existing genomic data [27], others are mining genetic and proteomic regulatory networks from different data sources [28], while even others develop methods for identifying SNPs and assessing their functional impact on the genome [29].

The simultaneous development and evolution of these diverse bioinformatics resources has resulted in an avalanche of publicly available databases [30], Web-based tools [31], downloadable software [32], and annotation projects [33] that provide tremendous advantages for those who can integrate and use them effectively.

Although there are multiple human genome web resources, including Ensembl (<http://www.ensembl.org/>) [34], NCBI (<http://www.ncbi.nlm.nih.gov/>) [35], and UCSC (<http://www.genome.ucsc.edu/>) [36], the most effective method of mining the human genome requires loading a local copy of the human genome and its associated annotation into a relational database. The reason for this requirement is that, through the use of a freely available relational database such as MySQL (<http://www.mysql.org/>) [37], one can ask whole-genome questions that are not possible within the confines of an online Web-based interface. With a local copy of the genome, one can generate project-specific annotation or accessory files as needed, followed by using the necessary data-querying capabilities enabled by SQL (Structured Query Language).

Obtaining a local copy of the human genome is not as difficult as one might imagine. Most of the existing resources (Ensembl, NCBI, and UCSC) provide FTP access to SQL database dumps that include both the data and the SQL commands for loading the data into a database. The database files can be downloaded and immediately used to generate secondary annotation, which can be also be loaded into the local version of the database and used for queries as needed.

Additionally, there are a number of open-source development tools and libraries that can drastically reduce the time and effort needed to set up the local informatics infrastructure. Some of these resources include BioPerl modules (<http://www.bioperl.org/>) [38], the NCBI Basic Local Alignment Search Tool (BLAST) package (<ftp://ftp.ncbi.nih.gov/blast/>) [39], the BLAT package (<http://genome.ucsc.edu/FAQ/FAQblat>) [40], and the entire suite of Ensembl genome tools (<http://cvsweb.sanger.ac.uk/cgi-bin/cvsweb.cgi/?cvsroot=Ensembl>) [41]. In addition, there are next-generation pharmacogenomics databases such as the Pharmacogenomics Knowledge Base (PharmGKB), which integrate phenotype, genotype, and drug information (<http://www.pharmgkb.org/>) [42].

Examples of valuable datasets and annotation ideal for local databases aimed at investigating the genetic basis of depression include the human reference set of mRNA sequences and corresponding protein sequences [43], the UniGene EST database which includes ESTs derived from annotated tissue- and disease-specific cDNA libraries [44], the SwissProt annotated protein database [45], pFAM protein motif database [46], OMIM database [47], and polymorphism databases including the dbSNP database, (<http://www.ncbi.nlm.nih.gov/SNP/>) [48], HGVbase (<http://hgvbase.cgb.ki.se/>) [49], and the SNP Consortium (<http://snp.cshl.org/>) [50]. One can find a substantial amount of third-party or user-contributed annotation files and genomic coordinate files at the UCSC Human Genome Annotation download

Table 36.1 Comprehensive list of genomic and proteomic resources. Many resources are available for use in identifying the functional regions of genes and proteins. These resources can be used to create a local version of the human genome database using a relational database server. Most of these resources are freely available to academic institutions, although a few may require a nominal licensing fee.

Resource	URL	Use/contents
BioBase	http://www.gene-regulation.com/	transcription
BLAST	ftp://ftp.ncbi.nih.gov/blast/	sequence homology
BLAT	http://www.cse.ucsc.edu/~kent/src/unzipped/blat/	sequence homology
BodyMap	http://bodymap.ims.u-tokyo.ac.jp/	gene expression
dbSNP	http://www.ncbi.nlm.nih.gov/SNP/	polymorphisms
EMBL	http://www.ebi.ac.uk/Databases/index.html	databases
Ensembl	http://www.ensembl.org/	databases
Entrez	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide	sequence data
Transcription Links	http://www.informatics.ucla.edu/expression.html	gene expression
Genome Links	http://www.informatics.ucla.edu/genomes.html	genomes
GEO	http://www.ncbi.nlm.nih.gov/geo/	gene expression
GOLD	http://www.genomesonline.org/	genomes
HGVbase	http://hgvbase.cgb.ki.se/	polymorphisms
HMMer	http://hmmmer.wustl.edu/	sequence annotation
Hugo	http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl	gene names
InterPro	http://www.ebi.ac.uk/interpro/	sequence annotation
Kegg	http://www.genome.jp/kegg/kegg3.html	pathways
LocusLink	http://www.ncbi.nlm.nih.gov/LocusLink/	genes and loci
Microarray Links	http://www.informatics.ucla.edu/microarrays.html	gene expression
NCBI Map View	http://www.ncbi.nlm.nih.gov/mapview/	genome
Omim	http://www3.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM	disease
Organism Links	http://www.informatics.ucla.edu/organisms.html	model organisms
Pathway Links	http://www.informatics.ucla.edu/pathways.html	pathways
PDB	http://www.rcsb.org/pdb/	protein structure
pFAM	http://www.sanger.ac.uk/Software/Pfam/	sequence annotation
ProDom	http://protein.toulouse.inra.fr/prodom/current/html/home.php	sequence annotation
Protein Links	http://www.informatics.ucla.edu/proteins.html	databases and tools
Proteomics Tools	http://us.expasy.org/tools/	databases and tools
PubMed	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=Limits&DB=PubMed	literature database
RefSeq	http://www.ncbi.nlm.nih.gov/RefSeq/	sequence data
Sanger	http://www.sanger.ac.uk/HGP/links.shtml	genome
SCOP	http://scop.mrc-lmb.cam.ac.uk/scop/	protein structure
SNP Consortium	http://snp.cshl.org/	polymorphisms
Software Links	http://bioinformatics.org/	software
SwissProt	http://www.expasy.org/cgi-bin/sprot-search-ful	sequence annotation
UCSC Genome	http://genome.ucsc.edu/	genome
UniGene	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=unigene	EST database

site (<http://hgdownload.cse.ucsc.edu/downloads.html#human>), which includes syntenic alignments [51] of the human genome with the mouse and rat genomes, as well as preliminary promoter coordinates [52]. The UCSC download site is organized by builds (e.g., hg15, hg16, hg17). These builds correspond to specific releases of the human genome from NCBI (e.g., release 34). One should be sure to obtain the correct coordinate files from UCSC that correspond to the NCBI version of the genome used.

Once a human genome database is implemented locally, one can use the BLAST software in conjunction with the *protein-feature* annotation in the SwissProt database or the motifs in pFAM to identify the functional protein domains in the entire set of human RefSeq protein sequences. These motifs can then be mapped to the chromosomal coordinates using either existing coordinate files, if available, or the BLAT software package along with the full-length human chromosomal FASTA sequences, available from NCBI. Finally, one can obtain coordinate files that map most publicly available reference SNPs to a unique location on a human chromosome [53]. Subsequently, those SNPs occurring in protein functional regions can be identified. Furthermore, one can use SQL to select those reference SNPs from dbSNP which cause nonsynonymous amino acid substitutions in the functional regions of proteins of interest [54].

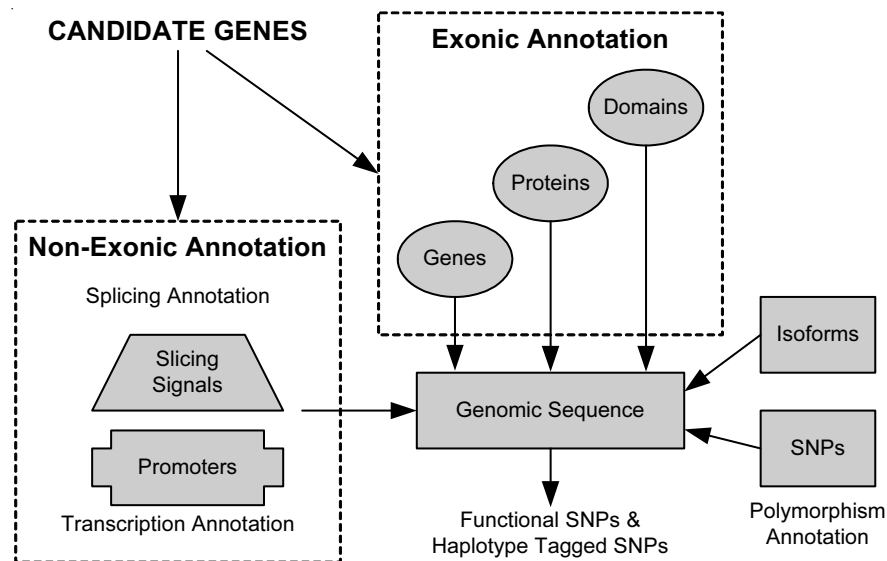


Figure 36.1 The flow of information in identifying single nucleotide polymorphisms (SNPs) through the use of multiple genomic resources. Once candidate genes have been selected based on relevant criteria, SNPs can be selected by combining the various types of genomic information that are publicly available. The resulting annotation can be used to identify the genomic coordinates of each candidate gene, as well as the various functional regions associated with each gene, such as functional protein domains, exons, promoters, and splicing signals.

Table 36.2 Bioinformatics pipelines and methods for annotating genomes. These references provide examples of various methods of combining datasets by using statistical methods. The resulting data are highly useful for making decisions, such as which SNPs to select for a genotyping study or which genes to include in a candidate gene set. Some of these references provide detailed examples of complete data pipelines, and others provide insight into a single step of genomic annotation. All of these references are cited throughout the text of this chapter; they are included here for ease of access.

<i>Method</i>	<i>Reference</i>	<i>Method</i>	<i>Reference</i>
Intragenic SNP selection	127	Gene prediction tools	67
In-silico psychiatric genetics	31	Protein networks	59
Text-mining PubMed	24	BioPerl software tools	39
Gene ontology annotation	26	Genome annotation	58
Microarray analysis	56	Genome annotation	62
Missing pathway nodes	68	Online resource detection	32
Protein structure	55	Coding region annotation	79
Genome annotation	34	Database searching	71
Signal peptides	74	BLAT	41
Genome annotation	33	BioPerl software tools	38
Detecting SNPs from ESTs	29	SNP analysis	54
Reducing genomic complexity	108	Promoter annotation	52
Genome annotation SNPs	53	Sequence annotation	60
Transmembrane topology	75	Intergenome comparisons	80
cDNA annotation	57	Regulatory networks	28
BLAST	40	Interaction annotation	63
Genome annotation	64	Regulatory SNP selection	61
PharmGKB	42	EST annotation of genome	44

Together, these resources provide the means to query the genome for genes and allelic variants likely to be involved in the genetic susceptibility and progression of depression. Table 36.1 provides a comprehensive list of resources, and Figure 36.1 illustrates the relationships between the different resources as well as the flow of information derived from their use. Numerous examples of data pipelines [55–58], secondary annotations [59–62], and other bioinformatics annotation examples [63, 64] constructed from similar types of resources, along with related methods, are summarized in Table 36.2.

36.4 Understanding False Positives and False Negatives

The previous section on bioinformatics resources for use in constructing local versions of the human genome outlines the basic steps taken to combine different data types in the process of generating a valuable local genomics resource. Of particular importance, however, is the proper use of statistical methods [65–70] to assure that the resulting annotations and datasets reduce the time for discovery.

Methods such as BLAST and other sequence-comparison methods such as BLAT provide a score and an expectation value [71] that indicate the degree of similarity or relatedness between the matched sequences. Other tools may or may not provide statistical measures of the results produced.

Because bioinformatics is a computational science, it relies on statistically sound biological models of the processes under investigation to rank-order predictions and to select only the subset of results that are most likely to be real. In other words, one wishes to maximize the number of true positives in the set of predictions or annotations while simultaneously attempting to minimize the number of false positives (these are also known as type I and type II errors, respectively) [72].

True positives correspond to computational results that prove to be verifiable or detectable experimentally. False positives correspond to computational predictions that cannot be experimentally verified. Similarly, true negatives correspond to features that were not computationally predicted and, consequently, cannot be experimentally verified, whereas false negatives correspond to features or annotations that were not predicted via bioinformatics methods but are experimentally verifiable (Figure 36.2).

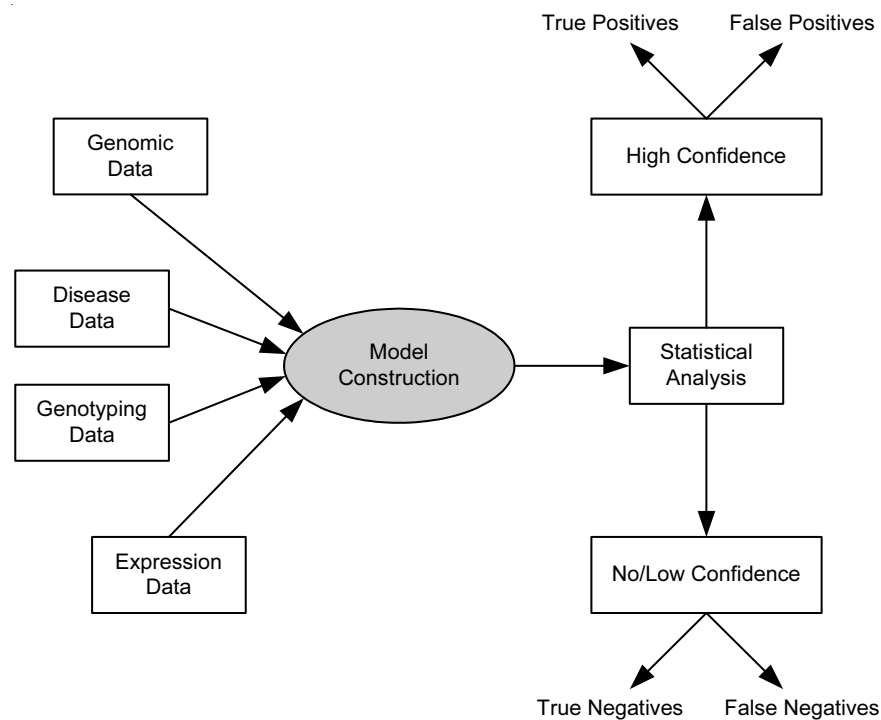


Figure 36.2 Understanding false positives and false negatives. Any statistical analysis that attempts to provide classification or prediction information inevitably produces some fraction of 'misclassified' high-confidence predictions, called false positives. In addition, some false negatives are also produced, entities that are misclassified as not belonging to the set of true positives.

The relationship between the true and false positives and negatives is intricately related to the sensitivity (ability to detect true positives) and selectivity (ability to avoid false positives) of the bioinformatics tool or process being used. If the tool has poor sensitivity, then it fails to predict many real and verifiable features in the resulting dataset. Moreover, if the selectivity is poor, the resulting annotations are incorrect. Typically, the ideal bioinformatics tool exhibits infinite sensitivity and infinite selectivity – getting every true positive and not a single false positive. However, in practice, such black-and-white boundaries between true positives and false positives are rarely encountered.

Because bioinformatics resources generally produce annotations or predictions across the entire genome or proteome [73–75], a metric is typically used to rank the predictions in order of decreasing confidence of being a true positive. Inevitably, as one increases the stringency of the metric to remove false positives, more and more true positives in the gray area are lost from the predictions (false negatives). And, as one relaxes the stringency to include more and more true positives, an increasing number of false positives end up in the predictions as well. Since the goal of bioinformatics is to reduce the time and cost for a discovery (relative to using experimental brute force across the entire genome), the relationship between true positives, false positives, true negatives, and false negatives must be carefully weighed to optimize the results from the specific research plan.

36.5

Combinatorial Complexity in the Human Genome

The human genome contains 3.2 billion nucleotides distributed across 24 chromosomes numbered 1–22, X, and Y [76, 77]. To date, the number of genes in the human genome has not been completely determined [78]. Estimates range from 25 000 to 40 000 or even higher [79–81]. Moreover, the proteomic diversity resulting from alternative splicing [82, 83] and tissue-specific isoforms [84, 85] may effectively result in hundreds of thousands of distinct gene products that interact in tissue- and time-specific patterns to create a human being.

This complexity of the human genome has been traditionally viewed as an impediment to identifying the genetic correlates of polygenic human diseases [86]. Because such complex phenotypes are attributed to the combined action of numerous genomic loci [87], attempts to identify the underlying multilocus interactions are typically unsuccessful, due to the exponential number of false-positive multilocus interactions that are detected in parallel with relatively few true positives [88]. This explosion of false-positive noise drowns out the true genetic signal (Figure 36.3).

The combined limitations imposed by current genetic models of depression and association study design cause some investigators to either choose a small number of high-confidence candidate genes [89, 90] or pursue a genome-wide approach [91, 92] to identify statistically significant region(s) of association. The two approaches can, in some instances, be considered equally limiting. The power to

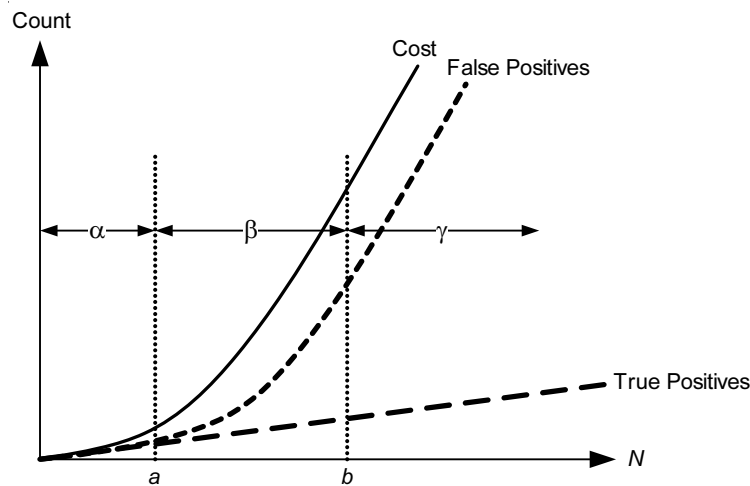


Figure 36.3 Reduced computational search space. This graph captures the behavior of the three most important features: the cost, the false positives, and the true positives. At relatively small N (which corresponds to the number of intervals or loci), there are fewer epistatic interactions and the fewest false positives. The interesting location in this graph is the region bounded by a and b and labeled β . In this portion of the curve, the relationship between the true positives and false positive appears almost linear, and at very small values of N within this middle region, the number

of true positives is almost the same as the number of false positives. The region of this curve to avoid is all portions to the right of b , the region labeled γ . At $N \geq b$, the false positives dominate and may actually hinder the detection of a real signal.

(This figure was taken with permission from Irizarry, K. J. L., Merriman, B., Bahamonde, M. E., Wong, M.-L., Licinio, J., The evolution of signaling complexity suggests a mechanism for reducing the genomic search space in human association studies [108].)

detect associations in candidate gene approaches relies on numerous factors, including the number of true-positive loci in the candidate set [93], and the familial-based linkage scan, if the sample size is not large enough, may also suffer from ineffective power to detect a genetic signal [94]. Hence, the researcher must either exclude all but a few genes or consider the entire genome but be unable to detect significant associations.

The desire to understand how complex phenotypes are encoded in the genome must begin with the realization that these phenotypes arise through the interactions of numerous genes with each other and the environment. But even more importantly – these complex interactions arose through an evolutionary process that integrated two or more simpler signaling processes to create some cellular functionality that was originally absent from the cell [95].

A well established notion in evolutionary biology is that cells have evolved through the continued use of adaptable reusable signaling components equivalent to switches, rheostats, amplifiers, noise filters, oscillators, memory elements, and homeostats [96]. These molecularly encoded functional components can be assembled during evolution to create simple circuits [97], which can grow into

pathways [98, 99], and ultimately into the genetic modules corresponding to distinct cellular programs [100]. Such modules might include transcription networks [101, 102], certain axis-specification systems in developmental biology [103], or any number of metabolic and/or signaling pathway components [104–106].

Because the purpose of evolution is to increase the quantity of information the genome contains regarding the environment [107], one can view the evolution of genomic complexity as the accumulation of environmental association ‘rules’ [108]. As presented in reference [108], the environmental information encoded in the genome couples a genomic interval of defined sequence and finite length to either: (1) some chemical structure that is not encoded by the same genome, (2) another sequence-specific genomic interval of fixed length within the same genome, or (3) a specific chemical or biochemical reaction.

Given the genome’s purpose of enhancing fitness via accumulating environmental association rules, there are only two organizational constraints placed on the evolving genome concerning encoding these association rules: first, association rules that are implemented (used by the cell) simultaneously must not adversely affect one another, and second, newly acquired association rules must not overwrite previously acquired association rules. While these two rules are maintained, the evolution of the rules may grow more complex.

Subsequently, the evolution of pathway modules and multimodule networks occurs through the gradual accumulation of genomic intervals encoding association rules corresponding to some (intracellular or extracellular) environmental features. Because of this genomic encoding, any cellular pathway can be mapped directly back to the genome as a set of discontinuous intervals that encode both the structural features, corresponding to RNA and proteins, as well as the regulatory features of the pathway, including transcriptional control elements such as promoters, splicing enhancers, and peptide localization signals (Figure 36.4).

In the context of genomic intervals mapping to some particular fractional length of the human genome, which may be considered a genomic subset, one can consider what fraction of that genomic subset is closed to genetic influence arising from regions (of the same genome) that lie outside this previously defined genomic subset.

By stating that a genome subset is ‘closed’ under a cellular program, ‘metabolism’ (for example), one would be stating that all genomic intervals affecting signaling, regulation, induction, and all other aspects of metabolic activity have been included in the subset and there are no other regions of the genome that can possibly contribute to the regulation of metabolic activity. Obviously, this is a very difficult condition to achieve. More likely, one might estimate that 75% of contributing genomic intervals are included in a genomic subset having 25% fractional length of the entire genome. One might call this 75% closure at 25% of the genomic length.

Through the use of genomic subsets, one can achieve a reduction in the combinatorial complexity of multilocus genetic association studies. As the fractional length of the genome decreases, the combinatorial explosion of false positives continues to drop. For some very small fractional lengths that exhibit significant

amounts of closure, the number of false positives may be just one or two times the number of real positives, meaning that potentially 15% to 30% of detected multilocus interactions may be true positives. In this manner, a reduction in search space complexity is accomplished by spiking a very small fraction of the genome with most of the contributing multilocus interactions. Because the genomic intervals are discontinuous and potentially correspond to only a single interacting domain or genomic signal, the fractional genomic length can be reduced substantially and the true-positive rate maximized to its theoretical limit.

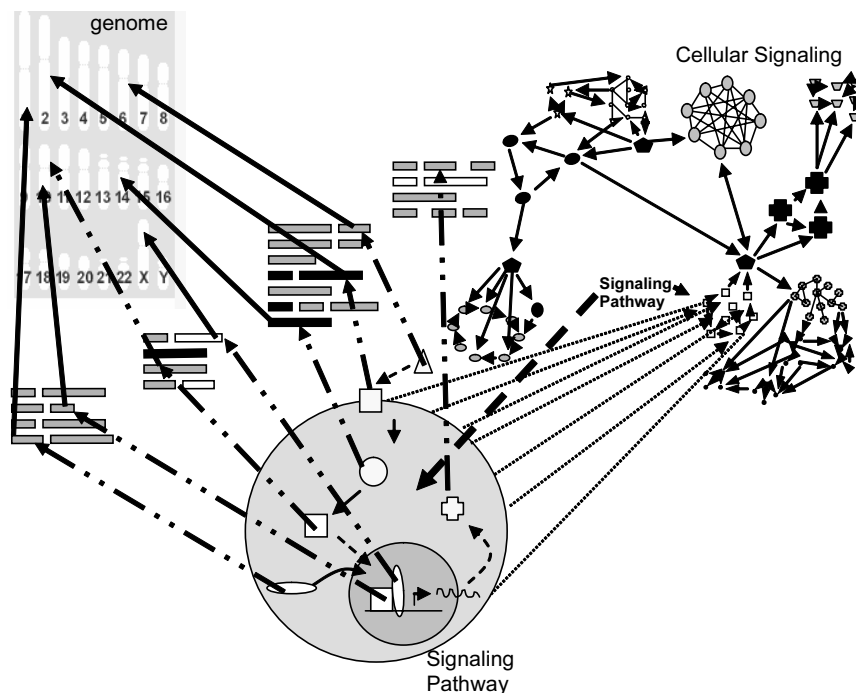


Figure 36.4 Mapping pathways to genomic intervals. A multimodule candidate gene set is illustrated in the upper right corner of this figure. A single module, corresponding to one pathway, is mapped to the genome as a combination of discontinuous intervals. Each interval contains an important regulatory signal, such as a promoter or enhancer, a protein domain, or a splicing signal.

Together, the set of intervals corresponding to the module or pathway constitutes a genomic subset.

(This figure was taken with permission from Irizarry, K. J. L., Merriman, B., Bahamonde, M. E., Wong, M.-L., Licinio, J., The evolution of signaling complexity suggests a mechanism for reducing the genomic search space in human association studies [108].)

36.6

Assembling Candidate Gene Sets

The continued quest to understand how the human brain functions contributed greatly to developmental insight gained from numerous model organisms such as *Drosophila* [109, 110], *Caenorhabditis elegans* [111], and *Mus musculus* [112–114]. Further advances have been made in the areas of learning and memory and synaptic plasticity [115–117]. The strides made in this arena during the last two decades have dramatically changed our understanding of neuronal plasticity. The implication of the NMDA glutamate receptor with temporal coordination of the conditioned and unconditioned stimuli in classical conditioning [118] has provided a molecular theory for the macroscopic phenomenon. Moreover, the recent advances in axonal guidance [119] and dendritic sprouting [120] have shed considerable light on the roles of adhesion molecules [121] and extracellular matrix reorganization [122] in these examples of synaptic plasticity.

Although our understanding of the molecular basis of brain development, function, and plasticity is far from complete, our understanding does provide considerable insight into the general molecular mechanisms underlying brain function and human behavioral phenotypes [123]. Therefore, even though the extent of our understanding is not complete enough to list with certainty all pathway members and all physical interactions, it is sufficient for generating large gene sets corresponding to diverse signaling pathways and signaling systems with fairly well defined functionality the nervous system [124–126].

Even though many of the specific downstream signaling molecules in neuronal and glial cells are either completely unknown or poorly characterized in terms of where they fit in a particular signaling cascade, the global properties of these signals are known, so that some genes can be easily excluded or included with varying degrees of certainty. For example, a candidate transcription factor that is responsible for the activation of an immediate early gene must exhibit the properties of a transcription factor. Therefore, it might contain some form of DNA binding motif and/or dimerization domain and possibly a nuclear localization signal. Although it is possible that a gene product playing the same role might have none of those protein features, the likelihood of each subsequent domain being absent from a true-positive gene product fulfilling the function of a transcription factor decays exponentially.

Therefore, although one or two genes might have atypical properties that make their functional annotation incomplete or wrong, the majority of annotated genes have fairly well characterized domains and known subcellular localizations.

The generation of these gene lists relies heavily on the use of genomic annotation. Genomic annotation has been extremely useful in the generation of large fully annotated genomic databases [127]. The generic model organism databases, such as FlyBase [128] and WormBase [129], have relied very heavily on homologous gene relationships to provide functional annotation across paralogs and orthologs [130]. Such homology-based annotation methods have proven very informative in identifying human genes of interest, both in neural development [131] and human disease [132].

Notwithstanding the fact that much more sophisticated methods can be designed to construct a genomic subset for investigating the genetic basis of depression and antidepressant treatment response, the following description relies on techniques that can be completely accomplished using only an Internet browser and a relational database. The algorithm of importance, so to speak, is the conceptual methodology used to construct the candidate gene set(s), which includes the rationale and justification for gene member inclusion as well as the design of a relational database table for loading the results.

A neural signaling depression-relevant gene set can be constructed by querying the Locus Link database (<http://www.ncbi.nlm.nih.gov/LocusLink/>) [133] for genes belonging to specific gene families and/or containing specific combinations of annotation features. The results of the LocusLink queries can be cut and pasted into a spreadsheet and then exported as a tab-delimited file, which is the default format for loading data into MySQL tables.

For example, the neurotransmitter receptors can be obtained by searching for each gene family using keyword searches such as 'serotonin receptor', 'adrenergic receptor', 'acetylcholine receptor', 'glutamate receptor'. Likewise, the neurotransmitter synthesis genes can be identified by using a combination of various search terms including 'tryptophan hydroxylase' and 'serotonin synthesis'. Similar searches can be used to identify genes for other transmitter-related biosynthetic enzymes. Genes for the neurotransmitter transporters can be easily identified by using the 'transporter' keyword. Additional genes outside of the specific neurotransmitter classes, such as the synaptic-vesicle associated genes, can be identified by searching for 'synaptic', 'vesicle brain', and 'synapse'. Even more relevant gene groups, such as genes involved in neuronal plasticity and neural development, can be assembled by using a complex arrangement of search terms followed by manual inspection of the resulting genes coupled with occasional searches in the PubMed database (<http://www.ncbi.nlm.nih.gov/>) to identify gene function in cases where the LocusLink annotation is sparse.

Modules within the candidate gene set are constructed through the use of an arbitrary classification of genes into functional groups based on the membership of their encoded proteins in a particular protein family, role in transducing a specific intracellular–cellular signal, and/or other relevant biological or biochemical trait. For the sake of simplicity, the construction of only eight modules is described below in the subsequent subsections of this portion of the chapter. These eight modules correspond to a large fraction of the types of genes included in the final candidate gene set; however, the candidate genes selected by using this method were actually classified into a finer resolution module map corresponding to 50 different modules (see Table 36.4).

36.6.1

Neurotransmitter-related Genes (Module 1)

The neurotransmitter signaling gene module can be constructed incrementally by first identifying all the genes that mediate neurotransmitter function. Within the

class of genes encoding monoamine neurotransmitters, one can identify 22 serotonergic-associated genes, 18 genes involved in the regulation of adrenergic signals, and 23 genes involved in dopaminergic signaling. The monoamine transmitter genes include 9 encoding for adrenergic receptors, 5 for dopamine receptors, 14 for serotonin receptors, as well as 16 genes directly involved in neurotransmitter production, transport, and/or degradation.

Within the excitatory glutaminergic signaling system, 25 glutamate receptors, a transporter, and three enzymes involved in the biosynthesis of glutamate can be identified. For the inhibitory GABA neurotransmitter, simple text queries produced 19 GABA receptors, four transporters, and four GABA biosynthesis enzymes. Searching for additional genes associated with various molecules loosely considered neurotransmitters, which include various neurotransmitters and other neural-signaling molecules, can generate a total of 171 genes.

36.6.2

G-protein α , β , and γ Subunits (Module 2)

Since the neurotransmitter gene set represents the most widely known neural signaling systems, it seems worthwhile to include genes in this gene set that may be just as important to neuronal signaling, but not be as ubiquitously studied. Therefore, the next most logical group of genes to consider for this set are those whose products transduce the neurotransmitter signals down into the cellular nucleus so as to rewire the genetic program of the neuron in response to changing environmental conditions.

Such genes include those encoding the G-protein α , β , and γ subunits as strong candidates for mediating a wide variety of brain signaling. Because the majority of monoamine neurotransmitters are G-protein-coupled receptors, we could choose to include genes for all identified G-protein subunits, independent of whether or not they exhibited evidence of neuronal expression. Although several distinct G- α subunits have been demonstrated to be mostly associated with specific neurotransmitter receptors [135], the minimal set of false positives introduced into the set by considering all of the subunits is negligible. Furthermore, the α , β , and γ subunits of the G-proteins are likely to cross-communicate with numerous different receptors and therefore engage in a wide variety of receptor-mediated signaling events [136]. By including genes for every G-protein identified, one could find 15 α subunits, 7 β subunits, and 9 γ subunits, corresponding to just over 30 distinct genes.

36.6.3

Adenylate Cyclase and Cyclic AMP Response Element Components (Module 3)

Within the signal-transduction cascade from neurotransmitter receptor to nucleus are a number of gene products that have been extensively studied in the context of activated neurotransmitter receptors and been shown to be translocated, phosphorylated, or otherwise 'activated' by the transmitter system [137]. One of these proteins, adenylate cyclase, after its activation, catalyzes the formation of cAMP, which serves

as a powerful second messenger signal inside neurons [138, 139]. Queries for this class identified nine of the known human adenylate cyclase genes. Even though only three were specifically annotated as neurally expressed, considering the additional six would barely affect the false positive rate in this gene set.

It is worthwhile to note that a lack of genomic evidence supporting neuronal expression does not conclusively rule out the possibility that a gene may still participate in brain signaling [140]. Furthermore, evidence that the brain exhibits some of the most diverse levels of gene expression, coupled with the fact that many genes, even when expressed, are expressed to such low levels that their detection is at or below the current limits of detection [141], suggests that the lack of evidence for expression may have nothing to do with whether a gene is truly expressed in the brain.

The incorporation of CRE (cAMP response element)-associated nuclear proteins drastically extends the cellular function of the existing gene set members from the cellular membrane components down into the nucleus. Many of these genes have been implicated in neuron-specific induction of downstream targets after exposure to antidepressants [142]. Subsequently, queries of LocusLink identified 13 genes, including *CREM*, *CREB1*, *CREB3*, *CREB4*, and *CREB5*, among those for other cAMP-responsive transcription factors.

36.6.4

Mitogen-activated Kinase Genes (Module 4)

Because the mitogen-activated kinases (MAP) play an important role in intracellular signaling events [143], in both neurons [144] and glial cells [145], it would be wise to include a large set of MAP kinase genes. These genes all encode kinases and may or may not be expressed in the brain. However as stated above, the lack of positive evidence for brain expression is no justification for excluding a gene from this list. In total, one can identify 20 MAP kinase genes using simple text-based keyword searches within the LocusLink database. Among those identified are *MAPK1*, *MAPK3*, *MAP2K2*, *MAP2K4*, and *MAP3K3*. These represent the MAPK, MAPKK, and MAPKKK members of this family.

36.6.5

Neural Hormones and Other Neural Signaling Molecules (Module 5)

Because neural hormones play a vital role in endocrine signals throughout the brain and body [146] and have been implicated in mediating the onset and duration of depression [147], including a number of genes from this category in the gene set would be wise. Several modules could be constructed around secretin, somatostatin, melanocortin, neuropeptide Y, and the corticotrophin-releasing hormone systems. Within these modules are genes for the somatostatin receptors *SSTR1*, *SSTR2*, *SSTR3*, *SSTR4* and the neuropeptide Y receptors *NPY1R*, *NPY2R*, and *NPY5R*. Genes for a number of protein ligands, including CRH, urocortin (*UCN*), *UCN2*, *NPY*, pro-opiomelanocortin (*POMC*), and CRH-binding protein (*CRHBP*), can also be included.

Additionally one could consider including genes for the cannabinoid receptors CNR1 and CNR2, based on the association of one of the cannabinoid receptors with the immune system [148], as well as the evidence demonstrating relations between endogenous cannabinoids and anxiety [149, 150], inflammation [151], and cytokine signaling [152]. The relations provide a relatively important link between neural signaling and immune pathways, both of which have been implicated in mediating aspects of depression [153].

36.6.6

Growth, Development, and Plasticity-associated Genes (Modules 6–8)

To enlarge the gene set, one could include many genes involved in patterning the brain and controlling neuronal differentiation. Because very little is known about the genetic circuits underlying human brain development [154], use of model organism neural development annotation can provide substantial insight. In total, it is possible to identify 182 genes associated with growth, cell adhesion, plasticity, and development of the brain. Some of the genes in the neural development module include genes for these homeobox transcription factors: OTX1, OTX2, DLX1, DLX2, DLX3, DLX4, DLX5, and DLX6 [155–157].

The module corresponding to the set of genes involved in neuronal plasticity that could be identified includes genes encoding several adhesion molecules such as LAMB1, LAMB2, LAMC1, LAMC2, LAMC3, and LAMR1. These genes, in combination with other types of genes, including those for kinases such as PAK3 [158] and for adaptor molecules like MYLIP, NAV1, and NAV2 [159], encompass the neuronal plasticity component or module of the gene set.

An additional module centered around nerve growth factor–associated genes includes genes involved in Notch-mediated developmental signals [160]. Some of the NGF components [161] in this module are NTRK1, NTRK2, NTRK3, and BTG2. The Notch signaling components are identified and represented by genes like *NOTCH1*, *NOTCH2*, *NOTCH3*, and *NOTCH4*, as well as the Notch-family ligand genes *JAG1* and *JAG2* [162].

36.6.7

Design of the Database Schema

The structure of a database for storing and querying the candidate gene set should be designed to enable effective queries across this diverse gene set (Figure 36.5). The first step in loading the data into a database is to select the set of additional data and/or annotation that will be included with this data. Documentation for using the MySQL database server and client is freely available from the MySQL website (<http://dev.mysql.com/doc/mysql/en/>).

If the gene identifiers are LocusLink identifiers (locusId's), then the spreadsheet might contain 650 locus identifiers in its first column. Additional fields can be added, such as an integer module identifier in the second column (moduleId) and a simple text-based module name (module) in the third column. The moduleId is

Genes		moduleSNP
locusId geneName moduleId module signal proteinType cellLocation geneGroup	geneSNP	module geneName totalGenes numSNPs nonsynSNPs untransSNPs intronSNPs totalSNPs
	rsId class locusId gene protPos refProtId	

Figure 36.5 Database architecture for candidate genes and SNP data. The ideal database schema includes tables for querying the resulting data across genes, modules, and SNPs. Therefore, the construction of three distinct database tables is warranted. Each table is used for a specific ‘slice’ of the data, such as SNPs or modules. The combination of tables (geneSNP and moduleSNP) allows for

obtaining SNP results that are based on features in the Genes table. For example, one could select all nonsynonymous SNPs that occur within the subset of genes that have proteinType = ‘receptor’. These three tables provide the minimal basic schema required for working with this candidate gene set and SNPs. Additional tables can be introduced for other annotation features of the data.

simply a list of integer identifiers for the modules (i.e., 1, 2, 3, 4, 5, ...), which map directly to module names such as ‘neurotransmitter-related genes’ in the eight-module example (or names like ‘serotonin receptor’, ‘adrenergic receptor’, ‘serotonin biosynthesis’, ‘neural apoptosis’, ‘neural adhesion’ in the 50-module example).

Then, for each gene in the candidate set, one records the signal or molecular process for the gene in the fourth column, using terms such as ‘serotonin’, ‘neural development’, ‘apoptosis’, or ‘adrenergic’. In the fifth column, list the protein type (‘transcription factor’, ‘receptor’, ‘enzyme’), so that queries can be made that include only subsets of the various protein types. Next, the subcellular localization can be obtained and recorded, so that queries can be performed according to the subcellular location of each gene product, such as the nucleus or membrane. Finally, the seventh column (geneGroup) can contain a very general term that indicates the major function of the gene, for example ‘neural development’, ‘neural plasticity’, ‘neurotransmitters’, to suggest a few. Once all the data have been recorded, the spreadsheet can be saved as a tab-delimited text file, which can then be loaded directly into the database after creating the table.

The design of the table structure should be optimized to allow for complex WHERE clauses in the SQL language based on specific gene parameters of interest such as: *protein cellular location*, *protein type*, *signaling process*, or *neural function*. The final structure of the geneModule database table should include the following fields: **locusId** INT(11) primary key, **gene** VARCHAR(16), **moduleId** INT(11), **module** VARCHAR(64), **signal** VARCHAR(255), **proteinType** VARCHAR(128), **cellLocation** VARCHAR(64), and **geneGroup** VARCHAR(128). To maximize the functionality of this table while minimizing its size, some fields can be used for

two or more purposes when the field had different or nonrelevant meanings across different gene modules. For example, all the serotonin receptors and serotonin-biosynthesis enzymes can clearly be considered part of the ‘serotonin’ signal; however, for modules like ‘neural development’ such a single signaling molecule cannot be ascribed to all the genes. When using a signal molecule name is not possible, we use the signal field as a more detailed extension of the module name. Therefore, within the ‘neural development’ module, the signal field contains entries such as ‘induce astrocytes’, ‘neural restrictive silencer’, ‘forebrain development’, ‘Notch regulated gene expression’, and ‘cortical neurogenesis’.

36.6.8

Distribution of Proteins among the Genes in the Candidate Gene Set

Overall, this candidate gene set construction method can produce a large neural multimodule gene set that represents a significant number of genes involved in neural development, growth, signaling, and plasticity. These genes can provide a powerful set of candidates for the exploration of genetic susceptibility and progression of major depression.

More than 60 distinct protein types are represented in the multimodule gene set (Table 36.3). Of particular interest are genes for 148 receptors, 35 ligands, 60 adhesion molecules, 48 voltage-dependent ion-channel family proteins, 30 G-protein subunits, 63 kinases, and 63 transcription factors. Additionally, there are genes for 22 transporters and 16 vesicle-associated genes.

When considered according to their subcellular locations, the proteins encoded by this 650-gene set include more than 274 membrane proteins and 131 with cytoplasmic localization, 95 additional proteins are associated with both a cytoplasmic and a nuclear localization, and 36 proteins are known to be associated with both the plasma membrane and the cytoplasm. Six of these proteins are annotated as mitochondrial and 13 have various other subcellular localization annotations.

36.7

Justification for Inferring Pathway Connections

The candidate gene sets and modules generated above represent likely members of multiple neurotransmitter-related signaling pathways, neural development pathways, as well as hormonal-signaling systems and signaling components mediating neural adhesion, dendritic sprouting, and synaptic plasticity. These genes also correspond to the exact types of genes that have been associated with unipolar major depression [162].

When building genomic subsets or candidate gene sets, it makes sense to include as many likely candidates as one can afford to assay in genetic studies. When selecting genes for inclusion in the gene set, one can focus on known genes whose expression has exhibited association with depression or antidepressant treatment

Table 36.3 Depression candidate genes by protein type. A set of 650 genes implicated in neuronal signaling, growth, and plasticity was constructed using a number of genomic resources such as LocusLink and PubMed. The candidate genes are listed in this table according to their protein type (i.e., receptor, ligand, enzyme). The table was produced by selecting the number of locusId's by proteinType and grouping the query by proteinType. Receptors, kinases, transcription factors, and adhesion molecules make up a significant fraction of these genes. This candidate gene set is highly enriched for genes that may contribute to the genetic susceptibility and progression of depression. Some of these genes may be involved in the phenotypic variation in response to antidepressant treatment.

<i>ProteinType</i>	<i>Number of genes</i>	<i>ProteinType</i>	<i>Number of genes</i>
ABC1 subfamily	1	Kinase anchor	13
Adapter protein	5	Kinesin	4
Adenylate cyclase	8	Ligand	35
Adhesion	60	Microtubule-associated	4
Adhesion/phosphatase	2	Microtubule binding	1
Aminotransferase	1	Mitochondrial	3
Annexin	9	Neuromodulin	1
Arrestin	8	Oxidase	2
BCL2-associated	1	Oxygenase	1
Calcium binding	2	PDZ-containing	2
Calcium storage	1	Phosphatase	2
Calmodulin	3	Phospholipase	25
Carboxylase	1	Presenilin	2
Channel	48	Protease	4
Co-activator	3	Receptor	148
Cobalamin synthesis	1	Reticulon	2
Cytoskeleton binding	1	Ring finger	1
Decarboxylase	3	Scaffolding protein	2
Dehydrogenase	3	Serine protease inhibitor	1
Dioxygenase	1	Synaptogyrin	1
Docking protein	7	Synthase	1
G-protein subunit	31	Synuclein	2
Glutathione S-transferase	1	Sythetase	1
GPI-anchored	1	Tetraspanin	1
GTPase activator	2	Thread protein	1
GTPase activating	1	Transcription factor	62
GTPase-activating protein	1	Transcription factor	1
Guanine nucleotide exchange	2	Transferase	2
Helicase	1	Transmembrane protein	1
Histone deacetylase	1	Transporter	22
Hydrolase	5	Tubulin	1
Hydroxylase	4	Ubiquitin ligase	1
Inhibitor	1	Unknown	1
Kinase	63	Vesicle	16

response in previous studies, such as the serotonin neurotransmitter receptor *5-HT2A* [163] and the transporter *SERT* [164]. However, the genetic association of a serotonin receptor and the modulator of effective serotonin concentration in the synapse (via the serotonin transporter) suggest that signaling through the serotonin system is clearly an important component of the neurobiology of depression. However, the fact that numerous other genes and signaling systems, such as *CRHBP* [165] and *CRHR1* [166], have been associated with depression and antidepressant treatment response, respectively [165], suggests a much more complex genetic circuitry than originally anticipated when the monoamine hypothesis was first postulated.

It is interesting to consider such complex genetic results in the context of degenerate genotypes that give rise to the same phenotypes in model organism mutagenesis studies [167]. In fact, considerable effort is typically made to genetically assess each instance of an observed phenotype to determine if the causative mutation maps to a previously detected gene or to a 'novel' gene. The genetic complementation analysis [168] that is carried has out shown, time and time again, that different mutations in different genes can cause the exact same or very similar phenotypes [169]. Moreover, in many cases, the degenerate genotypes map to all the members of a common pathway, such as the ligand and the receptor for that ligand [170].

The phenotypes observed in complex diseases like depression are likely the result of numerous gene–gene interactions that contribute in complex nonlinear ways to a disease phenotype. The foundation for complex signaling networks is the notion of multiple protein–protein and protein–nucleotide interactions [171]. Complex gene–gene interactions in model-organism genomes are both commonplace and very well understood. A classic example of such gene–gene interactions is the synthetic lethal phenotype observed in yeast, for which a double mutant results in lethality but yeast strains possessing each single mutation by itself remain viable [172, 173]. Such multilocus effects suggest that the phenotype is not only dependent on which specific allele is present at a particular locus but also on which other alleles are also present.

Examples of interacting loci and allelic combinations that drastically exacerbate human disease phenotypes are well known also. For example, the phenotype of the complex disease obesity is influenced toward extreme obesity by epistatic interactions between loci on chromosome 10 and chromosome 20 [174]. Another example is the increased synaptic norepinephrine released when the synergistic polymorphisms of B1 and 2C adrenergic receptors co-occur [175].

Such examples of interacting loci are not novel and not limited to human genetics. There is a long and solid history of suppressor and enhancer mutagenesis screens in numerous organisms that are designed to identify secondary mutations that either suppress or enhance, respectively, the severity of some primary mutation in a different locus [176–178]. The results of such studies have provided a systematic analysis of signaling pathways in a number of unicellular organisms and have unambiguously demonstrated the multiallelic nature of even unicellular phenotypes [179, 180]. Clearly, the implications for humans are that some polygenic diseases are the result of even more complex interactions spread across hundreds, if not

thousands, of loci. Additional evidence suggesting that complex interactions between multiple alleles are likely the norm rather than the exception comes from microarray experiments in which the overexpression [181, 182] or disruption [182, 183] of one gene alters the expression of numerous other genes.

Therefore, the notion that all people who suffer from a particular disorder share common alleles in one or more distinct loci may not be true. In fact, there is no reason why two individuals who share the same disorder must share the same genotype or haplotype [183]. Therefore, it may be reasonable to assume that the genetic basis of polygenic disorders arises from combinations of various alleles affecting one or more of the pathways that control normal function of the system or tissue that is perturbed in the course of the disease or disorder. In such a manner, many diverse genotypes may give rise to the same phenotype. In addition, the severity of the phenotype may be the result of the number and severity of malignant alleles occurring in numerous relevant loci [184].

Furthermore, a given allele may not be associated with the same phenotype in two different individuals or even two different populations if the phenotype results from a complex interaction of multiple genes with one another but only one contributing locus has been successfully associated with the phenotype. Such partial understanding of the genetic basis for a polygenic phenotype has likely been the cause of many failures to replicate a genetic association in different sample sets [185–187].

In light of all of these observations, it seems obvious that the best approach to studying complex genetic disorders is to incorporate as much prior knowledge as possible to identify candidate systems and pathways that contribute to the phenotypic variability, while simultaneously attempting to reduce the genomic search space so as to maximize the probability of identifying a real multiallelic interaction.

Recently, genetic associations between GPCR-mediated cAMP pathway members and major depression have been reported [188]. It is not surprising that associations exist in the genes whose products transduce the monoamine neurotransmitter signals down into the nucleus of the neuron where subsequent rounds of gene expression and genetic reprogramming occur. Such genetic reprogramming of neurons ultimately mediates the chronic aspects of antidepressant treatment response [189].

Many biological properties of signaling pathways and neurons are well known but rarely incorporated into the design of genetic studies. It is well known, for example, that intracellular signaling pathways undergo amplification as they descend into the cell [190]. Such phenomena suggest that the earliest transducer of the signal, i.e., the receptor, may contribute more phenotypic variability than a component that is closer to the nucleus. Accordingly, it is well known that the same intracellular messengers may mediate the effects of numerous receptors and signaling cascades through elaborate networks of cross-talk within the same cell [191].

Such a model suggests that, if drastic polymorphisms were present in these nuclear factors, they might result in a plethora of phenotypic effects and that therefore selection for drastic mutations might be very strongly negative. Accordingly, they might contribute very slightly to phenotypic variation, through subtle

variations in transduction efficiency. Such negative selection might suggest that the net transduction efficiency of a pathway may reside, not only in the alleles encoding the receptors and ligands, but also, to a lesser degree, be spread among all the members of a pathway. Such multilocus systems could exhibit substantial phenotypic variation as a result of the combinatorial effects of the multiple allelic combinations occurring through sexual reproduction. Therefore, if substantial progress is to be made in understanding the genetics of depression, all available knowledge must be utilized in order to develop the necessary genetic and statistical methodologies that can effectively handle combinatorial multilocus effects with small and potentially varying contributions to phenotypic variation.

36.8

Strategic Selection of Single Nucleotide Polymorphisms

36.8.1

SNP Introduction

Single nucleotide polymorphisms (SNPs) are the most common type of polymorphism in the human genome [192]. After the construction of a candidate gene set, the next most important step is the selection of SNPs. In the context of a particular gene structure, SNPs may be classified as intergenic, intronic, untranslated, or coding. SNPs occurring in coding regions can be further classified into three classes: 'synonymous', 'nonsynonymous and conservative', or 'nonsynonymous and nonconservative', based on the effect on the primary amino acid sequence resulting from the variant nucleotide [193].

Because of their relative abundance in the genome, SNPs have been postulated to be the causes for some common genetic diseases [194]. However, the extent of common SNPs (alleles with greater than 5% population frequency) that result in functional variants contributing to the susceptibility and progression of common genetic disorders has yet to be fully explored [195].

There are a number of different approaches for selecting SNPs in or around genes of interest, but most can be classified into two main approaches:

- selecting functional SNPs that are likely to directly affect phenotypic variation
- selecting SNPs as markers for their association with a functional polymorphism or haplotype

36.8.2

Selecting Functional SNPs

Functional SNPs can only be truly identified experimentally; however, a number of computational approaches have been developed for the identification of functional allelic variants in the human genome. The computational identification of functional SNPs requires:

- detailed knowledge of the structure of the gene in which the SNPs occur
- a method for identifying functionally important sequences within that gene
- a method for assessing the effect caused by the variant allele

Because of the relative ease of identifying protein domains, coding-region SNPs have been at the center of the functional SNP frenzy for quite some time. The most conservative approach to the identification of functional coding SNPs relies on identifying highly conserved residues within protein family alignments that occur within functionally important domains and exhibit evidence of nonconservative substitution when encoded by the variant allele. Although conceptually such SNPs are easy to identify, in practice such SNPs show dramatic evidence of negative selection and therefore occur only rarely (Figure 36.6).

Approaches that relax the constraints on either the location within the protein or the severity of the amino acid substitution result in more frequent detection of SNPs, but reduce the a priori confidence that the SNP has a functional effect. As the substituted amino acid shares more and more biochemical properties with the original amino acid, the perturbation to the protein is reduced. For SNPs resulting in a synonymous codon for the original amino acid, there is no chance of a functional effect resulting from the primary amino acid sequence of the protein. Evidence

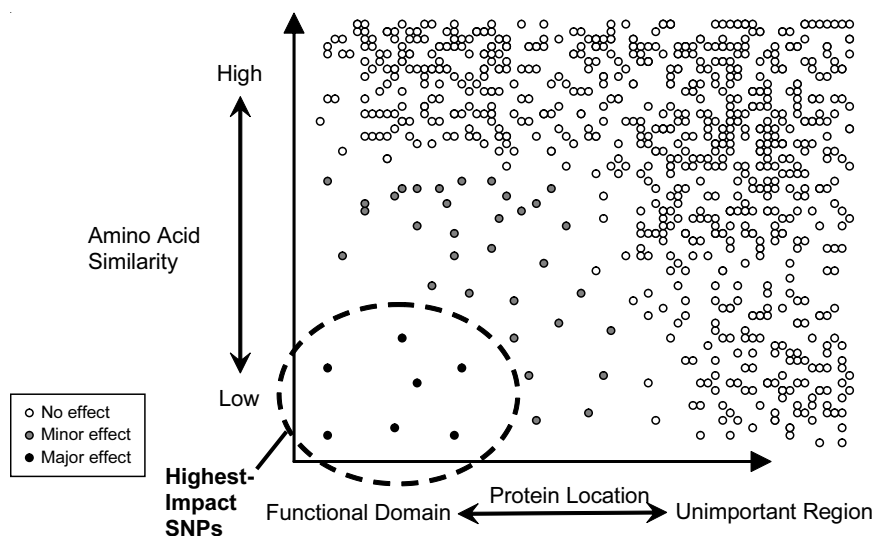


Figure 36.6 Negative selection of functional coding region SNPs. Functional coding region SNPs show strong evidence of negative selection. Therefore, the frequency of SNPs that ultimately have a deleterious effect on a protein is relatively low. Two constraints must be realized before a functional SNP can occur: first, the polymorphism must cause a biochemical change in the protein, and

second, this biochemical change must occur within a region of functional importance within the protein. If only one of these events occurs, the SNP does not have a functional consequence. Similar constraints and SNP distributions are likely to be observed for regulatory SNPs that occur within promoters, as well as for SNPs that occur within splicing signals.

exists for SNPs causing conservative amino acid substitutions to be associated with functional variation.

Not all functional SNPs need to alter the primary amino acid sequence. There are numerous examples of psychiatric genetic associations in which functional SNPs occur in transcriptional regulatory sequences [196–198]. Such SNPs alter the activity of the gene by presumably changing the timing, level, and/or tissue specificity of the transcript. The detection of regulatory SNPs is relatively easy when they are located just upstream of the transcription start site, but becomes more difficult as the location moves farther upstream from the core promoter [199]. The difficulty in identifying true distal enhancer elements in mammalian genomes (very far upstream from the start site) makes it almost impossible to computationally detect these functional SNPs.

Functional SNPs have also been identified in the untranslated regions of messenger RNA [200]. Such SNPs may disrupt secondary structures that are important for mRNA stability and/or localization. Because synonymous SNPs do change the codon in the mRNA, it is possible that such SNPs have effects on protein translation, especially under conditions in which the substituted codon has limiting amounts of that codon's tRNA synthetase within the cell [201]. Additionally, functional SNPs have been detected within exons [202] and introns [203] that effect alternative splicing and isoform production. Some of these splicing SNPs have been shown to be the genetic basis for a number of genetic diseases [204–206].

There are numerous bioinformatics approaches to detecting functional SNPs. Some methods focus only on regulatory regions [207], and others focus only on specific protein domains [208]. Other methods use a combination of genomic regions to search for functional SNPs [209]. Recent studies have suggested that the total fraction of SNPs that contribute to functional variation in genes is only 10% of all SNPs [210]. Such studies might be premature because, as bioinformatics algorithms improve, the detection of functional sequences in the genome will improve. But 10% can be considered a conservative lower bound for the fraction of functional SNPs within the SNP databases.

36.8.3

Selecting SNPs for Detecting Haplotypes

The selection of SNPs for the detection of haplotypes is ideally accomplished in a manner that produces the fewest number of SNPs (tagged SNPs) that still allow for the description of the greatest number of haplotypes within the gene occurring with a population frequency of at least 5% [211, 212]. Such maximally informative haplotype SNPs will be the first choice for selecting SNPs within genes in the candidate gene set, because such maximally informative haplotypes provide the greatest assessment of genetic variability within a gene. Furthermore, the SNPs associated with functional variants, where such SNPs exist, are inevitably associated with one or more haplotypes within the gene [213]. Although the maximal haplotyping method will provide the greatest statistical power for detecting deviations in allele frequency between depressed and nondepressed individuals

[214], in cases where such an approach is not possible (due to paucity of SNPs or other confounding issues), alternative SNP selection methods can be employed.

A popular alternative SNP selection method, termed the minimized LD method, uses fewer SNPs which are approximately evenly spaced across the gene and which exhibit a pair-wise linkage disequilibrium (LD) that is less than a specified threshold [215]. A measure of strong LD is defined as $r^2 > 1/3$, where r^2 corresponds to an established statistical measure of the strength of the LD [216]. Another common measure of LD is the statistic D' [217], where $D' > 0.7$ corresponds to high linkage disequilibrium. Therefore, SNPs can be selected by attempting to minimize the pair-wise measures of LD, using r^2 and D' as direct measures of the strength of LD between the SNPs.

36.8.4

Method for Mapping SNPs to a Candidate Gene Set

SNPs can be mapped and identified within the candidate gene set by using a number of methods. However, a simple method entails using existing annotation from the UCSC genome browser derived from various SNP annotation files (<http://genome.ucsc.edu/>) and data from the dbSNP database which includes allele frequency information, HapMap SNP sets, and dbSNP submitter data (<http://www.ncbi.nlm.nih.gov/SNP/>). The dbSNP rsId mappings to locusId can be loaded into the local genomics database along with the SNP location annotation corresponding to intronic, coding, synonymous, or nonsynonymous. After loading the SNP data into the database, multiple queries can be performed to assess the distribution of SNPs within the candidate gene class. Some typical queries might look like this:

```
SELECT module, count(rs_id) FROM neuroModule t1,
LOCUS_LINK.locusMapped_rsIDs t2 WHERE t1.locusId = t2.locus_id
group by module;
SELECT proteinType, count(rs_id) FROM neuroModule t1,
LOCUS_LINK.locusMapped_rsIDs t2 WHERE t1.locusId = t2.locus_id
and t2.class = 'nonsynonymous' group by proteinType;
```

36.8.5

Distribution of SNPs within a Candidate Gene Set

Using the above method, a total of 105 632 SNPs were identified in 615 of the candidate genes, with the following distribution: 89 926 intronic, 13 316 located in untranslated regions, and 2390 coding (1138 synonymous and 1252 nonsynonymous). When considered by neurotransmitter signal, 838 SNPs were detected in genes associated with acetylcholine signaling, over 3300 SNPs were associated with dopaminergic genes, 15 000 SNPs were mapped within GABA-related genes, and 1645 SNPs were detected in adrenergic genes. Additionally, there were 1604 SNPs in opioid-associated genes, 1468 in serotonergic genes, and 1696 SNPs in genes

generally associated with neurotransmitter release, such as synaptic vesicle-associated genes.

Over 55 distinct protein types are represented in the candidate gene set. When considering only nonsynonymous coding SNPs, the set of SNPs includes 175 in adhesion proteins, 102 in ion channel proteins, 120 in kinases or kinase-associated proteins, 71 in phospholipases, 285 in receptors, 87 in transcription factors, 53 in transporters, and 27 in vesicle-associated proteins. A complete breakdown of SNPs is provided in Table 36.4.

Table 36.4 Distribution of single nucleotide polymorphisms (SNPs) across the 50 modules. This table contains the SNPs that can be identified with the dbSNP database and the candidate gene set described in the text. There are more than 100 000 SNPs in these genes, and more than 1200 nonsynonymous SNPs alone. This set of SNPs can be used as a starting point for identifying a final set of SNPs for use in a genotyping association study aimed at identifying the genetic basis of depression and/or antidepressant treatment response. Many of these SNPs likely are in complete linkage disequilibrium with each other. Therefore, the minimum set of SNPs corresponding to the maximum number of haplotypes for each gene should be used (haplotype tagged SNPs).

<i>Module</i>	<i>total Genes</i>	<i>snp Genes</i>	<i>nonsyn SNPs</i>	<i>syn SNPs</i>	<i>untrans SNPs</i>	<i>intron SNPs</i>	<i>total SNPs</i>
Adenylate cyclase	8	7	7	11	46	1965	2029
Adrenergic receptor	9	9	25	20	34	389	468
Angiogenesis inhibitor	5	5	7	8	21	1523	1559
Annexin phospholipase inhibition	9	9	19	8	111	564	702
Arrestin GPCR inhibition	8	7	10	3	10	106	129
calc/calm-dependent protein kinase	10	10	10	9	84	2369	2472
calc/calm-dependent serine kinase	1	1	1	0	0	345	346
Calmodulin	3	3	0	1	18	59	78
cAMP response element	13	12	10	11	187	1138	1346
Cannabinoid receptor	2	2	2	8	232	0	242
Cholinergic receptor	21	20	19	43	78	685	825
CRH receptor	2	2	3	1	10	122	136
Diazepam binding inhibitor	4	0	0	0	0	0	0
Dopamine receptor	5	5	24	26	106	117	273
G-protein α subunit	15	15	19	24	262	1946	2251
G-protein β subunit	7	7	6	9	163	310	488
G-protein γ subunit	9	7	2	1	472	127	602
GABA receptor	19	19	19	26	210	2663	2918
Glial-derived neurotrophic signals	1	1	0	0	0	36	36
Glial neurotrophic receptor	3	3	2	4	15	549	570
Glutamate receptor	25	25	48	74	575	14088	14785
Histamine receptor	4	4	6	6	30	34	76

Table 36.4 (continued)

<i>Module</i>	<i>total Genes</i>	<i>snp Genes</i>	<i>nonsyn SNPs</i>	<i>syn SNPs</i>	<i>untrans SNPs</i>	<i>intron SNPs</i>	<i>total SNPs</i>
Melanocortin receptor	5	4	19	5	10	0	34
Melatonin receptor	2	2	5	3	5	39	52
Microtubule-related	12	11	59	38	283	1178	1558
Mitogen-activated kinase	20	19	12	27	550	1748	2337
Nerve growth factor	18	18	63	76	228	2535	2902
Neural cell adhesion	49	46	126	109	1742	6125	8102
Neural development	41	37	36	20	359	2261	2676
Neural signal transduction	41	40	87	72	1307	9179	10645
Neuronal apoptosis	23	20	33	17	484	1947	2481
Neuronal plasticity	42	41	114	80	2652	7702	10548
Neuropeptide Y receptor	3	3	2	3	15	0	20
Neurotransmitter production	24	23	59	34	315	1549	1957
Opioid receptor	8	8	14	13	28	1382	1437
Oxytocin receptor	1	1	3	2	16	40	61
Phospholipase	25	25	71	41	412	5973	6497
Protein kinase	21	19	15	28	383	4318	4744
Protein kinase A anchor protein	13	12	64	31	478	2502	3075
Putative neurotransmitter receptor	1	1	2	2	0	0	4
Secreted peptide ligand	13	12	12	9	126	108	255
Secretin receptor	1	1	2	1	1	179	183
Serotonin receptor	14	13	22	21	256	907	1206
Somatostatin receptor	4	4	12	14	0	0	26
Superconserved receptor	1	0	0	0	0	0	0
Transporter	22	20	53	46	177	1545	1821
Vesicle-associated	16	16	27	33	498	1138	1696
Voltage-dependent Ca ²⁺ channel	15	15	34	58	40	3883	4015
Voltage-dependent K ⁺ channel	17	17	26	29	141	3129	3325
Voltage-dependent Na ⁺ channel	15	14	41	33	146	1424	1644
Total	650	615	1252	1138	13 316	89 926	105 632

36.9

Reducing the Complexity in Multilocus SNP Analysis

With over 100 000 SNPs identified in 615 candidate genes, there are surely multiple SNP selection choices for numerous genotyping studies focused on identifying the genetic basis of depression or antidepressant treatment response. Because many of these 100 000 SNPs are likely in complete LD with each other, the effective haplotype tagged SNP set will be substantially fewer than this number [218].

Consider that, after all SNP selection criteria have been made, including the selection of the maximally informative haplotype tagged SNPs as well as some very interesting high-predicted candidate functional SNPs, there might be on average 20 SNPs per gene, resulting in roughly 12 500 total SNPs selected for genotyping.

Although as many as 10% of these SNPs might not be amenable to the genotyping assay, there would still be 11 250 SNPs for which genotyping data would be produced [219]. Such a large number of SNPs presents a significant challenge for multilocus-based data-analysis approaches [220]. However, this set of 615 genes is highly enriched for those genes that may be genetically associated with depression. Based on the gene coordinates obtained from the UCSC human genome knownGene annotation file and a file obtained from LocusLink that maps locusId's to refSeq identifiers, one could approximate the fractional length of the genome that this neural-signaling genomic subset corresponds to. Such a query could be accomplished by summing the lengths of each gene based on the transcription start and end sites on the appropriate chromosome. The actual SQL command for the query might look like this:

```
SELECT sum(txEnd-txStart+1) FROM MODULE.neuroModule t1,
LOCUS_LINK.loc2ref_dec03 t3, HUMAN_GENOME.refGene_sep03 t2
WHERE t1.locusId = t3.locus_id and t3.refseq_acc=t2.name;
```

The result is 93 254 210 nucleotides. The fractional genomic length can be calculated with the following equation:

$$f = \frac{\sum_{\text{Genomic Subset}} (\text{length}[\text{mRNA}])}{3.2 \cdot 10^9} \quad (1)$$

$$f = \frac{93,254,210}{3,200,000,000} \quad (2)$$

$$f \approx 0.02914194 \approx 2.9\% \quad (3)$$

This genomic subset covers only 3% of the genome and contains over 600 genes mediating neuronal signaling, neuronal growth, and neuronal plasticity. Surely this candidate gene set does not contain every single gene regulating these processes, but it probably contains at least 20% and possibly 33% or even 40% of the responsible genes (some may call this an optimistic estimate). Therefore, this genomic subset can be said to exhibit 25% to 30% closure at 3% genomic length. Through the use of 11 250 SNPs in only 3% of the genome, the SNP coverage approximates a whole-genome approach using $33.3 \cdot 11\,250 = 371\,250$ SNPs.

This huge reduction in genomic search space substantially increases the signal-to-noise ratio for detecting true-positive multiallelic SNPs and haplotypes associated with depression and/or antidepressant treatment response. Although a large fraction of the false positives are removed by the use of this genomic subset, the large number of SNPs genotyped precludes an all-against-all SNP analysis approach.

The number of ways groups of K SNPs can be assembled from a set of N SNPs is

$$\frac{N!}{(N - K)! K!} \quad (4)$$

For a candidate gene set with 11 250 SNPs, on the order of $6.3 \cdot 10^7$ pair-wise comparisons can be made – if one were to attempt to perform the analysis using all possible trios of SNPs, there would be $1.66 \cdot 10^{11}$ distinct groups of SNPs. With that many comparisons to make, it would be impossible to perform the statistical calculations on each SNP trio. Even if 1000 calculations could be performed every second, it would require 166 000 000 million seconds to complete the calculation, corresponding to over 5200 years of continuous statistical calculations!

To identify real multilocus interactions (corresponding to sets of 3, 4, and even 5 loci), additional methods to further reduce the combinatorial complexity are required. One simple method that can be implemented very easily makes use of the inherent modular structure of the candidate gene set to restrict the potential number of SNP groupings during the multilocus SNP analysis. If there are J modules, then, to a rough approximation, there are N/J SNPs per module. Therefore, the number of possible groupings of K SNPs within a module is reduced to

$$\frac{\left(\frac{N}{J}\right)!}{\left(\frac{N}{J} - K\right)! K!} \quad (5)$$

For a candidate gene set composed of 50 modules, the number of SNPs per module averages 225 and the number of possible pairings drops from 10^7 to only 2520. This corresponds to a reduction in the combinatorial complexity by three orders of magnitude. Subsequently, it now becomes possible to consider all intramodular SNP groupings for:

$$\begin{aligned} K = 3 \text{ SNPs} &\rightarrow 1.873 \cdot 10^6 \\ K = 4 \text{ SNPs} &\rightarrow 1.040 \cdot 10^8 \\ K = 5 \text{ SNPs} &\rightarrow 4.595 \cdot 10^9 \end{aligned} \quad (6)$$

Using the same estimates as before, 1000 calculations per second, the analysis of groupings of 3 SNPs takes only approximately 15 min. The time for the $K = 4$ calculations takes just over a day (28 h), and the $K = 5$ analysis is completed in just under two months (53.1 days). These processing times are substantially less than 5000 years. If one attempted to consider intramodular groupings of 6 SNPs, the number of comparisons is too large, at $1.685 \cdot 10^{11}$. Even if 1000 calculations were performed every second, it would still take 5000 years to finish, unless there was access to a supercomputer cluster that could compute $5 \cdot 10^6$ calculations per second – then the analysis would take only one year. To process such large datasets, the statistical analysis must be automated and the results loaded into a relational database as they are produced.

The ability to consider multilocus interactions underlying depression and antidepressant treatment response requires well planned strategies for dealing with combinatorial complexity. The dramatic reduction in combinatorial complexity was achieved in two steps. The first step excluded 97% of the genome from the search space while simultaneously enriching the genome subset for genes and pathways with high probability of contributing to or mediating the susceptibility to and progression of depression. The second stage of complexity reduction was achieved by letting the biological relationships between the candidate genes guide the multilocus data analysis.

36.10 Conclusions

Bioinformatics approaches for the identification and interpretation of allelic variants within candidate genes and pathways relevant to depression and antidepressant treatment response can substantially reduce the computational and genomic complexity involved in multilocus genetic association studies. The use of detailed biological knowledge in conjunction with high-throughput methods of statistical analysis provides a straightforward method for selecting and analyzing SNPs.

A candidate gene set for use in allele identification can be selected by assembling genes based on their obvious association with pathways or systems underlying depression or treatment response (such as genes for the monoamine-associated receptors, biosynthetic enzymes, and transporters). Then additional genes can be included in the set of candidates by extending the gene set to include pathway members acting either upstream or downstream of the genes previously selected. Such pathway member genes include those that encode G-protein subunits, adenylate cyclase, protein kinases, and phosphodiesterases, to name a few. Additional genes can be included by including those with functions that may underlie the activity and efficacy of antidepressant treatment response, such as genes involved in neurogenesis, neuronal growth and migration, and synaptic plasticity.

Once the candidate genes are selected, they can be assembled into functional modules by grouping them in one or more of the following ways: (1) genes relating to a similar protein function can be grouped together, (2) genes acting within the same pathway can be grouped together, (3) genes whose products have similar neural function can be grouped together, (4) genes mediating the effects of a specific neural signal can be grouped together, (5) genes whose products regulate the effects of one or more antidepressants can be grouped together, and finally, (6) genes acting in one or more specific brain regions can be grouped together.

Once these modules have been created within the candidate gene set, the SNPs can be identified and selected. SNPs can be identified through the use of existing polymorphism databases. SNPs can be selected for use in association studies based on their association with haplotypes or on a direct association with a predicted (or known) functional effect. Additionally, SNPs can be selected based on a pair-wise

method of minimizing LD while attempting to distribute the SNPs evenly across the gene or genes of interest.

By limiting the genomic search space to only those regions that map to the candidate genes, one can limit the number of false-positive associations detected when one considers the effects of multiple SNPs on the susceptibility to and progression of depression and the response to antidepressants. To extend any multilocus analysis beyond considering only pairs of SNPs at a time, one can limit the comparisons of SNPs to those SNPs that are found only within a module. Through these constraints, the computational complexity of multilocus genetic analysis of a complex genetic disorder can become tractable to current genetic and pharmacogenomic methods of investigation.

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References

- 1 LESCH, K. P., Gene–environment interaction and the genetics of depression. *J. Psychiatry Neurosci.* **2004**, *29*, 174–184.
- 2 ELHWUEGLI, A. S., Central monoamines and their role in major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2004**, *28*, 435–451.
- 3 VAN PRAAG, H. M., DE HAAN, S., Central serotonin deficiency: a factor which increases depression vulnerability? *Acta Psychiatr. Scand. Suppl.* **1980**, *280*, 89–96.
- 4 SVENSSON, T. H., Brain noradrenaline and the mechanisms of action of antidepressant drugs. *Acta Psychiatr. Scand. Suppl.* **2000**, *402*, 18–27.
- 5 AYSEGUL, Y., ALI, S. G., TAMAM, L., Mechanism of actions of antidepressants: beyond the receptors. *Bull. Clin. Psychopharmacol.* **2002**, *12*, 194–200.
- 6 FRAZER, A., BENMANSOUR, S., Delayed pharmacological effects of antidepressants. *Mol. Psych.* **2002**, *7* (Suppl. 1), S23–S28.
- 7 SEMINOWICZ, D. A., MAYBERG, H. S., MCINTOSH, A. R., GOLDAPPLE, K., KENNEDY, S., SEGAL, Z., RAFI-TARI, S., Limbic–frontal circuitry in major depression: a path modeling metaanalysis. *Neuroimage* **2004**, *22*, 409–018.
- 8 MANJI, H. K., DREVETS, W. C., CHARNEY, D. S., The cellular neurobiology of depression. *Nat. Med.* **2001**, *7*, 541–547.
- 9 CARROLL, B. J., Untreated depression and hippocampal volume loss. *Am. J. Psychiatry* **2004**, *161*, 101–112.
- 10 ALFAREZ, D. N., JOELS, M., KRIGERS, H. J., Chronic unpredictable stress impairs long-term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro. *Eur. J. Neurosci.* **2003**, *17*, 1928–1934.
- 11 ALTIERI, M., MARINI, F., ARBAN, R., VITULLI, G., JANSSON, B. O., Expression analysis of brain-derived neurotrophic factor (BDNF) mRNA isoforms after chronic and acute antidepressant treatment. *Brain Res.* **2004**, *1000*, 148–155.
- 12 SAARELAINEN, T., HENDOLIN, P., LUCAS, G., KOPONEN, E., SAIRANEN, M., MACDONALD, E., AGERMAN, K., HAAPASALO, A., NAWA, H., ALOYZ, R., ERNFORS, P., CASTREN, E., Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.* **2003**, *23*, 349–357.

- 13 TAKAHASHI, M., TERWILLIGER, R., LANE, C., MEZES, P. S., CONTI, M., DUMAN, R. S., Chronic antidepressant administration increases the expression of cAMP-specific phosphodiesterase 4A and 4B isoforms. *J. Neurosci.* **1999**, *19*, 610–618.
- 14 BUMEISTER, R., ROSSE, C., ANSELMO, A., CAMONIS, J., WHITE, M. A., CNK2 couples NGF signal propagation to multiple regulatory cascades driving cell differentiation. *Curr. Biol.* **2004**, *9*, 439–445.
- 15 DE-FRAJA, C., CONTI, L., GOVONI, S., BATTAINI, F., CATTANEO, E., STAT signalling in the mature and aging brain. *Int. J. Dev. Neurosci.* **2000**, *18*, 439–446.
- 16 ZHENG, W. H., KAR, S., QUIRION, R., FKHL1 and its homologs are new targets of nerve growth factor Trk receptor signaling. *J. Neurochem.* **2002**, *80*, 1049–1061.
- 17 LICINTO, J., WONG, M. L., The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol. Psychiatry* **1999**, *4*, 317–327.
- 18 DUMAN, R. S., Pathophysiology of depression: the concept of synaptic plasticity. *Eur. Psychiatry* **2002**, *Suppl. 3*, 306–310.
- 19 MOORE, J. H., The ubiquitous nature of epistasis in determining susceptibility to common human diseases. *Hum. Hered.* **2003**, *56*, 73–82.
- 20 FITCH, W. M., Locating gaps in amino acid sequences to optimize the homology between two proteins. *Biochem. Genet.* **1969**, *3*, 99–108.
- 21 NEEDLEMAN, S. B., WUNSCH, C. D., A general method applicable to the search for similarities in the amino acid sequence of two proteins. *J. Mol. Biol.* **1970**, *48*, 443–453.
- 22 ADAMS, M. D., CELNIKER, S. E., HOLT, R. A., EVANS, C. A., GOCAYNE, J. D., et al., The genome sequence of *Drosophila melanogaster*. *Science* **2000**, *287*, 2185–2195.
- 23 FALLER, D., VOSS, H. U., TIMMER, J., HOBBOHM, U., Normalization of DNA-microarray data by nonlinear correlation maximization. *J. Comput. Biol.* **2003**, *10*, 751–762.
- 24 CRASTO, C. J., MORSE, T. M., MIGLIORE, M., NADKARNI, P., HINES, M., BRASH, D. E., MILLER, P. L., SHEPHERD, G. M., Creating knowledgebases to text-mine PUBMED articles using clustering techniques. *Proc. AMIA Symp.* **2003**, 821.
- 25 SPALDING, J. B., LAMMERS, P. J., BLAST Filter and GraphAlign: rule-based formation and analysis of sets of related DNA and protein sequences. *Nucleic Acids Res.* **2004**, *32*, W26–32.
- 26 GENE ONTOLOGY CONSORTIUM. Creating the gene ontology resource: design and implementation. *Genome Res.* **2001**, *11*, 1425–1433.
- 27 HELT, G. A., LEWIS, S., LORAIN, A. E., RUBIN, G. M., BioViews: Java-based tools for genomic data visualization. *Genome Res.* **1998**, *8*, 291–305.
- 28 YEGER-LOTEM, E., MARGALIT, H., Detection of regulatory circuits by integrating the cellular networks of protein–protein interactions and transcription regulation. *Nucleic Acids Res.* **2003**, *31*, 6053–6061.
- 29 IRIZARRY, K., KUSTANOVICH, V., LI, C., BROWN, N., NELSON, S., WONG, W., LEE, C. J., Genome-wide analysis of single-nucleotide polymorphisms in human expressed sequences. *Nat. Genet.* **2000**, *26*, 233–236.
- 30 YU, U., LEE, S. H., KIM, Y. J., KIM, S., Bioinformatics in the post-genome era. *J. Biochem. Mol. Biol.* **2004**, *37*, 75–82.
- 31 BARNES, M. R., Psychiatric genetics in silico: databases and tools for psychiatric geneticists. *Psychiatr. Genet.* **2002**, *12*, 67–73.
- 32 ROCCO, D., CRITCHLOW, T., Automatic discovery and classification of bioinformatics web sources. *Bioinformatics* **2003**, *12*, 1927–1933.
- 33 ILIOPOULOS, I., TSOKA, S., ANDRADE, M. A., ENRIGHT, A. J., CARROLL, M., POULLET, P., PROMPONAS, V., et al., Evaluation of annotation strategies using an entire genome sequence. *Bioinformatics* **2003**, *19*, 717–726.
- 34 HAMMOND, M. P., BIRNEY, E., Genome information resources: developments at Ensembl. *Trends Genet.* **2004**, *20*, 268–272.
- 35 WHEELER, D. L., CHURCH, D. M., FEDERHEN, S., LASH, A. E., MADDEN, T. L., PONTIUS, J. U., SCHULER, G. D.,

- SCHRIML, L. M., SEQUEIRA, E., TATUSOVA, T. A., WAGNER, L., Database resources of the National Center for Biotechnology. *Nucleic Acids Res.* **2003**, *31*, 28–33.
- 36 KAROLCHIK, D., BAERTSCH, R., DIEKHANS, M., FUREY, T. S., HINRICH, A., LU, Y. T., ROSKIN, K. M., SCHWARTZ, M., SUGNET, C. W., THOMAS, D. J., WEBER, R. J., HAUSSLER, D., KENT, W. J., The UCSC Genome Browser Database. *Nucleic Acids Res.* **2003**, *31*, 51–54.
- 37 IVANCIUC, O., SCHEIN, C. H., BRAUN, W., Data mining of sequences and 3D structures of allergenic proteins. *Bioinformatics* **2002**, *18*, 1358–1364.
- 38 STAJICH, J. E., BLOCK, D., BOULEZ, K., BRENNER, S. E., CHERVITZ, S. A., DAGDIGIAN, C., FUELLEN, G., GILBERT, J. G., KORF, I., LAPP, H., LEHVASLAIHO, H., MATSALLA, C., et al., The BioPerl toolkit: Perl modules for the life sciences. *Genome Res.* **2002**, *12*, 1611–1618.
- 39 MCGINNIS, S., MADDEN TL., BLAST: at the core of a powerful and diverse set of sequence analysis tools. *Nucleic Acids Res.* **2004**, *32*, W20–W25.
- 40 KENT, W. J., BLAT: the BLAST-like alignment tool. *Genome Res.* **2002**, *12*, 656–664.
- 41 STABENAU, A., MCVICKER, G., MELSOPP, C., PROCTOR, G., CLAMP, M., BIRNEY, E., The Ensembl core software libraries. *Genome Res.* **2004**, *14*, 929–933.
- 42 KLEIN, T. E., ALTMAN, R. B., PharmGKB: the pharmacogenetics and pharmacogenomics knowledge base. *Pharmacol. Rev.* **2003**, *4*, 1.
- 43 PRUITT, K. D., MAGLOTT, D. R., RefSeq and LocusLink: NCBI gene-centered resources. *Nucleic Acids Res.* **2001**, *29*, 137–140.
- 44 ZHUO, D., ZHAO, W. D., WRIGHT, F. A., YANG, H. Y., WANG, J. P., SEARS, R., BAER, T., KWON, D. H., GORDON, D., GIBBS, S., DAI, D., YANG, Q., SPITZNER, J., KRAHE, R., STREDNEY, D., STUTZ, A., YUAN, B., Assembly, annotation, and integration of UNIGENE clusters into the human genome draft. *Genome Res.* **2001**, *11*, 904–918.
- 45 BOECKMANN, B., BAIROCH, A., APWEILER, R., BLATTER, M. C., ESTREICHER, A., GASTEIGER, E., MARTIN, M. J., MICHOD, K., O'DONOVAN, C., PHAN, I., PILBOUT, S., SCHNEIDER, M., The Swiss-Prot protein knowledgebase and its supplement TrEMBL in **2003**. *Nucleic Acids Res.* **2003**, *31*, 365–370.
- 46 BATEMAN, A., COIN, L., DURBIN, R., FINN, R. D., HOLLICH, V., GRIFFITHS-JONES, S., KHANNA, A., MARSHALL, M., MOXON, S., SONNHAMMER, E. L., STUDHOLME, D. J., YEATS, C., EDDY, S. R., The Pfam protein families database. *Nucleic Acids Res.* **2004**, *32*, D138–D141.
- 47 HAMOSH, A., SCOTT, A. F., AMBERGER, J., BOCCHINI, C., VALLE, D., MCKUSICK, V. A., Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. *Nucleic Acids Res.* **2002**, *30*, 52–55.
- 48 SHERRY, S. T., WARD, M. H., KHOLODOV, M., BAKER, J., PHAN, L., SMIGIELSKI, E. M., SIROTKIN, K., dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res.* **2001**, *29*, 308–311.
- 49 FREDMAN, D., MUNNS, G., RIOS, D., SJOHOLM, F., SIEGFRIED, M., LENHARD, B., LEHVASLAIHO, H., BROOKES, A. J., HGVbase: a curated resource describing human DNA variation and phenotype relationships. *Nucleic Acids Res.* **2004**, *32*, D516–D519.
- 50 THORISSON, G. A., STEIN, L. D., The SNP Consortium website: past, present and future. *Nucleic Acids Res.* **2003**, *31*, 124–127.
- 51 PENNACCHIO, L. A., Insights from human/mouse genome comparisons. *Mamm. Genome* **2003**, *14*, 429–436.
- 52 TRINKLEIN, N., FORCE ALDRED, S., SALDANHA, A., MYERS, R. M., Identification and functional analysis of human transcriptional promoters. *Genome Res.* **2003**, *13*, 308–312.
- 53 JIANG, R., DUAN, J., WINDEMUTH, A., STEPHENS, J. C., JUDSON, R., XU, C., Genome-wide evaluation of the public SNP databases. *Pharmacogenomics* **2003**, *4*, 779–789.
- 54 STRYKE, D., HUANG, C. C., KAWAMOTO, M., JOHNS, S. J., CARLSON, E. J., DEYOUNG, J. A., LEABMAN, M. K., HERSKOWITZ, I., GIACOMINI, K. M., FERRIN, T. E., SNP analysis and presentation in the Pharmacogenetics of Membrane Transporters Project. *Pac. Symp. Biocomput.* **2003**, 535–547.
- 55 GUO, J. T., ELLROTT, K., CHUNG, W. J., XU, D., PASSOVETS, S., XU, Y., PROSPECT-PSPP: an automatic computational

- pipeline for protein structure prediction. *Nucleic Acids Res.* **2004**, 32,W522–W525.
- 56 GRANT, J. D., SOMERS, L. A., ZHANG, Y., MANION, F. J., BIDAUT, G., OCHS, M. F., FGDP: functional genomics data pipeline for automated, multiple microarray data analyses. *Bioinformatics* **2004**, 20, 282–283.
 - 57 KASUKAWA, T., FURUNO, M., NIKAI, D. I., BONO, H., HUME, D. A., BULT, C., HILL, D. P., BALDARELLI, R., GOUGH, J., KANAPIN, A., MATSUDA, H., SCHIRIML, L. M., HAYASHIZAKI, Y., OKAZAKI, Y., QUACKENBUSH, J., Development and evaluation of an automated annotation pipeline and cDNA annotation system. *Genome Res.* **2003**, 13, 1542–1551.
 - 58 MUNGALL, C. J., MISRA, S., BERMAN, B. P., CARLSON, J., FRISE, E., HARRIS, N., MARSHALL, B., SHU, S., KAMINKER, J. S., PROCHNIK, S. E., SMITH, C. D., SMITH, E., TUPY, J. L., WIEL, C., RUBIN, G. M., LEWIS, S. E., An integrated computational pipeline and database to support whole-genome sequence annotation.
 - 59 McDERMOTT, J., SAMUDRALA, R., Enhanced functional information from predicted protein networks. *Trends Biotechnol.* **2004**, 22, 60–62.
 - 60 TURNER, F. S., CLUTTERBUCK, D. R., SEMPLE, C. A., POCUS: mining genomic sequence annotation to predict disease genes. *Genome Biol.* **2003**, 4,R75.
 - 61 ZHAO, T., CHANG, L. W., McLEOD, H. L., STORMO, G. D., PromoLign: a database for upstream region analysis and SNPs. *Hum. Mutat.* **2004**, 23, 524–529.
 - 62 POTTER, S. C., CLARKE, L., CURWEN, V., KEENAN, S., MONGIN, E., SEARLE, S. M., STABENAU, A., STOREY, R., CLAMP, M., The Ensembl analysis pipeline. *Genome Res.* **2004**, 14, 934–941.
 - 63 YU, H., LUSCOMBE, N. M., LU, H. X., ZHU, X., XIA, Y., HAN, J. D., BERTIN, N., CHUNG, S., VIDAL, M., GERSTEIN, M., Annotation transfer between genomes: protein–protein interologs and protein–DNA regulogs. *Genome Res.* **2004**, 14, 1107–1118.
 - 64 KERLAVAGE, A., BONAZZI, V., DI TOMMASO, M., LAWRENCE, C., LI, P., MAYBERRY, F., MURAL, R., NODELL, M., YANDELL, M., ZHANG, J., THOMAS, P., The Celera Discovery System. *Nucleic Acids Res.* **2002**, 30, 129–136.
 - 65 BROBERG, P., Statistical methods for ranking differentially expressed genes. *Genome Biol.* **2003**, 4, R41.
 - 66 CSERZO, M., EISENHABER, F., EISENHABER, B., SIMON, I., On filtering false positive transmembrane protein predictions. *Protein Eng.* **2002**, 15, 745–752.
 - 67 MAKAROV, V., Computer programs for eukaryotic gene prediction. *Brief Bioinform.* **2002**, 3, 195–199.
 - 68 GREEN, M. L., KARP, P. D., A Bayesian method for identifying missing enzymes in predicted metabolic pathway databases. *BMC Bioinformatics* **2004**, 5, 76.
 - 69 SOMMER, I., ZIEN, A., VON OHSEN, N., ZIMMER, R., LENGAUER, T., Confidence measures for protein fold recognition. *Bioinformatics* **2002**, 18, 802–812.
 - 70 LI, L. M., KIM, J. H., WATERMAN, M. S., Haplotype reconstruction from SNP alignment. *J. Comput. Biol.* **2004**, 11, 505–516.
 - 71 SANSOM, C., Database searching with DNA and protein sequences: an introduction. *Brief Bioinform.* **2000**, 1, 22–32.
 - 72 BELKNAP, J. K., MITCHELL, S. R., O'TOOLE, L. A., HELMS, M. L., CRABBE, J. C., Type I and type II error rates for quantitative trait loci (QTL) mapping studies using recombinant inbred mouse strains. *Behav. Genet.* **1996**, 26, 149–160.
 - 73 POWER, P. M., JONES, R. A., BEACHAM, I. R., BUCHOLTZ, C., JENNINGS, M. P., Whole genome analysis reveals a high incidence of non-optimal codons in secretory signal sequences of *Escherichia coli*. *Biochem. Biophys. Res. Commun.* **2004**, 322, 1038–1044.
 - 74 HILLER, K., GROTE, A., SCHEER, M., MUNCH, R., JAHN, D., PrediSi: prediction of signal peptides and their cleavage positions. *Nucleic Acids Res.* **2004**, 32, W375–W379.
 - 75 KALL, L., KROGH, A., SONNHAMMER, E. L., A combined transmembrane topology and signal peptide prediction method. *J. Mol. Biol.* **2004**, 338, 1027–1036.
 - 76 McPHERSON, J. D., MARRA, M., HILLIER, L., WATERSTON, R. H., CHINWALLA, A., WALLIS, J., SEKHON, M., WYLIE, K., MARDIS, E. R., WILSON, R. K., FULTON, R., KUCABA, T. A., WAGNER-McPHERSON, C., BARBAZUK, W. B., GREGORY, S. G., HUMPHRAY, S. J., FRENCH, L., et al.,

- A physical map of the human genome. *Nature* **2001**, 409, 934–941.
- 77 VENTER, J. C., ADAMS, M. D., MYERS, E. W., LI, P. W., MURAL, R. J., SUTTON, G. G., SMITH, H. O., YANDELL, M., EVANS, C. A., HOLT, R. A., GOCAYNE, J. D., AMANATIDES, P., BALLEW, R. M., HUSON, D. H., WORTMAN, J. R., ZHANG, Q., et al., The sequence of the human genome. *Science* **2001**, 291, 1304–1351.
 - 78 SOUTHAN, C., Has the yo-yo stopped? An assessment of human protein-coding gene number. *Proteomics* **2004**, 4, 1712–1726.
 - 79 SAHA, S., SPARKS, A. B., RAGO, C., AKMAEV, V., WANG, C. J., VOGELSTEIN, B., KINZLER, K. W., VELCULESCU, V., Using the transcriptome to annotate the genome. *Nat. Biotech.* **2002**, 19, 508–512.
 - 80 XUAN, Z., WANG, J., ZHANG, M. Q., Computational comparison of two mouse draft genomes and the human golden path. *Genome Research* **2002**, 4, R1–R10.
 - 81 LIANG, F., HOLT, I., PERTEA, G., KARAMYCHEVA, S., SALZBERG, S. L., QUACKENBUSH, J., Gene index analysis of the human genome estimates approximately 120,000 genes. *Nat. Genet.* **2000**, 25, 239–240.
 - 82 BLACK, D. L., Protein diversity from alternative splicing: a challenge for bioinformatics and post-genome biology. *Cell* **2000**, 103, 367–370.
 - 83 GRAVELEY, B. R., Alternative splicing: increasing diversity in the proteomic world. *Trends Genet.* **2001**, 17, 100–107.
 - 84 GRABOWSKI, P. J., BLACK, D. L., Alternative RNA splicing in the nervous system. *Prog. Neurobiol.* **2001**, 65, 289–308.
 - 85 LEE, C. J., IRIZARRY, K., Alternative splicing in the nervous system: an emerging source of diversity and regulation. *Biol. Psychiatry* **2003**, 54, 771–776.
 - 86 SCHORK, N. J., Genetics of complex disease: approaches, problems, and solutions. *Am. J. Respir. Crit. Care Med.* **1997**, 156, S103–S109.
 - 87 RANNALA, B., Finding genes influencing susceptibility to complex diseases in the post-genome era. *Am. J. Pharmacogenomics* **2001**, 1, 203–221.
 - 88 CHAPMAN, J. M., COOPER, J. D., TODD, J. A., CLAYTON, D. G., Detecting disease associations due to linkage disequilibrium using haplotype tags: a class of tests and the determinants of statistical power. *Hum. Hered.* **2003**, 56, 18–31.
 - 89 ZALSMAN, G., FRISCH, A., APTER, A., WEIZMAN, A., Genetics of suicidal behavior: candidate association genetic approach. *Isr. J. Psychiatry Relat. Sci.* **2002**, 39, 252–261.
 - 90 BARON, M., Manic-depression genes and the new millennium: poised for discovery. *Mol. Psychiatry* **2002**, 7, 342–358.
 - 91 ZUBENKO, G. S., MAHER, B., HUGHES 3RD, H. B., ZUBENKO, W. N., STIFFLER, J. S., KAPLAN, B. B., MARAZITA, M. L., Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. *Am. J. Med. Genet.* **2003**, 123B, 1–18.
 - 92 HOLMANS, P., ZUBENKO, G. S., CROWE, R. R., DEPAULO JR JR, SCHEFTNER, W. A., WEISSMAN, M. M., ZUBENKO, W. N., BOUTELLE, S., MURPHY-EBERENZ, K., MACKINNON, D., MCINNIS, M. G., MARTA, D. H., ADAMS, P., KNOWLES, J. A., GLADIS, M., THOMAS, J., CHELLIS, J., MILLER, E., LEVINSON, D. F., Genome-wide significant linkage to recurrent, early-onset major depressive disorder on chromosome 15q. *Am. J. Hum. Genet.* **2004**, 74, 1154–1167.
 - 93 LONG, A. D., LANGLEY, C. H., The power of association studies to detect the contribution of candidate genetic loci to variation in complex traits. *Genome Res.* **1999**, 9, 720–731.
 - 94 KAPLAN, N. L., MARTIN, E. R., WEIR, B. S., Power studies for the transmission/disequilibrium tests with multiple alleles. *Am. J. Hum. Genet.* **1997**, 60, 691–702.
 - 95 CALABRETTA, R., DI FERDINANDO, A., WAGNER, G., PARISI, D., What does it take to evolve behaviorally complex organisms? *BioSystems* **2003**, 245–262.
 - 96 WOLF, D. M., ARKIN, A. P., Motifs, modules and games in bacteria. *Curr. Opin. Microbiol.* **2003**, 6, 125–134.
 - 97 HASTY, J., PRADINES, J., DOLNIK, M., COLLINS, J. J., Noise-based switches and amplifiers for gene expression. *Proc. Natl. Acad. Sci. USA* **2000**, 97, 2075–2080.
 - 98 CONANT, G. C., WAGNER, A., Convergent evolution of gene circuits. *Nat. Genet.* **2003**, 34, 264–266.

- 99 YOKOBAYASHI, Y., WEISS, R., ARNOLD, F. H., From the cover: directed evolution of a genetic circuit. *Proc. Natl. Acad. Sci. USA* **2002**, 99, 16587–16591.
- 100 HOLME, P., HUSS, M., JEONG, H., Subnetwork hierarchies of biochemical pathways. *Bioinformatics* **2003**, 19, 532–538.
- 101 THIEFFRY, D., HUERTA, A. M., PEREZ-RUEDA, E., COLLADO-VIDES, J., From specific gene regulation to genomic networks: a global analysis of transcriptional regulation in *Escherichia coli*. *Bioessays* **1998**, 20, 433–440.
- 102 IHMELS, J., FRIEDLANDER, G., BERGMANN, S., SARIG, O., ZIV, Y., BARKAI, N., Revealing modular organization in the yeast transcriptional network. *Nat. Genet.* **2002**, 31, 370–377.
- 103 VON DASSOW, G., MEIR, E., MUNRO, E. M., ODELL, G. M., The segment polarity network is a robust developmental module. *Nature* **2000**, 406, 188–192.
- 104 THIEFFRY, D., ROMERO, D., The modularity of biological regulatory networks. *Biosystems* **1999**, 50, 49–59.
- 105 TORNOW, S., MEWES, H. W., Functional modules by relating protein interaction networks and gene expression. *Nucleic Acids Res.* **2003**, 31, 6283–6289.
- 106 HAZZALIN, C. A., MAHADEVAN, L. C., MAPK-regulated transcription: a continuously variable gene switch? *Nat. Rev. Mol. Cell Biol.* **2002**, 3, 30–40.
- 107 ADAMI, C., What is complexity? *Bioessays* **2002**, 24, 1085–1094.
- 108 IRIZARRY, K. J. L., MERRIMAN, B., BAHAMONDE, M. E., WONG, M.-L., LICINIO, J., The evolution of signaling complexity suggests a mechanism for reducing the genomic search space in human association studies. *Mol. Psych.* **2005**, 10, 14–26.
- 109 URBACH, R., TECHNAU, G. M., Neuroblast formation and patterning during early brain development in *Drosophila*. *Bioessays* **2004**, 26, 739–751.
- 110 PROKOP, A., Integrating bits and pieces: synapse structure and formation in *Drosophila* embryos. *Cell Tissue Res.* **1999**, 297, 169–186.
- 111 WADSWORTH, W. G., HEDGECOCK, E. M., Guidance of neuroblast migrations and axonal projections in *Caenorhabditis elegans*. *Curr. Opin. Neurobiol.* **1992**, 2, 36–41.
- 112 BANG, A. G., GOULDING, M. D., Regulation of vertebrate neural cell fate by transcription factors. *Curr. Opin. Neurobiol.* **1996**, 6, 25–32.
- 113 CREMISI, F., PHILPOTT, A., OHNUMA, S., Cell cycle and cell fate interactions in neural development. *Curr. Opin. Neurobiol.* **2003**, 13, 26–33.
- 114 ALTMANN, C. R., BRIVANLOU, A. H., Neural patterning in the vertebrate embryo. *Int. Rev. Cytol.* **2001**, 203, 447–482.
- 115 POPOLI, M., GENNARELLI, M., RACAGNI, G., Modulation of synaptic plasticity by stress and antidepressants. *Bipolar Disorders* **2002**, 4, 166–182.
- 116 LYNCH, M. A., Long-term potentiation and memory. *Physiol. Rev.* **2004**, 84, 87–136.
- 117 BLITZ, D. M., FOSTER, K. A., REGEHR, W. G., Short-term synaptic plasticity: a comparison of two synapses. *Nat. Rev. Neurosci.* **2004**, 5, 630–640.
- 118 TANG, Y. P., SHIMIZU, E., DUBE, G. R., RAMPON, C., KERCHNER, G. A., ZHUO, M., LIU, G., TSJEN, J. Z., Genetic enhancement of learning and memory in mice. *Nature* **1999**, 401, 63–69.
- 119 YAMAMOTO, N., TAMADA, A., MURAKAMI, F., Wiring of the brain by a range of guidance cues. *Prog. Neurobiol.* **2002**, 68, 393–407.
- 120 JAN, Y. N., JAN, L. Y., The control of dendrite development. *Neuron* **2003**, 40, 229–242.
- 121 BENSON, D. L., SCHNAPP, L. M., SHAPIRO, L., HUNTLEY, G. W., Making memories stick: cell-adhesion molecules in synaptic plasticity. *Trends Cell Biol.* **2000**, 10, 473–482.
- 122 PAVLOV, I., LAURI, S., TAIRA, T., RAUVALA, H., The role of ECM molecules in activity-dependent synaptic development and plasticity. *Birth Defects Res. Part C Embryo Today* **2004**, 72, 12–24.
- 123 PHILLIPS, M. L., DREVETS, W. C., RAUCH, S. L., LANE, R., Neurobiology of emotion perception. II. Implications for major psychiatric disorders. *Biol. Psychiatry* **2003**, 54, 515–528.
- 124 HUSI, H., Grant SGN. Proteomics of the nervous system. *Trends Neurosci.* **2001**, 24, 259–265.
- 125 SHARP, D. J., ROGERS, G. C., SCHOLEY, J. M., Roles of motor proteins in building microtubule-based structures: a basic

- principle of cellular design. *Biochim. Biophys. Acta* **2000**, 1496, 128–141.
- 126 GARLAND, E. M., HAHN, M. K., KETCH, T. P., KELLER, N. R., KIM, C. H., KIM, K.-S., BIAGGIONI, I., SHANNON, J. R., BLAKELY, R. D., ROBERTSON, D., Genetic basis of clinical catecholamine disorders. *Ann. NY Acad. Sci.* **2002**, 971, 506–514.
 - 127 AERTS, J., WETZELS, Y., COHEN, N., AERSSENS, J., Data mining of public SNP databases for the selection of intragenic SNPs. *Human Mutation* **2002**, 20, 162–173.
 - 128 GELBART, W. M., CROSBY, M., MATTHEWS, B., RINDONE, W. P., CHILLEMI, J., RUSSO TWOMBLY, S., EMMERT, D., ASHBURMER, M., DRYSDALE, R. A., et al., The FlyBase Consortium. *Nucleic Acids Res.* **1997**, 25, 63–66.
 - 129 HARRIS, T. W., CHEN, N., CUNNINGHAM, F., TELLO-RUIZ, M., ANTOSHECHKIN, I., BASTIANI, C., BIERI, T., BLASIAI, D., BRADNAM, K., CHAN, J., CHEN, C. K., CHEN, W. J., DAVIS, P., KENNY, E., KISHORE, R., LAWSON, D., LEE, R., MULLER, H. M., NAKAMURA, C., OZERSKY, P., PETCHERSKI, A., ROGERS, A., SABO, A., SCHWARZ, E. M., VAN AUKEN, K., WANG, Q., DURBIN, R., SPIETH, J., STERNBERG, P. W., STEIN, L. D., WormBase: a multi-species resource for nematode biology and genomics. *Nucleic Acids Res.* **2004**, 34,D411–D417.
 - 130 LI, W., GODZIK, A., Discovering new genes with advanced homology detection. *Trends Biotechnol.* **2002**, 20, 315–316.
 - 131 LORD-GRIGNON, J., TETREAU, N., MEARS, A. J., SWAROOP, A., BERNIER, G., Characterization of new transcripts enriched in the mouse retina and identification of candidate retinal disease genes. *Invest. Ophthalmol. Vis. Sci.* **2004**, 45, 3313–3319.
 - 132 HUANG, H., WINTER, E. E., WANG, H., WEINSTOCK, K. G., XING, H., GOODSTADT, L., STENSON, P. D., COOPER, D. N., SMITH, D., ALBA, M. M., PONTING, C. P., FECHTEL, K., Evolutionary conservation and selection of human disease gene orthologs in the rat and mouse genomes. *Genome Biol.* **2004**, 5,R47.
 - 133 MAGLOTT, D. R., KATZ, K. S., SICOTTE, H., PRUITT, K. D., NCBI's LocusLink and RefSeq. *Nucleic Acids Res.* **2000**, 28, 126–128.
 - 134 KEMPERMANN, G., KRONENBERG, G., Depressed new neurons: adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. *Biol. Psychiatry* **2003**, 54, 499–503.
 - 135 KREIENKAMP, H.-J., Organization of G-protein coupled receptor signaling complexes by scaffolding complexes. *Curr. Opin. Pharmacol.* **2002**, 2, 581–586.
 - 136 DUMONT, J. E., PECASSE, F., MAENHAUT, C., Crosstalk and specificity in signaling are we crosstalking ourselves into general confusion? *Cellular Signaling* **2001**, 13, 457–463.
 - 137 PAUWELS, P. J., Diverse signaling by 5-hydroxytryptamine (5-HT) receptors. *Biochem. Pharmacol.* **2000**, 60, 1743–1750.
 - 138 RAYMOND, J. R., MUKHIN, Y. V., GELASCO, A., TURNER, J., COLLINSWORTH, G., GETTYS, T. W., GREWAL, J. S., GARNOVSKAYA, M. N., Multiplicity of mechanisms of serotonin receptor transduction. *Pharmacol. Therapeutics* **2001**, 92, 179–212.
 - 139 DOWLATSHAHI, D., MACQUEEN, G. M., WANG, J. F., REIACH, J. S., YOUNG, L. T., G Protein-coupled cyclic AMP signaling in postmortem brain of subjects with mood disorders: effects of diagnosis, suicide, and treatment at the time of death. *Neurochem.* **1999**, 73, 1121–1126.
 - 140 CARTER, K., OKA, A., TAMIYA, G., BELLGARD, M. I., Bioinformatics issues for automating the annotation of genomic sequences. *Genome Inform. Ser. Workshop Genome Inform.* **2001**, 12, 204–211.
 - 141 RAJEEVAN, M. S., RANAMUKHAARACHCHI, D. G., VERNON, S. D., UNGER, E. R., Use of real-time quantitative PCR to validate the results of cDNA array and differential display PCR technologies. *Methods* **2001**, 25, 443–451.
 - 142 SULSER, F., The role of CREB and other transcription factors in the pharmacotherapy and etiology of depression. *Ann. Med.* **2002**, 34, 348–356.
 - 143 ALBERT, P. R., TIBERI, M., Receptor signaling and structure: insights from serotonin-1 receptors. *Trends Endocrinol. Metabol.* **2001**, 12, 453–460.
 - 144 KARASEWSKI, L., FERREIRA, A., MAPK signal transduction pathway mediates agrin effects on neurite elongation in cultured hippocampal neurons. *J. Neurobiol.* **2003**, 55, 14–24.
 - 145 STARIHA, R. L., KIM, S. U., Mitogen-activated protein kinase signalling in

- oligodendrocytes: a comparison of primary cultures and CG-4. *Int. J. Dev. Neurosci.* **2001**, *19*, 427–437.
- 146 GARCIA-SEGURA, L. M., CHOWEN, J. A., NAFTOLIN, F., Endocrine glia: roles of glial cells in the brain actions of steroid and thyroid hormones and in the regulation of hormone secretion. *Front Neuroendocrinol.* **1996**, *17*, 180–211.
 - 147 DE KLOET, E. R., Hormones and the stressed brain. *Ann. NY Acad. Sci.* **2004**, *1018*, 1–15.
 - 148 KAMINSKI, N. E., Regulation of the cAMP cascade, gene expression and immune function by cannabinoid receptors. *J. Neuroimmunol.* **1998**, *83*, 124–132.
 - 149 HALLER, J., VARGA, B., LEDENT, C., FREUND, T. F., CB1 cannabinoid receptors mediate anxiolytic effects: convergent genetic and pharmacological evidence with CB1-specific agents. *Behav. Pharmacol.* **2004**, *15*, 229–304.
 - 150 VALVERDE, O., LEDENT, C., BESLOT, F., PARMENTIER, M., ROQUES, B. P., Reduction of stress-induced analgesia but not of exogenous opioid effects in mice lacking CB1 receptors. *Eur. J. Neurosci.* **2000**, *12*, 533–539.
 - 151 MBVUNDULA, E. C., RAINSFORD, K. D., BUNNING, R. A., Cannabinoids in pain and inflammation. *Inflammopharmacology* **2004**, *12*, 99–114.
 - 152 KLEIN, T. W., LANE, B., NEWTON, C. A., FRIEDMAN, H., The cannabinoid system and cytokine network. *Proc. Soc. Exp. Biol. Med.* **2000**, *225*, 1–8.
 - 153 MAIER, S. F., WATKINS, L. R., Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol. Rev.* **1998**, *105*, 83–107.
 - 154 LENDAHL, U., Gene regulation in the formation of the central nervous system. *Acta Paediatr. Suppl.* **1997**, *422*, 8–11.
 - 155 KAMMERMEIER, L., REICHERT, H., Common developmental genetic mechanisms for patterning invertebrate and vertebrate brains. *Brain Res. Bull.* **2001**, *55*, 675–682.
 - 156 BOYL, P. P., SIGNORE, M., ANNINO, A., BARBERA, J. P., ACAMPORA, D., SIMEONE, A., *Otx* genes in the development and evolution of the vertebrate brain. *Int. J. Dev. Neurosci.* **2001**, *19*, 353–363.
 - 157 ANDERSON, S., MIONE, M., YUN, K., RUBENSTEIN, J. L., Differential origins of neocortical projection and local circuit neurons: role of *Dlx* genes in neocortical interneuronogenesis. *Cereb. Cortex* **1999**, *9*, 646–654.
 - 158 GEDEON, A. K., NELSON, J., GECZ, J., MULLEY, J. C., X-linked mild non-syndromic mental retardation with neuropsychiatric problems and the missense mutation A365E in PAK3. *Am. J. Med. Genet.* **2003**, *120A*.
 - 159 MAES, T., BARCELO, A., BUESA, C., Neuron navigator: a human gene family with homology to *unc-53*, a cell guidance gene from *Caenorhabditis elegans*. *Genomics* **2002**, *80*, 21–30.
 - 160 ARIAS, A. M., New alleles of *Notch* draw a blueprint for multifunctionality. *Trends Genetics* **2002**, *18*, 168–170.
 - 161 HUANG, E. J., REICHARDT, L. F., Trk receptors: roles in neuronal signal transduction. *Annu. Rev. Biochem.* **2003**, *72*, 609–642.
 - 162 LERER, B., MACCIARDI, F., Pharmacogenetics of antidepressant and mood-stabilizing drugs: a review of candidate gene studies and future directions. *Int. J. Neuropsychopharmacol.* **2002**, *5*, 255–275.
 - 163 CHOI, M. J., LEE, H. J., LEE, H. J., HAM, B. J., CHA, J. H., RYU, S. H., LEE, M. S., Association between major depressive disorder and the –1438A/G polymorphism of the serotonin 2A receptor gene. *Neuropsychobiology* **2004**, *49*, 38–41.
 - 164 HAHN, M. K., BLAKELY, R. D., Monoamine transporter gene structure and polymorphisms in relation to psychiatric and other complex disorders. *The Pharmacogen. J.* **2002**, *217*–235.
 - 165 THOME, J., HENN, F. A., DUMAN, R. S., Cyclic AMP response element binding protein and depression. *Expert Rev. Neurotherapeut.* **2002**, *2*, 347–354.
 - 166 J LICINIO, F O'KIRWAN, K IRIZARRY, B MERRIMAN, S THAKUR, R JEPSON, S LAKE, KG TANTISIRA, S. T., Weiss, M.-L. Wong. Association of a corticotropin-releasing hormone receptor 1 haplotype and antidepressant treatment response in Mexican-Americans. *Mol. Psych.* **2004**, in press.
 - 167 ST. JOHNSTON, D., The art and design of genetic screens: *Drosophila melanogaster*. *Nat. Rev. Genet.* **2002**, *3*, 176–188.

- 168 LEVINE, K., OEHLER, L. J., CROSS, F. R., Isolation and characterization of new alleles of the cyclin-dependent kinase gene *CDC28* with cyclin-specific functional and biochemical defects. *Mol. Cell Biol.* **1998**, *18*, 290–302.
- 169 ANTONOPOULOU, I., MAVROGIANNIS, L. A., WILKIE, A. O., MORRIS-KAY, G. M., *Alx4* and *Msx2* play phenotypically similar and additive roles in skull vault differentiation. *J. Anat.* **2004**, *204*, 487–499.
- 170 CHEN, H. W., CHEN, X., OH, S. W., MARINISSEN, M. J., GUTKIND, J. S., HOU, S. X., *mom* identifies a receptor for the *Drosophila* JAK/STAT signal transduction pathway and encodes a protein distantly related to the mammalian cytokine receptor family. *Genes Dev.* **2002**, *16*, 388–398.
- 171 YEGER-LOTEM, E., SATTATH, S., KASHTAN, N., ITZKOVITZ, S., MILO, R., PINTER, R. Y., ALON, U., MARGALIT, H., Network motifs in integrated cellular networks of transcription-regulation and protein–protein interaction. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5934–5939.
- 172 DELABRE, M. L., KESSL, J., KARAMANOU, S., TRUMPOWER, B. L., RPL29 codes for a non-essential protein of the 60S ribosomal subunit in *Saccharomyces cerevisiae* and exhibits synthetic lethality with mutations in genes for proteins required for subunit coupling. *Biochim. Biophys. Acta* **2002**, *1574*, 255–261.
- 173 MAFTAH, M., HOPE, J. C., DELGADO-CRUZATA, L., HAN, C. S., FREYER, G. A., The severe slow growth of *Deltasr2* is suppressed by loss of recombination and checkpoint genes. *Nucleic Acids Res.* **2002**, *30*, 4781–4792.
- 174 DONG, C., WANG, S., LI, W. D., LI, D., ZHAO, H., PRICE, R. A., Interacting genetic loci on chromosomes 20 and 10 influence extreme human obesity. *Am. J. Hum. Genet.* **2003**, *72*, 115–124.
- 175 SMALL, K. M., WAGONER, L. E., LEVIN, A. M., KARDIA, S. L., LIGGETT, S. B., Synergistic polymorphisms of β 1- and α 2C-adrenergic receptors and the risk of congestive heart failure. *N. Engl. J. Med.* **2002**, *10*, 1135–1142.
- 176 WIECZOREK, D. J., DIDION, L., FEISS, M., Alterations of the portal protein, gpB, of bacteriophage lambda suppress mutations in *cosQ*, the site required for termination of DNA packaging. *Genetics* **2002**, *161*, 21–31.
- 177 DEAK, P., DONALDSON, M., GLOVER, D. M., Mutations in *makos*, a *Drosophila* gene encoding the Cdc27 subunit of the anaphase promoting complex, enhance centrosomal defects in *polo* and are suppressed by mutations in *twins/aar*, which encodes a regulatory subunit of PP2A. *J. Cell Sci.* **2003**, *116*, 4147–4158.
- 178 KIM, I. G., RHEE, D. K., JEONG, J. W., KIM, S. C., WON, M., LEE, J., SONG, K. W., KIM, H. B., Mad1p, a component of the spindle assembly checkpoint in fission yeast, suppresses a novel septation-defective mutant, *sun1*, in a cell-division cycle. *FEMS Microbiol. Lett.* **2003**, *227*, 183–188.
- 179 TRACHTULCOVA, P., FRYDLOVA, I., JANATOVA, I., DOROSH, A., HASEK, J., The W303 genetic background affects the *isw2 delta* mutant phenotype in *Saccharomyces cerevisiae*. *Folia Microbiol. (Praha)* **2003**, *48*, 745–753.
- 180 CHAUHAN, B. K., REED, N. A., YANG, Y., CERMAK, L., RENEKER, L., DUNCAN, M. K., CVEKL, A., A comparative cDNA microarray analysis reveals a spectrum of genes regulated by *Pax6* in mouse lens. *Genes. Cells* **2002**, *7*, 1267–1283.
- 181 JACOBSON, C., DUGGAN, D., FISCHBACH, G., Neuregulin induces the expression of transcription factors and myosin heavy chains typical of muscle spindles in cultured human muscle. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12218–12223.
- 182 YAO, W. D., GAINETDINOV, R. R., ARBUCKLE, M. I., SOTNIKOVA, T. D., CYR, M., BEAULIEU, J. M., TORRES, G. E., GRANT, S. G., CARON, M. G., Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity. *Neuron* **2004**, *41*, 625–638.
- 183 LIVESY, F. J., FURUKAWA, T., STEFFEN, M. A., CHURCH, G. M., CEPKO, C. L., Microarray analysis of the transcriptional network controlled by the photoreceptor homeobox gene *Crx*. *Curr. Biol.* **2000**, *10*, 301–310.
- 184 DEAN, M., Approaches to identify genes for complex human diseases: lessons from Mendelian disorders. *Human Mutation* **2003**, *22*, 261–274.

- 185 GLATT, C. E., FREIMER, N. B., Association analysis of candidate genes for neuropsychiatric disease: the perpetual campaign. *Trends Genet.* **2002**, *8*, 307–312.
- 186 HIRSCHHORN, J. N., Once and again: issues surrounding replication in genetic association studies. *J. Clin. Endocrinol. Metab.* **2002**, *87*, 4438–4441.
- 187 HIRSCHHORN, J. N., LOHMEYER, K., BYRNE, E., HIRSCHHORN, K., A comprehensive review of genetic association studies. *Genet. Med.* **2002**, *4*, 45–61.
- 188 TOYOTA, T., HATTORI, E., MEERABUX, J., YAMADA, K., SAITO, K., SHIBUYA, H., NANKAI, M., YOSHIKAWA, T., Molecular analysis, mutation screening, and association study of adenylate cyclase type 9 gene (*ADCY9*) in mood disorders. *Am. J. Med. Genet.* **2002**, *114*, 84–92.
- 189 YOUNG, L. T., BAKISH, D., BEAULIEU, S., The neurobiology of treatment response to antidepressants and mood stabilizing medications. *J. Psychiatry Neurosci.* **2002**, *27*, 260–265.
- 190 LI, G., QIAN, H., Sensitivity and specificity amplification in signal transduction. *Cell Biochem. Biophys.* **2003**, *39*, 45–59.
- 191 BLIER, P., Crosstalk between the norepinephrine and serotonergic systems and its role in antidepressant treatment response. *J. Psychiatry Neurosci.* **2001**, *26* Suppl., S3–10.
- 192 BROOKES, A. J., The essence of SNPs. *Gene* **1999**, *234*, 177–186.
- 193 IRIZARRY, K., HU, G., WONG, M.-L., LICINIO, J., LEE, C. J., Single nucleotide polymorphism identification in candidate gene systems of obesity. *Pharmacogenom. J.* **2001**, *1*, 193–203.
- 194 SHASTRY, B. S., SNP alleles in human disease and evolution. *J. Hum. Genet.* **2002**, *47*, 561–566.
- 195 CARGILL, M., DALEY, G. Q., Mining for SNPs: putting the common variants: common disease hypothesis to the test. *Pharmacogenomics* **2000**, *1*, 27–37.
- 196 STROBEL, A., GUTKNECHT, L., ROTHE, C., REIF, A., MOSSNER, R., ZENG, Y., BROCKE, B., LESCH, K. P., Allelic variation in 5-HT1A receptor expression is associated with anxiety- and depression-related personality traits. *J. Neural. Transm.* **2003**, *110*, 1445–1453.
- 197 SATO, K., YOSHIDA, K., TAKAHASHI, H., ITO, K., KAMATA, M., HIGUCHI, H., SHIMIZU, T., ITOH, K., INOUE, K., TEZUKA, T., SUZUKI, T., OHKUBO, T., SUGAWARA, K., OTANI, K., Association between –1438G/A promoter polymorphism in the 5-HT(2A) receptor gene and fluvoxamine response in Japanese patients with major depressive disorder. *Neuropsychobiology* **2002**, *46*, 136–140.
- 198 BARRETT, T. B., HAUGER, R. L., KENNEDY, J. L., SADOVNIK, A. D., REMICK, R. A., KECK, P. E., McELROY, S. L., ALEXANDER, M., SHAW, S. H., KESOE, J. R., Evidence that a single nucleotide polymorphism in the promoter of the G protein receptor kinase 3 gene is associated with bipolar disorder. *Mol. Psychiatry* **2003**, *8*, 546–557.
- 199 PONOMARENKO, J. V., ORLOVA, G. V., MERKULOVA, T. I., GORSHKOVA, E. V., FOKIN, O. N., VASILIEV, G. V., FROLOV, A. S., PONOMARENKO, M. P., rSNP_Guide: an integrated database–tools system for studying SNPs and site-directed mutations in transcription factor binding sites. *Hum. Mutat.* **2002**, *20*, 239–248.
- 200 DUAN, J., SANDERS, A. R., MOLEN, J. E., MARTINOLICH, L., MOWRY, B. J., LEVINSON, D. F., CROWE, R. R., SILVERMAN, J. M., GEJMAN, P. V., Polymorphisms in the 5′-untranslated region of the human serotonin receptor 1B (*HTR1B*) gene affect gene expression. *Mol. Psychiatry* **2003**, *8*, 901–910.
- 201 DUAN, J., WAINWRIGHT, M. S., COMERON, J. M., SAITOU, N., SANDERS, A. R., GELERTNER, J., GEJMAN, P. V., Synonymous mutations in the human dopamine receptor D2 (*DRD2*) affect mRNA stability and synthesis of the receptor. *Hum. Mol. Genet.* **2003**, *12*, 205–216.
- 202 STEINER, B., TRUNINGER, K., SANZ, J., SCHALLER, A., GALLATI, S., The role of common single-nucleotide polymorphisms on exon 9 and exon 12 skipping in nonmutated *CFTR* alleles. *Hum. Mutat.* **2004**, *24*, 120–129.
- 203 VON AHSEN, N., OELLERICH, M., The intronic prothrombin 19911A>G polymorphism influences splicing efficiency and modulates effects of the

- 20210G>A polymorphism on mRNA amount and expression in a stable reporter gene assay system. *Blood* **2004**, *103*, 586–593.
- 204 RIZZO, W. B., CARNEY, G., LIN, Z., The molecular basis of Sjogren–Larsson syndrome: mutation analysis of the fatty aldehyde dehydrogenase gene. *Am. J. Hum. Genet.* **1999**, 1547–1560.
- 205 VOS, M., ADAMS, C. H., VICTOR, T. C., VAN HELDEN, P. D., Polymorphisms and mutations found in the regions flanking exons 5 to 8 of the *TP53* gene in a population at high risk for esophageal cancer in South Africa. *Cancer Genet. Cytogenet.* **2003**, *140*, 23–30.
- 206 LYNCH, K. W., WEISS, A., A *CD45* polymorphism associated with multiple sclerosis disrupts an exonic splicing silencer. *J. Biol. Chem.* **2001**, *276*, 24341–24347.
- 207 PONOMARENKO, J. V., ORLOVA, G. V., MERKULOVA, T. I., GORSHKOVA, E. V., FOKIN, O. N., VASILIEV, G. V., FROLOV, A. S., PONOMARENKO, M. P., rSNP_Guide: an integrated database–tools system for studying SNPs and site-directed mutations in transcription factor binding sites. *Hum. Mutat.* **2002**, *20*, 239–248.
- 208 CAI, Z., TSUNG, E. F., MARINESCU, V. D., RAMONI, M. F., RIVA, A., KOHANE, I. S., Bayesian approach to discovering pathogenic SNPs in conserved protein domains. *Hum. Mutat.* **2004**, *24*, 178–184.
- 209 ZHANG, J., ROWE, W. L., STRUEWING, J. P., BUETOW, K. H., HapScope: a software system for automated and visual analysis of functionally annotated haplotypes. *Nucleic Acids Res.* **2002**, *30*, 5213–5221.
- 210 WJST, M., Target SNP selection in complex disease association studies. *BMC Bioinformatics* **2004**, *5*, 92.
- 211 JOHNSON, G., ESPOSITO, L., BARATT, B., SMITH, A., HEWARD, J., GENOOVA, G. D., UEDA, H., CORDELL, H., EAVES, I., DDBRIDGE, F., TWELLS, R., PAYNE, F., HUGHES, W., NUTLAND, S., STEVANS, H., CARR, P., TUOMILEHTO, J., GOUGH, S., CLAYTON, D., TODD, J., Haplotype tagging for the identification of common disease genes. *Nat. Genet.* **2001**, *29*, 233–237.
- 212 BYNG, M. C., WHITTATEK, J. C., CUTHBERT, A. P., MATHEW, C. G., LEWIS, C. M., SNP subset selection for genetic association studies. *Ann. Hum. Genet.* **2003**, *67*, 543–553.
- 213 BARTON, A., CHAPMAN, P., MYERSCOUGH, A., PINEL, T., DAVIES, N., WORTHINGTON, J., JOHN, S., The single-nucleotide polymorphism lottery: how useful are a few common SNPs in identifying disease-associated alleles? *Genet. Epidemiol.* **2001**, *21 Suppl.*, S384–S389.
- 214 HUANG, Q., FU, Y., BOERWINKLE, E., Comparison of strategies for selecting single nucleotide polymorphisms for case/control association studies. *Human Genet.* **2003**, *113*, 253–257.
- 215 MENG, Z., ZAYKIN, D., XU, C., WAGNER, M., EHM, M. G., Selection of genetic markers for association analysis, using linkage disequilibrium and haplotypes. *Am. J. Hum. Genet.* **2003**, *73*, 115–130.
- 216 ARDLIE, K. G., KRUGLYAK, L., SEIELSTAD, M., Patterns of linkage disequilibrium in the human genome. *Nat. Rev. Genet.* **2002**, *3*, 299–309.
- 217 GABRIEL, S. B., SCHAFFNER, S. F., NGUYEN, H., MOORE, J. M., ROY, J., BLUMENSTIEL, B., HIGGINS, J., DEFELICE, M., LOCHNER, A., FAGGART, M., LIUCORDERO, S. N., ROTIMI, C., ADEYEMO, D., The structure of haplotype blocks in the human genome. *Science* **2002**, *296*, 2225–2229.
- 218 STUMPF, M. P., Haplotype diversity and SNP frequency dependence in the description of genetic variation. *Eur. J. Hum. Genet.* **2004**, *12*, 469–477.
- 219 YURYEV, A., HUANG, J., POHL, M., PATCH, R., WATSON, F., BELL, P., DONALDSON, M., PHILLIPS, M. S., BOYCE-JACINO, M. T., Predicting the success of primer extension genotyping assays using statistical modeling. *Nucleic Acids Res.* **2002**, *30*, e131.
- 220 IRIZARRY, K. J., GALBRAITH, S. J., Significance of SNP combination patterns. *Mol. Psych.* **2004**, *9*, 430.

37

Emerging Treatments for Depression: Beyond the Monoamine Hypothesis

Julio Licinio

*"The question was put to him, what hope is,
and his answer was 'The dream of a waking man.'"*

Laertius Diogenes (ca. 320 BCE)

Abstract

Depression is a common and complex disorder of gene–environment interactions for which there are no curative treatments. All therapeutic strategies available today, which include more than 40 FDA-approved compounds, were initially discovered by serendipity; once aspects of their mechanism of action were identified as targeting monoamines, strategies to develop increasingly refined modulators of monoaminergic neurotransmission led to the new antidepressants available today. Conceptually novel treatments have not yet reached the market but loom promisingly on the horizon. These include drugs aimed at neuropeptidergic systems that have been associated with depression for over two decades, such as CRH. Efforts are also underway to address new targets that have been explored in more depth or unveiled in the last decade, including glutamate, BDNF, CREB, and reward-related molecules such as opioids and cannabinoids. The field has had for nearly a century one standard, highly effective nonpharmacological approach, namely electroconvulsive therapy. Two additional new approaches are now being tested clinically: transcranial magnetic stimulation and vagal nerve stimulation. The pharmacological and nonpharmacological pipeline has interesting elements but it is not replete with excitement and opportunity. This should not be so. The World Health Organization and World Bank acknowledge depression to be a major public health problem worldwide. Depression is among the most lucrative drug targets. Basic neuroscience, molecular neurobiology, genomics, and pharmacogenomics have grown explosively in the last decade. It is a reality that at the present time, translation of such exciting new science into much-needed new therapeutic opportunities has lagged behind in the field of depression research. Recognition of

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key pitfalls provides a foundation for bridging the gap between fundamental science and innovative clinical research treatments in a process that facilitates the discovery and successful implementation of novel, and hopefully individualized, therapies.

37.1

Introduction

Major depression is a common and complex disorder of gene–environment interactions [1]. Regrettably, the specific genetic substrates and necessary precipitating environmental factors have not yet been unveiled. For this reason, there are no curative treatments. Existing treatments work by causing temporary symptomatic improvement. As soon as treatment is discontinued, patients are at risk for relapse. Clinical tradition recommended that treatment had to last the same as the average duration of a naturally occurring depressive episode, which is about nine months. Empirical data however show that if antidepressant drugs are given for periods as long as five years, treated patients are less likely to relapse than those on placebo [2].

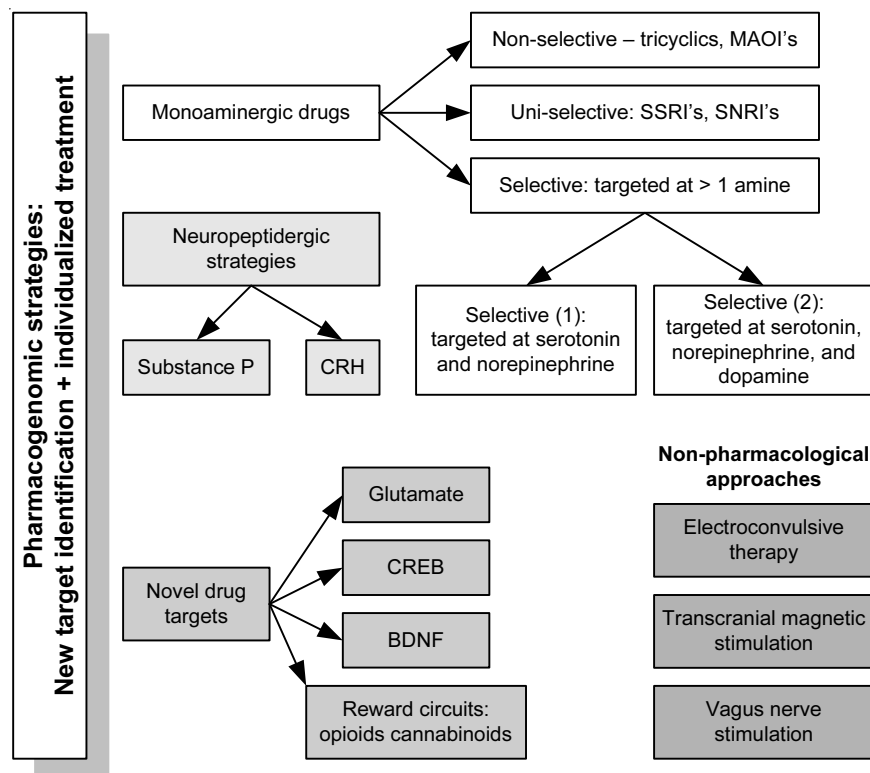


Figure 37.1 Schematic representation of existing and new targets and approaches for treatment development in depression.

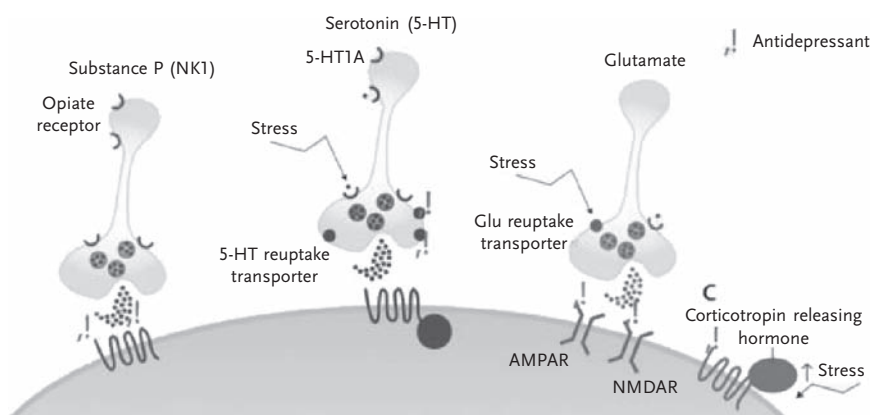


Figure 37.2 Visual representation at the cellular level of new antidepressants. Seeking new antidepressants, pharmaceutical companies are developing compounds that affect (a) the neurotransmitters serotonin, norepinephrine, and dopamine; (b) glutamate; (c) stress hormones; and (d) brain-specific proteins such as substance P. Reproduced with permission from [3].

Several chapters in this book address issues related to treatment. I focus here, not on existing treatments, but on what is on the horizon for future treatment strategies for this challenging disorder. These are summarized in Figure 37.1 and depicted at the cellular level in Figure 37.2. Even though the market for antidepressants is estimated to be at least 17 billion US\$ annually [3], the pipeline for new antidepressants is relatively limited.

37.2

Further Developments on the Monoamine Front

Within the monoamine spectrum, after much emphasis on selective reuptake blockade of specific monoamines, newer drugs such as duloxetine, just released in the United States, offer blockade of both serotonin and norepinephrine [4–8]. The next step in this field is the use of drugs that simultaneously increase the synaptic availability of three monoamines. These drugs, known as ‘broad-spectrum’ antidepressants, include compounds that inhibit the reuptake of norepinephrine, serotonin, and dopamine, the three biogenic amines most closely linked to depression. Azabicyclo[3.1.0]hexane compounds such as DOV 21,947 and DOV 216,303 potently inhibit norepinephrine, serotonin, and dopamine reuptake by the corresponding human transporter proteins. These drugs are effective in swim and tail suspension tests, preclinical procedures that can be predictive of antidepressant action in humans. Based on the presumptive role of dopamine in depression, it has been hypothesized that a broad-spectrum antidepressant produces a more rapid onset and/or higher efficacy than agents inhibiting the reuptake of only serotonin and/or norepinephrine. Those broader drugs are now undergoing

early clinical trials as antidepressants [9, 10]. It remains to be determined whether there are additional antidepressant effects or any other clinical advantages from selectively blocking two or three monoamine transporters in comparison to blocking just one transporter.

37.3 Neuropeptide-based Strategies

Possibly the most promising new antidepressant strategy at present is aimed at blocking the central effects of corticotropin-releasing hormone (CRH). There are abundant and independent lines of evidence linking disrupted hypothalamic–pituitary–adrenal (HPA) function, ultimately attributed to CRH dysregulation, to depression (Table 37.1). These include the following key observations: increased 24-h elevations in cortisol production [11], lack of suppression of plasma cortisol levels by dexamethasone [12], increased concentrations of CRH in cerebrospinal fluid [13], dysregulation of HPA responses to exogenous CRH administration [14–16], and loss of the negative correlation between plasma cortisol and continuously collected CSF CRH [17]. It is noteworthy that antidepressants of various classes suppress *CRH* gene expression [18–20] in rodents as well as in depressed [21] and healthy humans [22]. It has therefore been proposed that suppression of CRH activity is a common final effect of antidepressant treatment. CRH receptor antagonists have been identified preclinically and have effects that are suggestive of anxiolytic and antidepressant activity [23–26]. We showed that chronic treatment with this type of compound does not block the HPA response to acute stress, which is of potential clinical importance for situations of prolonged treatment, such as that required in depression [27]. Small clinical trials with a nonpeptide CRH antagonist revealed antidepressant efficacy [28]. However, hepatotoxicity led to a

Table 37.1 Independent lines of evidence linking disrupted HPA function and CRH dysregulation to depression.

Reference	Finding
11	Increased 24-h elevations in cortisol production
12	Lack of suppression of plasma cortisol levels by dexamethasone
13	Increased concentrations of CRH in cerebrospinal fluid
14–16	Dysregulation of HPA responses to exogenous CRH administration
17	Loss of the negative correlation between plasma cortisol and continuously collected CSF CRH
18–20	Suppression of <i>CRH</i> gene expression in rodents by various classes of antidepressants
21, 22	Suppression of HPA activity in depressed and healthy humans by antidepressants

halt of existing human trials [29]. It is thought that this adverse drug reaction (ADR) is specific to existing compounds; for this reason, companies are currently developing novel compounds that can block central CRH receptors without causing liver damage. Moreover, because cortisol regulates immune response to infections, a successful CRH antagonist would have to act on the brain receptors but not in the periphery [3].

We recently showed that a specific haplotype in the CRH receptor 1 (*CRHR1*) gene is associated with response to antidepressant treatment with either the selective serotonin reuptake inhibitor fluoxetine or the tricyclic desipramine, but only in patients who were depressed and highly anxious [30]. Utilizing the haplotype-tag single nucleotide polymorphisms (htSNPs) rs1876828, rs242939, and rs242941 of *CRHR1*, we tested for haplotypic association between *CRHR1* and eight-week response to daily antidepressant treatment. In the high-anxiety group (HA) group, defined as having a Hamilton anxiety rating scale (HAM-A) score of 18 or higher, homozygosity for the GAG haplotype was associated with a relative 70% greater reduction in HAM-A scores compared to heterozygous ($63.1 \pm 4.5\%$ vs. $37.1 \pm 6.9\%$, respectively, $P = 0.002$). For the Hamilton depression rating scale (HAM-D), GAG haplotype homozygosity was associated with a 31% greater reduction in scores after treatment compared to heterozygous ($67.3 \pm 4.3\%$ vs. $51.2 \pm 6.0\%$, respectively, $P = 0.03$). In persons with lower anxiety levels at screening, there were no associations between *CRHR1* genotype and percent change in HAM-A or HAM-D. Because CRH is involved not only in depression, but also in anxiety, it is not surprising that variations in *CRHR1* are only associated with antidepressant response in patients who are both depressed and highly anxious. This work supports the hypotheses that response to antidepressant treatment is heterogeneous and that the *CRHR1* gene and possibly other genes in stress-inflammatory pathways are involved in the response to antidepressant treatment. These findings also suggest that variations in the *CRHR1* gene may affect response to *CRHR1* antagonists used as antidepressants. Results of future studies on this target are therefore more likely to yield interesting results if they are stratified by genotype.

Another neuropeptidergic approach to depression involves the use of substance-P antagonists. In 1998 Kramer et al. [31] published an exciting report of robust antidepressant effects in humans of the substance-P antagonist MK-869. This established the proof-of-concept that drugs targeted at neuropeptidergic systems could function as antidepressants. However, subsequent studies failed to show consistent antidepressant effects. That drug was eventually found to also prevent 'delayed' nausea, which takes place two to five days after cancer chemotherapy with high-dose cisplatin and has been approved for such use, under the name aprepitant [32, 33]. Most companies have closed their substance-P programs for depression, except for GSK, which continues to pursue this strategy [3].

37.4

The Glutamate System as a Target for Antidepressants

The glutamate system offers promise in antidepressant drug development. Glutamate is thought to underlie the synaptic substrate of memory. Clinically, there is obviously dysregulation of memory-related experiences in depression, characterized by two key events. (1) Over-representation of negative experiences: depressed patients remember in excruciating detail negative experiences and experience substantial amounts of time reexperiencing them psychologically; in contrast, positive experiences are deemphasized. (2) Even though patients with recurrent depression can recall past improvement after treatment, they psychologically experience a level of despair that is disconnected to their own ability to overcome depression. This suggests dysregulation of memory-affective connections in the depressed state. It is consequently noteworthy that Nowak et al. [34] showed that radioligand binding to NMDA receptors is altered in the frontal cortex of suicide victims (compared to age and postmortem interval-matched controls). Using an independent approach to examine the relevance of glutamate to depression, Skolnick and colleagues demonstrated that chronic (14 days) but not acute (1 day) administration of 17 different antidepressants to mice produced adaptive changes in radioligand binding to NMDA receptors. Studies with three antidepressants (imipramine, citalopram, and electroconvulsive shock) showed that these changes develop slowly, persist for some time after cessation of treatment, and (for imipramine and citalopram) are dose-dependent. Moreover, following chronic treatment with imipramine, these changes in radioligand binding to NMDA receptors appear restricted to the cerebral cortex. Based on the consistency of these effects across antidepressant treatments, the authors proposed that adaptive changes in NMDA receptors may be a final common pathway for antidepressant action [35].

Within the glutamatergic system, glutamate α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors mediate most of the excitatory neurotransmission in the mammalian central nervous system and also participate in forms of synaptic plasticity thought to underlie memory and learning and the formation of neural networks during development. Several classes of AMPA receptor potentiators have been reported, including pyrrolidones (piracetam, aniracetam), benzothiazides (cyclothiazide), benzylpiperidines (CX-516, CX-546), and more recently, biarylpropylsulfonamides (LY392098, LY404187, and LY503430). Several independent studies have suggested that AMPA receptors can increase BDNF expression by both calcium-dependent and -independent pathways. For example, recent studies have shown that AMPA receptors interact with the protein tyrosine kinase Lyn. Activation of Lyn can recruit the mitogen-activated protein kinase (MAPK) signaling pathway and increase the expression of BDNF. Therefore, in addition to directly enhancing glutamatergic synaptic transmission, AMPA receptor activation can increase the expression of BDNF *in vitro* and *in vivo*. This may account for activity of AMPA receptor potentiators in rodent models predictive of antidepressant activity (forced swim and tail suspension tests). These AMPA receptor potentiators may represent a new class of drugs with potential for treating depression [36].

37.5

cAMP Response Element-binding Protein (CREB)

Additional targets for novel antidepressant strategies include CREB, a member of the bZIP family of transcription factors. CREB is a ubiquitous key element of intracellular signal transduction cascades, and its transcriptional activity depends on phosphorylation at Ser133. Several lines of evidence suggest a role for CREB in antidepressant treatment response. CREB expression and phosphorylation of CRE binding protein (CREB) in several limbic brain regions thought to mediate the action of antidepressants (including the cerebral cortex, hippocampus, amygdala, and hypothalamus) are regulated by various types of antidepressant treatments [37–39]. At the clinical level, Koch et al. [40] showed that CREB phosphorylation occurred in T-lymphocytes of patients before and at the end of weeks one and two of either psychopharmacological or psychotherapeutic treatment. After two weeks, 75% patients met the criteria of treatment response (i.e., 30% reduction in HAM-D score compared to baseline), whereas 25% patients did not. At the end of week two, the responders showed a significant increase in CREB phosphorylation compared to the nonresponders. This was true for all patients in either treatment regimen. The authors concluded that an increase in CREB phosphorylation might be a molecular state marker for the response to antidepressant treatment [40]. It seems that, eight weeks after antidepressant treatment, a significant decrease in *CREB* gene expression, as measured by quantitative reverse transcriptase–polymerase chain reaction, also occurs in peripheral lymphocytes of depressed subjects. The expression change was not associated with the type of antidepressants and therapeutic response. Moreover, *pCREB* is down-regulated in human fibroblasts from patients with major depression and in postmortem brain of suicide victims having a history of depression [41]. Genetic studies by Zubenko's group [42] showed evidence of linkage of unipolar depression to a 451-kb region of 2q33-34 flanked by D2S2321 and D2S2208 in families with recurrent early-onset major depression. The region between the markers that yielded the peak LOD score includes the *CREB1* gene.

37.6

Brain-derived Neurotrophic Factor (BDNF) and *trkB*

CREB is known to affect the expression of BDNF [43] and its receptor, *trkB* [44], which are also modulated by antidepressant treatment and dysregulated in depression. BDNF and its receptor *trkB* may therefore represent an additional target for antidepressant drug development. An informative postmortem study using postmortem anterior hippocampus sections obtained from the Stanley Foundation Neuropathology Consortium examined tissue from subjects with major depression, bipolar disorder, schizophrenia, and nonpsychiatric control subjects after immunohistochemical staining for BDNF. The authors observed that increased BDNF expression was found in dentate gyrus, hilus, and supragranular regions in subjects

treated with antidepressant medications at the time of death, compared with antidepressant-untreated subjects [45]. The same authors had previously reported increased temporal cortex CREB concentrations with antidepressant treatment in major depression [46]. Because the clinical effects of antidepressants occur only after chronic use, it is very relevant that BDNF is modulated in the brain after chronic treatment and is thought to mediate at least in part the chronic effects of antidepressants. Additionally, BDNF administration to rodents causes antidepressant-like effects in behavioral models of depression. Additionally, activation of the trkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects [45, 47–56]. Those interested in antidepressant drug development are now asking the question: Will drugs acting at the level of BDNF and trkB function eventually emerge as clinically useful antidepressants?

37.7

Opioids and Cannabinoids: Targets for New Antidepressants?

The last item in terms of potential new drug targets to be covered here is related to reward systems traditionally seen as relevant to drug abuse, namely opioids and cannabinoids. Opiates were used to treat major depression until the mid 1950s. Bodkin and colleagues [57] published in 1995 a small report of subjects with treatment-refractory unipolar nonpsychotic major depression treated with the opioid partial agonist buprenorphine in an open-label study, with highly encouraging results. Four years later, Stoll and Rueter [58] reported early findings on treatment augmentation with opioids in severe depression.

Evidence for involvement of the cannabinoid system in depression is more recent. In 2004, Hungund and colleagues reported a study on the levels of cannabinoid 1 [CB(1)] receptors and mediated signaling in the dorsolateral prefrontal cortex (DLPFC) of subjects with major depression who had died by suicide (depressed suicides, DS). They showed significant up-regulation of CB(1) receptor density (B_{\max}) in DS compared with matched controls. However, there was no significant change in the affinity of the receptor. A higher density of CB(1) receptors in DS was also demonstrated by Western blot analysis. CB(1) receptor-stimulated [35 S]GTP γ S binding was significantly greater in the DLPFC of DS compared with matched controls. The observed up-regulation of CB(1) receptors with concomitant increase in CB(1) receptor-mediated [35 S]GTP γ S binding suggests a role for enhanced cannabinoidergic signaling in the prefrontal cortex of DS. The authors concluded that the cannabinoidergic system may be a novel therapeutic target in the treatment of depression and/or suicidal behavior [59].

It remains to be determined whether interventions at the level of opioid and cannabinoid systems will prove to be of general use in the treatment of depression, particularly in treatment-refractory patients.

37.8

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a technology that allows for noninvasive modulation of the excitability and function of discrete brain cortical areas. TMS interferes with the function of small cortical areas through currents induced by alternating magnetic fields emanating from a handheld coil placed directly above the targeted area. This technique has clear effects on a whole range of measures of brain function and has become an important research tool in neuropsychiatry [60]. In psychiatry, TMS has been studied primarily as a potential treatment for refractory major depression [60–67]. Most studies indicate that slow-frequency repetitive TMS (rTMS) and higher frequency rTMS have antidepressant properties [64].

In 1996 Conca et al. [67] conducted a controlled clinical trial on a small number of patients affected by major depression (DSM-III-R). One group ($n = 12$) underwent TMS as an add-on therapy to standard antidepressants, while another group ($n = 12$) was treated only with antidepressants. They observed that a significantly greater remission of depressive symptoms occurred in the patients treated with TMS. In 1999 Klein and colleagues [66] conducted a double-blind placebo-controlled study to assess the efficacy of slow repetitive TMS in 70 patients with major depression. Treatment was administered in 10 daily sessions during a two-week period. They documented that patients who received rTMS had a significantly greater improvement in depression scores than those who received sham treatment. At the end of two weeks, 17 of 35 patients in the rTMS group, but only 8 of 32 in the sham-treated group, had an improvement of greater than 50% in their depression ratings.

George et al. [61] conducted a parallel-design double-masked sham-controlled study to address whether two weeks of daily TMS over the left prefrontal cortex has antidepressant activity greater than sham. They studied 30 medication-free adult outpatients with nonpsychotic major depressive ($n = 21$) or bipolar ($n = 9$) (depressed phase) disorder who were in a current major depression (HAM-D 21-item score of > 18) and were treated each weekday for two weeks. Subjects were randomly assigned to receive either daily active (20 subjects) or sham (10 subjects) stimulation. Additionally, the 20 active subjects were divided equally between slower (5 Hz) and faster (20 Hz) frequency treatments. Active TMS resulted in significantly more responders (9/20) than did sham (0/10), defined as a greater than a 50% improvement in the baseline HAM-D. The authors concluded that daily left prefrontal TMS for two weeks significantly reduced depression symptoms more than did sham and that the two forms of active TMS treatment did not differ significantly.

Burt and colleagues [64] conducted a meta-analysis of controlled studies, which indicated that this effect is fairly robust from a statistical viewpoint. However, effect sizes were heterogeneous, few studies showed that rTMS results in substantial rates of clinical response or remission, and the durability of antidepressant effects was largely unknown. TMS is a highly promising nonpharmacological method for antidepressant treatment. Its long-term efficacy and tolerability should be the topic of future studies.

37.9**Vagus Nerve Stimulation**

Vagus nerve stimulation (VNS) builds on a long history of investigating the relationship of autonomic signals to limbic and cortical function and is one of the newest methods used to physically alter brain function [68–73]. Intermittent electrical stimulation of the vagus nerve produces inhibition of neural processes, which can alter brain electrical activity and terminate seizures. Several thousand people worldwide have received vagus nerve stimulation for treatment-resistant epilepsy [73]. Pilot data suggest that this approach has potential as an antidepressant therapy.

Rush et al. [72] conducted a multicenter study of 30 adult outpatients with nonpsychotic treatment-resistant major depressive ($n = 21$) or bipolar I ($n = 4$) or II ($n = 5$; depressed phase) disorders who had failed at least two robust medication trials in the current major depressive episode (MDE). While on stable medication regimens they completed a baseline period followed by implantation of the NeuroCybernetic Prosthesis (NCP) System [72]. A two-week single-blind recovery period (no stimulation) was followed by 10 weeks of VNS. They found that baseline 28-item HAM-D [28] scores averaged 38.0. Response rates ($\geq 50\%$ reduction in baseline scores) were 40% for both the HAM-D [28] and the Clinical Global Impressions-Improvement index (score of 1 or 2) and 50% for the Montgomery–Åsberg Depression Rating Scale (MADRS). Symptomatic responses (accompanied by substantial functional improvement) were largely sustained during long-term follow up to date. Those early data suggested that VNS has antidepressant effects in treatment-resistant depressions.

Sackeim and colleagues [70] studied 60 outpatients with nonatypical nonpsychotic major depressive or bipolar disorder who had not responded to at least two medication trials from different antidepressant classes in the current episode. They reported a response rate of 30.5% for the primary HAM-D [28] measure, 34.0% for the MADRS, and 37.3% for the Clinical Global Impression-Improvement Score (CGI-I of 1 or 2). The most common side effect was voice alteration or hoarseness, 55.0% (33/60), which was generally mild and related to output current intensity. History of treatment resistance was predictive of VNS outcome. Patients who had never received ECT (lifetime) were 3.9 times more likely to respond. Of the 13 patients who had not responded to more than seven adequate antidepressant trials in the current episode, none responded, compared to 39.1% of the remaining 46 patients. The authors concluded that VNS appeared to be most effective in patients with low to moderate, but not extreme, antidepressant resistance. They further commented that evidence concerning VNS's long-term therapeutic benefits and tolerability will be critical in determining its role in treatment-resistant depression.

In a naturalistic follow-up study, Marangell et al. [69] followed 30 adult outpatients in a treatment-resistant nonpsychotic major depressive episode who received an additional nine months of vagus nerve stimulation treatment after exit from the three-month acute study. They found that the response rate was sustained and the remission rate significantly increased [17% (5/30) to 29% (8/28); $P = 0.045$] with the additional nine months of long-term vagus nerve stimulation (a total of one

year of vagus nerve stimulation treatment). Significant improvements in function between acute-study exit and the one-year follow-up assessment as measured by the Medical Outcomes Study Short Form-36 were observed. They concluded that longer-term vagus nerve stimulation treatment was associated with sustained symptomatic benefit and sustained or enhanced functional status in their setting.

It seems that VNS can be a safe and effective treatment alternative that can be used acutely and chronically with success, particularly in patients who have a mild to moderate refractoriness to antidepressant treatment.

37.10

Pitfalls, Challenges, and Opportunities in Antidepressant Drug Development

37.10.1

Lack of Etiologically Based Findings

The treatment of depression according to current and future approaches does not take into consideration the causes of the disease, which are unknown. In another major psychiatric disorder, schizophrenia, recent advances in genetics have identified completely novel genes that may have potential to serve as targets for drug development. Those include *neuregulin* [74–86], *G72/G30* [87–94], *Disrupted-in-Schizophrenia-1* (DISC-1) [95–103], and *DTNBP1* (human dysbindin) [104–116]. In contrast to these advances in schizophrenia research, for depression as of today genetics has not led to the identification of new targets with potential for drug development. When these are discovered there may be new opportunities for drug development guided by etiologically relevant pathways.

A word of caution is needed though. The pathways related to disease causation and symptom amelioration may not necessarily be identical. Continuing the analogy with schizophrenia, it seems that the etiology of the disease may be related at least in part to abnormal migration of neurons during development. If that is true, when a patient presents with the disease in adulthood, it will most likely be impossible to undo the abnormal neuronal migration process. For that reason, strategies aimed at reversing the functional consequences of altered development will be of greater therapeutic relevance than approaches directly aimed at gene products that caused the disease in the first place, but which may no longer be relevant when the patient presents to treatment. If genes identified for the etiology of depression likewise exert their effects early in life, altering developmental patterns, they may not necessarily represent the most optimal targets for drugs used to treat depression presenting in adulthood.

37.10.2

Search for Downstream Targets

In contrast, pharmacogenetic and pharmacogenomic approaches can be of much help. Our own working hypothesis has been based on three features of anti-

depressant treatment: (1) drugs acting on different targets (e.g., norepinephrine, serotonin, and dopamine) can be equally efficacious; (2) effects on monoamines are rapid and fully established within hours of drug administration; and (3) clinical effects take weeks to occur. Based on these facts, we and others have hypothesized that there must be unidentified common final downstream targets that are elicited by chronic antidepressant treatment with drugs of various classes. Once those targets are identified, new compounds that activate them directly and rapidly could be identified or created. Those would represent a breakthrough for treatment.

37.10.3

Suicidality during Treatment

Finally, I present here some general comments on adverse outcomes to new drugs, particularly suicide, which is the topic of Chapter 38 and is therefore covered here only briefly. In the clinical pharmacology of adverse drug reactions, the greatest challenge is posed by adverse events that overlap with features of the disease. For example, a drug such as tolcapone which is used to treat Parkinson's disease can also cause hepatotoxicity. In this context, monitoring plasma levels of liver enzymes can be highly effective. As soon as these levels rise beyond an established threshold (say, 1.5 times the normal baseline values), the drug can be discontinued with the assumption that the changes in hepatic function were drug-induced. If, however, a drug that is used to treat hepatitis causes hepatotoxicity, how can that be monitored? First, the baseline of liver enzyme levels is very high in hepatitis, so determining a threshold for diagnosing drug-induced hepatotoxicity is particularly hard. Moreover, the baseline disease causes waxing and waning of liver function. How can one ascertain whether worsening of liver function is caused by exacerbation of the underlying disease or if it is an adverse result of drug treatment?

The exact same considerations apply to the issues of suicidality and depression. Passive and active suicidal ideation are symptoms of depression, so intrinsically tied up to the disease that they are part of the diagnostic criteria. Thus, it is challenging to determine whether suicidality occurring in the context of antidepressant treatment is a feature of the underlying disorder or an adverse event caused by treatment. For this reason, trials of new drugs should be closely monitored for the presence of suicidality. A detailed baseline history is indispensable, but even in the absence of previous suicidal ideation, it is always possible that in some instances emerging new suicidality during experimental treatment can be due to exacerbation of depression, while in other instances it might be drug-induced.

Finally, an additional set of considerations must be addressed on the issue of possible association of suicidal ideation and new antidepressants. Existing drugs, and most likely new drugs as well, treat the constellation of symptoms that constitute the depression syndrome. These include fatigue; psychomotor retardation; changes in appetite and sleep patterns; feelings of guilt, despair, and worthlessness; and suicidality. Often patients have suicidal ideation that they may or may not talk about, but they lack the energy and disposition to execute suicidal plans because they are fatigued and psychomotorically retarded. There is no synchronicity in

symptom improvement during the course of treatment. Typically, fatigue and psychomotor retardation are among the first symptoms to improve by treatment, while existential sadness, feelings of despair and worthlessness, and suicidality are among the last to go. Therefore, it is in my opinion inherent to antidepressant treatment that a dangerous window of time is created during which the patient is still feeling sad, desperate, worthless, and suicidal, but thanks to (usually recently initiated) treatment, she or he is no longer fatigued and psychomotorically retarded and therefore has the (antidepressant-induced) increased energy and wherewithal to carry out often lethal suicide plans. Close monitoring of depressant patients, especially in the critical period of up to eight weeks after initiation of drug treatment, is therefore a necessity. By that time the new drug will either have resolved the symptoms of sadness, despair, worthlessness, and suicidality or will have been discontinued. It goes without saying that continued clinical follow up is required on a long-term basis for this chronic disorder.

37.11 Conclusions

I hope that in the not-too-distant future a combination of new and exciting treatment strategies that go beyond the monoamine hypotheses can be used to effectively treat depression. The time frame for such developments is unclear. To be pessimistic, one could claim that, even though clear evidence of the role of CRH in depression is more than 20 years old, roadblocks such as toxicity still prevent CRH-based approaches from reaching the market. On the other hand, it could be reasoned that advances in genetics and pharmacogenomics may accelerate drug discovery and development in this field, potentially facilitating more effective and individualized drug therapy for depressive disorders within the next 10 years. I optimistically believe that rapid advances in neuroscience, genetics, and pharmacogenomics will eventually result in major breakthroughs in translational research, ushering in a new era in antidepressant treatment. To quote Bacon, “there is no greater wisdom than well to time the beginnings and onsets of things.” Regrettably, based on current knowledge, the timing of such advances cannot be predicted yet.

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References

- 1 LICINIO, J., WONG, M. L., The pharmacogenomics of depression. *Pharmacogenomics J.* **2001**, 1, 175–177.
- 2 KUPFER, D. J., FRANK, E., PEREL, J. M., CORNES, C., MALLINGER, A. G., THASE, M. E., et al., Five-year outcome for maintenance therapies in recurrent depression. *Arch. Gen. Psychiatry* **1992**, 49, 769–773.
- 3 MANDAVILLI, A., Mood swings. *Nat. Med.* **2004**, Published online: 08 September 2004, doi:10.1038/040906-12.
- 4 BYMASTER, F. P., BEEDLE, E. E., FINDLAY, J., GALLAGHER, P. T., KRUSHINSKI, J. H., MITCHELL, S., et al., Duloxetine (cymbalta), a dual inhibitor of serotonin and norepinephrine reuptake. *Bioorg. Med. Chem. Lett.* **2003**, 13, 4477–4480.
- 5 GOLDSTEIN, D. J., LU, Y., DETKE, M. J., WILTSE, C., MALLINCKRODT, C., DEMITRACK, M. A., Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J. Clin. Psychopharmacol.* **2004**, 24, 389–399.
- 6 MALLINCKRODT, C. H., RASKIN, J., WOHLREICH, M. M., WATKIN, J. G., DETKE, M. J., The efficacy of duloxetine: a comprehensive summary of results from MMRM and LOCF_ANCOVA in eight clinical trials. *BMC Psychiatry* **2004**, 4 (AOP September 8, 2004), doi:10.1186/1471-244X-4-26.
- 7 NEMEROFF, C. B., SCHATZBERG, A. F., GOLDSTEIN, D. J., DETKE, M. J., MALLINCKRODT, C., LU, Y., et al., Duloxetine for the treatment of major depressive disorder. *Psychopharmacol. Bull.* **2002**, 36, 106–132.
- 8 RASKIN, J., GOLDSTEIN, D. J., MALLINCKRODT, C. H., FERGUSON, M. B., Duloxetine in the long-term treatment of major depressive disorder. *J. Clin. Psychiatry* **2003**, 64, 1237–1244.
- 9 SKOLNICK, P., POPIK, P., JANOWSKY, A., BEER, B., LIPPA, A. S., Antidepressant-like actions of DOV 21,947: a 'triple' reuptake inhibitor. *Eur. J. Pharmacol.* **2003**, 461, 99–104.
- 10 SKOLNICK, P., POPIK, P., JANOWSKY, A., BEER, B., LIPPA, A. S., 'Broad spectrum' antidepressants: is more better for the treatment of depression? *Life Sci.* **2003**, 73, 3175–3179.
- 11 SACHAR, E. J., HELLMAN, L., FUKUSHIMA, D. K., GALLAGHER, T. F., Cortisol production in depressive illness: a clinical and biochemical clarification. *Arch. Gen. Psychiatry* **1970**, 23, 289–298.
- 12 CARROLL, B. J., FEINBERG, M., GREDEN, J. F., A specific laboratory test for the diagnosis of melancholia. *Arch. Gen. Psychiatry* **1981**, 38, 15–22.
- 13 NEMEROFF, C. B., WILDERLOV, E., BISETTE, G., WALLEUS, H., KARLSSON, I., EKLUND, K., et al., Elevated concentrations of CSF corticotropin-releasing-factor-like immunoreactivity in depressed patients. *Science* **1984**, 226, 1342–1344.
- 14 GOLD, P. W., CHROUSOS, G., KELLNER, C., POST, R., ROY, A., AUGERINOS, P., et al., Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am. J. Psychiatry* **1984**, 141, 619–627.
- 15 HOLSBOER, F., MULLER, O. A., DOERR, H. G., ACTH and multiteroid responses to corticotropin-releasing factor in depressive illness: relationship to multiteroid responses after ACTH stimulation and dexamethasone suppression. *Psychoneuroendocrinology* **1984**, 9, 147–160.
- 16 GOLD, P. W., LORIAUX, D. L., ROY, A., KLING, M. A., CALABRESE, J. R., KELLNER, C. H., et al., Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease: pathophysiologic and diagnostic implications. *N. Engl. J. Med.* **1986**, 314, 1329–1335.
- 17 WONG, M. L., KLING, M. A., MUNSON, P. J., LISTWAK, S., LICINIO, J., PROLO, P., et al., Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl. Acad. Sci. USA* **2000**, 97, 325–330.
- 18 BRADY, L. S., WHITFIELD JR., H. J., FOX, R. J., GOLD, P. W., HERKENHAM, M., Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in

- rat brain: therapeutic implications. *J. Clin. Invest.* **1991**, 87, 831–837.
- 19 BRADY, L. S., GOLD, P. W., HERKENHAM, M., LYNN, A. B., WHITFIELD HJ Jr. The antidepressants fluoxetine, idazoxan and phenelzine alter corticotropin-releasing hormone and tyrosine hydroxylase mRNA levels in rat brain: therapeutic implications. *Brain Res.* **1992**, 572, 117–125.
 - 20 REUL, J. M., STEC, I., SODER, M., HOLLSBOER, F., Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic–pituitary–adrenocortical system. *Endocrinology* **1993**, 133, 312–320.
 - 21 GOLD, P. W., CHROUSOS, G. P., Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol. Psychiatry* **2002**, 7, 254–275.
 - 22 MICHELSON, D., GALLIVEN, E., HILL, L., DEMITRACK, M., CHROUSOS, G., GOLD, P., Chronic imipramine is associated with diminished hypothalamic–pituitary–adrenal axis responsiveness in healthy humans. *J. Clin. Endocrinol. Metab.* **1997**, 82, 2601–2606.
 - 23 SCHULZ, D. W., MANSBACH, R. S., SPROUSE, J., BRASELTON, J. P., COLLINS, J., CORMAN, M., et al., CP-154,526: a potent and selective nonpeptide antagonist of corticotropin releasing factor receptors. *Proc. Natl. Acad. Sci. USA* **1996**, 93, 10477–10482.
 - 24 HABIB, K. E., WELD, K. P., RICE, K. C., PUSHKAS, J., CHAMPOUX, M., LISTWAK, S., et al., Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc. Natl. Acad. Sci. USA* **2000**, 97, 6079–6084.
 - 25 DEAK, T., NGUYEN, K. T., EHRLICH, A. L., WATKINS, L. R., SPENCER, R. L., MAIER, S. F., et al., The impact of the nonpeptide corticotropin-releasing hormone antagonist antalarmin on behavioral and endocrine responses to stress. *Endocrinology* **1999**, 140, 79–86.
 - 26 WEBSTER, E. L., LEWIS, D. B., TORPY, D. J., ZACHMAN, E. K., RICE, K. C., CHROUSOS, G. P., In vivo and in vitro characterization of antalarmin, a nonpeptide corticotropin-releasing hormone (CRH) receptor antagonist: suppression of pituitary ACTH release and peripheral inflammation. *Endocrinology* **1996**, 137, 5747–5450.
 - 27 WONG, M. L., WEBSTER, E. L., SPOKES, H., PHU, P., EHRHART-BORNSTEIN, M., BORNSTEIN, S., et al., Chronic administration of the non-peptide CRH type 1 receptor antagonist antalarmin does not blunt hypothalamic–pituitary–adrenal axis responses to acute immobilization stress. *Life Sci.* **1999**, 65, L53–L8.
 - 28 ZOBEL, A. W., NICKEL, T., KUNZEL, H. E., ACKL, N., SONNTAG, A., ISING, M., et al., Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J. Psychiatr. Res.* **2000**, 34, 171–181.
 - 29 PALKHIVALA, A., New antidepressant class may be on its way. *DG News* **2001**.
 - 30 LICINIO, J., O'KIRWAN, F., IRIZARRY, K., MERRIMAN, B., THAKUR, S., JEPSON, R., et al., Association of a corticotropin-releasing hormone receptor 1 haplotype and antidepressant treatment response in Mexican Americans. *Mol. Psychiatry* **2004**, AOP September 14, 2004, 9, 1075–1082.
 - 31 KRAMER, M. S., CUTLER, N., FEIGHNER, J., SHRIVASTAVA, R., CARMAN, J., SRAMEK, J. J., et al., Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* **1998**, 281, 1640–1645.
 - 32 DANDO, T. M., PERRY, C. M., Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* **2004**, 64, 777–794.
 - 33 DE WIT, R., HERRSTEDT, J., RAPOPORT, B., CARIDES, A. D., GUOQUANG-MA, J., ELMER, M., et al., The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. *Eur. J. Cancer* **2004**, 40, 403–410.
 - 34 NOWAK, G., ORDWAY, G. A., PAUL, I. A., Alterations in the N-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. *Brain Res.* **1995**, 675, 157–164.

- 35 SKOLNICK, P., LAYER, R. T., POPIK, P., NOWAK, G., PAUL, I. A., TRULLAS, R., Adaptation of N-methyl- D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry* **1996**, *29*, 23–26.
- 36 O'NEILL, M. J., BLEAKMAN, D., ZIMMERMAN, D. M., NISENBAUM, E. S., AMPA receptor potentiators for the treatment of CNS disorders. *Curr. Drug Targets CNS Neurol. Disord.* **2004**, *3*, 181–194.
- 37 SCHWANINGER, M., SCHOFEL, C., BLUME, R., ROSSIG, L., KNEPEL, W., Inhibition by antidepressant drugs of cyclic AMP response element-binding protein/cyclic AMP response element-directed gene transcription. *Mol. Pharmacol.* **1995**, *47*, 1112–1118.
- 38 THOME, J., SAKAI, N., SHIN, K., STEFFEN, C., ZHANG, Y. J., IMPEY, S., et al., cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *J. Neurosci.* **2000**, *20*, 4030–4036.
- 39 NIBUYA, M., NESTLER, E. J., DUMAN, R. S., Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J. Neurosci.* **1996**, *16*, 2365–2372.
- 40 KOCH, J. M., KELL, S., HINZE-SELCH, D., ALDENHOFF, J. B., Changes in CREB-phosphorylation during recovery from major depression. *J. Psychiatr. Res.* **2002**, *36*, 369–375.
- 41 SULSER, F., The role of CREB and other transcription factors in the pharmacotherapy and etiology of depression. *Ann. Med.* **2002**, *34*, 348–356.
- 42 ZUBENKO, G. S., HUGHES 3RD, H. B., MAHER, B. S., STIFFLER, J. S., ZUBENKO, W. N., MARAZITA, M. L., Genetic linkage of region containing the CREB1 gene to depressive disorders in women from families with recurrent, early-onset, major depression. *Am. J. Med. Genet.* **2002**, *114*, 980–987.
- 43 ZHA, X. M., BISHOP, J. F., HANSEN, M. R., VICTORIA, L., ABBAS, P. J., MOURADIAN, M. M., et al., BDNF synthesis in spiral ganglion neurons is constitutive and CREB-dependent. *Hear Res.* **2001**, *156*, 53–68.
- 44 DEOGRACIAS, R., ESPLIGUERO, G., IGLESIAS, T., RODRIGUEZ-PENA, A., Expression of the neurotrophin receptor trkB is regulated by the cAMP/CREB pathway in neurons. *Mol. Cell Neurosci.* **2004**, *26*, 470–480.
- 45 CHEN, B., DOWLATSHAHI, D., MACQUEEN, G. M., WANG, J. F., YOUNG, L. T., Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol. Psychiatry* **2001**, *50*, 260–265.
- 46 DOWLATSHAHI, D., MACQUEEN, G. M., WANG, J. F., YOUNG, L. T., Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. *Lancet* **1998**, *352*, 1754–1755.
- 47 ALTIERI, M., MARINI, F., ARBAN, R., VITULLI, G., JANSSON, B. O., Expression analysis of brain-derived neurotrophic factor (BDNF) mRNA isoforms after chronic and acute antidepressant treatment. *Brain Res.* **2004**, *1000*, 148–155.
- 48 DIAS, B. G., BANERJEE, S. B., DUMAN, R. S., VAIDYA, V. A., Differential regulation of brain derived neurotrophic factor transcripts by antidepressant treatments in the adult rat brain. *Neuropharmacology* **2003**, *45*, 553–563.
- 49 NIBUYA, M., NESTLER, E. J., DUMAN, R. S., Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J. Neurosci.* **1996**, *16*, 2365–2372.
- 50 NIBUYA, M., MORINOBU, S., DUMAN, R. S., Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci.* **1995**, *15*, 7539–7547.
- 51 SIUCIAK, J. A., LEWIS, D. R., WIEGAND, S. J., LINDSAY, R. M., Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol. Biochem. Behav.* **1997**, *56*, 131–137.
- 52 RUSSO-NEUSTADT, A., HA, T., RAMIREZ, R., KESSLAK, J. P., Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. *Behav. Brain Res.* **2001**, *120*, 87–95.
- 53 SHIRAYAMA, Y., CHEN, A. C., NAKAGAWA, S., RUSSELL, D. S., DUMAN, R. S., Brain-

- derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J. Neurosci.* **2002**, *22*, 3251–3261.
- 54 SAARELAINEN, T., HENDOLIN, P., LUCAS, G., KOPONEN, E., SAIRANEN, M., MACDONALD, E., et al., Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.* **2003**, *23*, 349–357.
 - 55 COPPELL, A. L., PEI, Q., ZETTERSTROM, T. S., Bi-phasic change in BDNF gene expression following antidepressant drug treatment. *Neuropharmacology* **2003**, *44*, 903–910.
 - 56 IVY, A. S., RODRIGUEZ, F. G., GARCIA, C., CHEN, M. J., RUSSO-NEUSTADT, A. A., Noradrenergic and serotonergic blockade inhibits BDNF mRNA activation following exercise and antidepressant. *Pharmacol. Biochem. Behav.* **2003**, *75*, 81–88.
 - 57 BODKIN, J. A., ZORNBERG, G. L., LUKAS, S. E., COLE, J. O., Buprenorphine treatment of refractory depression. *J. Clin. Psychopharmacol.* **1995**, *15*, 49–57.
 - 58 STOLL, A. L., RUETER, S., Treatment augmentation with opiates in severe and refractory major depression. *Am. J. Psychiatry* **1999**, *156*, 2017.
 - 59 HUNGUND, B. L., VINOD, K. Y., KASSIR, S. A., BASAVARAJAPPA, B. S., YALAMANCHILI, R., COOPER, T. B., et al., Upregulation of CB1 receptors and agonist-stimulated [³⁵S]GTPgammaS binding in the prefrontal cortex of depressed suicide victims. *Mol. Psychiatry* **2004**, *9*, 184–190.
 - 60 SCHLAEPFER, T. E., KOSEL, M., NEMEROFF, C. B., Efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of affective disorders. *Neuropsychopharmacology* **2003**, *28*, 201–205.
 - 61 GEORGE, M. S., NAHAS, Z., MOLLOY, M., SPEER, A. M., OLIVER, N. C., LI, X. B., et al., A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biol. Psychiatry* **2000**, *48*, 962–970.
 - 62 PADBERG, F., MOLLER, H. J., Repetitive transcranial magnetic stimulation: does it have potential in the treatment of depression? *CNS Drugs* **2003**, *17*, 383–403.
 - 63 PAUS, T., BARRETT, J., Transcranial magnetic stimulation (TMS) of the human frontal cortex: implications for repetitive TMS treatment of depression. *J. Psychiatry Neurosci.* **2004**, *29*, 268–279.
 - 64 BURT, T., LISANBY, S. H., SACKEIM, H. A., Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int. J. Neuropsychopharmacol.* **2002**, *5*, 73–103.
 - 65 ESCHWEILER, G. W., PLEWNIA, C., BATRA, A., BARTELS, M., Does clinical response to repetitive prefrontal transcranial magnetic stimulation (rTMS) predict response to electroconvulsive therapy (ECT) in cases of major depression? *Can. J. Psychiatry* **2000**, *45*, 845–846.
 - 66 KLEIN, E., KREININ, I., CHISTYAKOV, A., KOREN, D., MECZ, L., MARMUR, S., et al., Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch. Gen. Psychiatry* **1999**, *56*, 315–320.
 - 67 CONCA, A., KOPPI, S., KONIG, P., SWOBODA, E., KRECKE, N., Transcranial magnetic stimulation: a novel antidepressive strategy? *Neuropsychobiology* **1996**, *34*, 204–207.
 - 68 GOODNICK, P. J., RUSH, A. J., GEORGE, M. S., MARANGELL, L. B., SACKEIM, H. A., Vagus nerve stimulation in depression. *Expert Opin. Pharmacother.* **2001**, *2*, 1061–1063.
 - 69 MARANGELL, L. B., RUSH, A. J., GEORGE, M. S., SACKEIM, H. A., JOHNSON, C. R., HUSAIN, M. M., et al., Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol. Psychiatry* **2002**, *51*, 280–287.
 - 70 SACKEIM, H. A., RUSH, A. J., GEORGE, M. S., MARANGELL, L. B., HUSAIN, M. M., NAHAS, Z., et al., Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* **2001**, *25*, 713–728.
 - 71 GEORGE, M. S., SACKEIM, H. A., MARANGELL, L. B., HUSAIN, M. M., NAHAS, Z., LISANBY, S. H., et al., Vagus nerve stimulation: a potential therapy for resistant depression? *Psychiatr. Clin. North Am.* **2000**, *23*, 757–783.

- 72 RUSH, A. J., GEORGE, M. S., SACKEIM, H. A., MARANGELL, L. B., HUSAIN, M. M., GILLER, C., et al., Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol. Psychiatry* **2000**, *47*, 276–286.
- 73 GEORGE, M. S., SACKEIM, H. A., RUSH, A. J., MARANGELL, L. B., NAHAS, Z., HUSAIN, M. M., et al., Vagus nerve stimulation: a new tool for brain research and therapy. *Biol. Psychiatry* **2000**, *47*, 287–295.
- 74 STEFANSSON, H., SIGURDSSON, E., STEINTHORSDDOTTIR, V., BJORNSDOTTIR, S., SIGMUNDSSON, T., GHOSH, S., et al., Neuregulin 1 and susceptibility to schizophrenia. *Am. J. Hum. Genet.* **2002**, *71*, 877–892.
- 75 STEFANSSON, H., SARGINSON, J., KONG, A., YATES, P., STEINTHORSDDOTTIR, V., GUDFINNSSON, E., et al., Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. *Am. J. Hum. Genet.* **2003**, *72*, 83–87.
- 76 WILLIAMS, N. M., PREECE, A., SPURLOCK, G., NORTON, N., WILLIAMS, H. J., ZAMMIT, S., et al., Support for genetic variation in neuregulin 1 and susceptibility to schizophrenia. *Mol. Psychiatry* **2003**, *8*, 485–487.
- 77 STEFANSSON, H., THORGEIRSSON, T. E., GULCHER, J. R., STEFANSSON, K., Neuregulin 1 in schizophrenia: out of Iceland. *Mol. Psychiatry* **2003**, *8*, 639–640.
- 78 YANG, J. Z., SI, T. M., RUAN, Y., LING, Y. S., HAN, Y. H., WANG, X. L., et al., Association study of *neuregulin 1* gene with schizophrenia. *Mol. Psychiatry* **2003**, *8*, 706–709.
- 79 HASHIMOTO, R., STRAUB, R. E., WEICKERT, C. S., HYDE, T. M., KLEINMAN, J. E., WEINBERGER, D. R., Expression analysis of neuregulin-1 in the dorso-lateral prefrontal cortex in schizophrenia. *Mol. Psychiatry* **2004**, *9*, 299–307.
- 80 TANG, J. X., CHEN, W. Y., HE, G., ZHOU, J., GU, N. F., FENG, G. Y., et al., Polymorphisms within 5' end of the *neuregulin 1* gene are genetically associated with schizophrenia in the Chinese population. *Mol. Psychiatry* **2004**, *9*, 11–12.
- 81 LI, T., STEFANSSON, H., GUDFINNSSON, E., CAI, G., LIU, X., MURRAY, R. M., et al., Identification of a novel neuregulin 1 at-risk haplotype in Han schizophrenia Chinese patients, but no association with the Icelandic/Scottish risk haplotype. *Mol. Psychiatry* **2004**, *9*, 698–704.
- 82 CORVIN, A. P., MORRIS, D. W., MCGHEE, K., SCHWAIGER, S., SCULLY, P., QUINN, J., et al., Confirmation and refinement of an 'at-risk' haplotype for schizophrenia suggests the EST cluster, Hs.97362, as a potential susceptibility gene at the *neuregulin-1* locus. *Mol. Psychiatry* **2004**, *9*, 208–213.
- 83 HALL, D., GOGOS, J. A., KARAYIORGOU, M., The contribution of three strong candidate schizophrenia susceptibility genes in demographically distinct populations. *Genes. Brain Behav.* **2004**, *3*, 240–248.
- 84 LAW, A. J., SHANNON WEICKERT, C., HYDE, T. M., KLEINMAN, J. E., HARRISON, P. J., Neuregulin-1 (NRG-1) mRNA and protein in the adult human brain. *Neuroscience* **2004**, *127*, 125–136.
- 85 CORFAS, G., ROY, K., BUXBAUM, J. D., Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia. *Nat. Neurosci.* **2004**, *7*, 575–580.
- 86 OKADA, M., CORFAS, G., Neuregulin1 downregulates postsynaptic GABAA receptors at the hippocampal inhibitory synapse. *Hippocampus* **2004**, *14*, 337–344.
- 87 CHUMAKOV, I., BLUMENFELD, M., GUERASSIMENKO, O., CAVAREC, L., PALICIO, M., ABDERRAHIM, H., et al., Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 13675–13680.
- 88 HATTORI, E., LIU, C., BADNER, J. A., BONNER, T. I., CHRISTIAN, S. L., MAHESHWARI, M., et al., Polymorphisms at the G72/G30 gene locus, on 13q33, are associated with bipolar disorder in two independent pedigree series. *Am. J. Hum. Genet.* **2003**, *72*, 1131–1140.
- 89 SCHUMACHER, J., JAMRA, R. A., FREUDENBERG, J., BECKER, T., OHLRAUN, S., OTTE, A. C., et al., Examination of G72 and D-amino-acid oxidase as genetic risk factors for schizophrenia and bipolar affective disorder. *Mol. Psychiatry* **2004**, *9*, 203–207.
- 90 ADDINGTON, A. M., GORNICK, M., SPORN, A. L., GOGTAY, N., GREENSTEIN,

- D., LENANE, M., et al., Polymorphisms in the 13q33.2 gene *G72/G30* are associated with childhood-onset schizophrenia and psychosis not otherwise specified. *Biol. Psychiatry* **2004**, *55*, 976–980.
- 91 WANG, X., HE, G., GU, N., YANG, J., TANG, J., CHEN, Q., et al., Association of *G72/G30* with schizophrenia in the Chinese population. *Biochem. Biophys. Res. Commun.* **2004**, *319*, 1281–1286.
- 92 SHIRTS, B. H., NIMGAONKAR, V., The genes for schizophrenia: finally a breakthrough? *Curr. Psychiatry Rep.* **2004**, *6*, 303–312.
- 93 HARRISON, P. J., WEINBERGER, D. R., Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol. Psychiatry* **2004**, AOP July 20, 2004, doi:10.1038/sj.mp.4001558.
- 94 KOROSTISHEVSKY, M., KAGANOVICH, M., CHOLOSTOY, A., ASHKENAZI, M., RATNER, Y., DAHARY, D., et al., Is the *G72/G30* locus associated with schizophrenia? Single nucleotide polymorphisms, haplotypes, and gene expression analysis. *Biol. Psychiatry* **2004**, *56*, 169–176.
- 95 OZEKI, Y., TOMODA, T., KLEIDERLEIN, J., KAMIYA, A., BORD, L., FUJII, K., et al., *Disrupted-in-Schizophrenia-1 (DISC-1)*: mutant truncation prevents binding to Nudel-like (NUDEL) and inhibits neurite outgrowth. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 289–294.
- 96 MILLAR, J. K., WILSON-ANNAN, J. C., ANDERSON, S., CHRISTIE, S., TAYLOR, M. S., SEMPLE, C. A., et al., Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Hum. Mol. Genet.* **2000**, *9*, 1415–1423.
- 97 MILLAR, J. K., CHRISTIE, S., ANDERSON, S., LAWSON, D., HSIAO-WEI LOH, D., DEVON, R. S., et al., Genomic structure and localisation within a linkage hotspot of *Disrupted In Schizophrenia 1*, a gene disrupted by a translocation segregating with schizophrenia. *Mol. Psychiatry* **2001**, *6*, 173–178.
- 98 DEVON, R. S., ANDERSON, S., TEAGUE, P. W., BURGESS, P., KIPARI, T. M., SEMPLE, C. A., et al., Identification of polymorphisms within *Disrupted in Schizophrenia 1* and *Disrupted in Schizophrenia 2*, and an investigation of their association with schizophrenia and bipolar affective disorder. *Psychiatr. Genet.* **2001**, *11*, 71–78.
- 99 AUSTIN, C. P., MA, L., KY, B., MORRIS, J. A., SHUGHRUE, P. J., *DISC1 (Disrupted in Schizophrenia-1)* is expressed in limbic regions of the primate brain. *Neuroreport* **2003**, *14*, 951–954.
- 100 MORRIS, J. A., KANDPAL, G., MA, L., AUSTIN, C. P., *DISC1 (Disrupted-In-Schizophrenia 1)* is a centrosome-associated protein that interacts with MAP1A, MIPT3, ATF4/5 and NUDEL: regulation and loss of interaction with mutation. *Hum. Mol. Genet.* **2003**, *12*, 1591–1608.
- 101 AUSTIN, C. P., KY, B., MA, L., MORRIS, J. A., SHUGHRUE, P. J., Expression of *Disrupted-In-Schizophrenia-1*, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. *Neuroscience* **2004**, *124*, 3–10.
- 102 BRANDON, N. J., HANDFORD, E. J., SCHUROV, I., RAIN, J. C., PELLING, M., DURAN-JIMENIZ, B., et al., Disrupted in Schizophrenia 1 and Nudel form a neurodevelopmentally regulated protein complex: implications for schizophrenia and other major neurological disorders. *Mol. Cell Neurosci.* **2004**, *25*, 42–55.
- 103 KOCKELKORN, T. T., ARAI, M., MATSUMOTO, H., FUKUDA, N., YAMADA, K., MINABE, Y., et al., Association study of polymorphisms in the 5' upstream region of human *DISC1* gene with schizophrenia. *Neurosci. Lett.* **2004**, *368*, 41–45.
- 104 STRAUB, R. E., JIANG, Y., MACLEAN, C. J., MA, Y., WEBB, B. T., MYAKISHEV, M. V., et al., Genetic variation in the 6p22.3 gene *DTNBP1*, the human ortholog of the mouse *dysbindin* gene, is associated with schizophrenia. *Am. J. Hum. Genet.* **2002**, *71*, 337–348.
- 105 SCHWAB, S. G., KNAPP, M., MONDABON, S., HALLMAYER, J., BORRMANN-HASSENBAACH, M., ALBUS, M., et al., Support for association of schizophrenia with genetic variation in the 6p22.3 gene, *dysbindin*, in sib-pair families with linkage and in an additional sample of triad families. *Am. J. Hum. Genet.* **2003**, *72*, 185–190.
- 106 MORRIS, D. W., MCGHEE, K. A., SCHWAIGER, S., SCULLY, P., QUINN, J.,

- MEAGHER, D., et al., No evidence for association of the dysbindin gene [*DTNBP1*] with schizophrenia in an Irish population-based study. *Schizophr. Res.* **2003**, *60*, 167–172.
- 107 WILLIAMS, M., Genome-based drug discovery: prioritizing disease-susceptibility/disease-associated genes as novel drug targets for schizophrenia. *Curr. Opin. Investig. Drugs* **2003**, *4*, 31–36.
- 108 SILLITOE, R. V., BENSON, M. A., BLAKE, D. J., HAWKES, R., Abnormal dysbindin expression in cerebellar mossy fiber synapses in the mdx mouse model of Duchenne muscular dystrophy. *J. Neurosci.* **2003**, *23*, 6576–6585.
- 109 MCGUFFIN, P., TANDON, K., CORSICO, A., Linkage and association studies of schizophrenia. *Curr. Psychiatry Rep.* **2003**, *5*, 121–127.
- 110 VAN DEN BOGAERT, A., SCHUMACHER, J., SCHULZE, T. G., OTTE, A. C., OHLRAUN, S., KOVALENKO, S., et al., The *DTNBP1* (*dysbindin*) gene contributes to schizophrenia, depending on family history of the disease. *Am. J. Hum. Genet.* **2003**, *73*, 1438–1443.
- 111 OWEN, M. J., WILLIAMS, N. M., O'DONOVAN, M. C., *Dysbindin-1* and schizophrenia: from genetics to neuropathology. *J. Clin. Invest.* **2004**, *113*, 1255–1257.
- 112 TALBOT, K., EIDEM, W. L., TINSLEY, C. L., BENSON, M. A., THOMPSON, E. W., SMITH, R. J., et al., Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *J. Clin. Invest.* **2004**, *113*, 1353–1363.
- 113 KOHN, Y., DANILOVICH, E., FILON, D., OPPENHEIM, A., KARNI, O., KANYAS, K., et al., Linkage disequilibrium in the *DTNBP1* (*dysbindin*) gene region and on chromosome 1p36 among psychotic patients from a genetic isolate in Israel: findings from identity by descent haplotype sharing analysis. *Am. J. Med. Genet.* **2004**, *128B*, 65–70.
- 114 WEICKERT, C. S., STRAUB, R. E., MCCLINTOCK, B. W., MATSUMOTO, M., HASHIMOTO, R., HYDE, T. M., et al., Human *dysbindin* (*DTNBP1*) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Arch. Gen. Psychiatry* **2004**, *61*, 544–555.
- 115 BENSON, M. A., SILLITOE, R. V., BLAKE, D. J., Schizophrenia genetics: *dysbindin* under the microscope. *Trends Neurosci.* **2004**, *27*, 516–519.
- 116 NUMAKAWA, T., YAGASAKI, Y., ISHIMOTO, T., OKADA, T., SUZUKI, T., IWATA, N., et al., Evidence of novel neuronal functions of *dysbindin*, a susceptibility gene for schizophrenia. *Hum. Mol. Genet.* **2004**, *13*, 2699–2708.

38

Antidepressants and Suicide: Clinical Considerations*Julio Licinio***Abstract**

An association between antidepressant use and suicidality is currently the topic of considerable study, debate, and controversy. This has generated enormous public interest. The United States Food and Drug Administration (FDA) and the United Kingdom Medicines and Healthcare Products Regulatory Agency have placed warnings on the use of antidepressants. In both countries only fluoxetine has been approved for use in children, while other drugs are not shown to be effective and can increase the risk of suicide in that age group. For adults use, the FDA has asked manufacturers to change the labels of 10 drugs to include stronger cautions and warnings about the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening. These drugs are bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine. Moreover, on October 15, 2004, the FDA directed the manufacturers of all antidepressants to add a "black box" warning that describes the increased risk of suicidality in children and adolescents given antidepressant medications and notes what uses the drugs have been approved or not been approved for in these patients. Antidepressants should no longer be associated with the terms "cosmetic psychopharmacology" and "lifestyle drugs". This is a medically necessary treatment that requires expertise and close monitoring. It should be kept in mind however that the greatest cause of suicide is not antidepressant use, but untreated depression. Over 50% of all suicides, including over 70% of suicides in children are caused by depression. At autopsy, less than 20% of suicide cases have measurable antidepressant in postmortem toxicology testing. Because most suicide victims suffer from major depression and commit suicide as a result of untreated or inadequately treated depression, suicide prevention in depression should therefore be addressed with expert treatment.

38.1

Introduction

"I am now the most miserable man living. If what I feel were equally distributed to the whole human family, there would be not one cheerful face on earth. Whether I shall ever be better, I cannot tell. I awfully forebode I shall not. To remain as I am is impossible. I must die or be better it appears to me."

Abraham Lincoln (cited in "Dealing with the depths of depression",
by Liora Nordenberg, FDA Consumer 1998; 32:
http://www.fda.gov/fdac/features/1998/498_dep.html)

According to the article by Nordenberg cited above and published in the *FDA Consumer* magazine, the top medical diagnoses in doctors' visits in 1995 were:

1. Hypertension, 5%
2. Otitis media, 2.4%
3. Routine child health exam, 2.3%
4. Acute upper respiratory infection, 2.1%
5. Diabetes mellitus, 2.0%
6. Routine pregnancy exam, 1.7%
7. Acute pharyngitis, 1.7%
8. Chronic sinusitis, 1.6%
9. Bronchitis, 1.6%
10. Surgery follow-up, 1.3%
11. Depressive disorder, 1.1%
12. Asthma, 1.1%

Depression was then – as now – a very common disorder, included among the top reasons why patients go to the doctor. At that time there was no great concern regarding antidepressant treatment. The newer drugs offered a high therapeutic index, and were seen as effective, and easy to use by general practitioners [1–4], and even by non-medically trained psychologists [5]. Insurance companies greatly reduced compensation for hospital stays related to depression and physicians were encouraged to rapidly discharge hospitalized patients, *before the antidepressant effects of prescribed drugs could be clinically evident*, because the medications were considered effective and safe for unsupervised outpatient use.

How things have changed! As this book is ready to go to press, it has become nearly impossible to read a national newspaper without finding a story on suicide risk in the course of antidepressant treatment. These range from balanced editorials that look at this critical issue from various perspectives (e.g. "Children and antidepressants", Editorial, *The Philadelphia Inquirer*, September 17, 2004: <http://www.philly.com/mld/inquirer/9684215.htm?1c>) to highly personalized articles, such as "How Paxil killed our son" by Susan Edelman (*New York Post* online edition, September 19, 2004: <http://www.nypost.com/news/nationalnews/30505.htm>). A Google® search conducted on September 20 and restricted to the period September

13–20, 2004, shows 866 popular media articles on this topic. While websites may change over time, the titles and dates of some of these articles illustrate how topical this issue is now:

- *Boston Globe*, September 20, 2004. Prescription anxiety by Jerry Avorn. http://www.boston.com/news/globe/editorial_opinion/oped/articles/2004/09/20/prescription_anxiety/
- *The Salt Lake Tribune*, September 19, 2004. Warnings labels urged for kids' antidepressants, suicide risk FDA advisers say: Youths and their parents need more detailed information about the treatment, by Lauran Neergaard (The Associated Press). http://www.sltrib.com/nationworld/ci_2412512
- *San Francisco Chronicle*, September 18, 2004. Mere suggestion of warning label already prompting more caution by Diedra Henderson, AP Science Writer. <http://www.sfgate.com/cgi-bin/article.cgi?f=/news/archive/2004/09/18/national1206EDT0513.DTL&type=health>
- *The New York Times*, September 16, 2004. Doctors say they will cut antidepressant use by Gardiner Harris. <http://www.nytimes.com/2004/09/16/health/16depress.html>
- *Cincinnati Enquirer*, September 16, 2004. Fair warning on antidepressants, editorial. http://www.enquirer.com/editions/2004/09/16/editorial_ed1a.html
- *USA Today*, September 15, 2004. Kids and antidepressants: The mix raises questions. http://www.usatoday.com/news/health/2004-09-15-antidepressants_x.htm
- *Wall Street Journal*, September 15, 2004. Antidepressants urged to have stern warnings: FDA panel recommends forcing drug makers to cite risk of suicidal tendency for youth by Anna Wilde Mathews and Christopher Windham. <http://online.wsj.com/article/0,,SB109519560258917722,00.html>
- *Los Angeles Times*, September 14, 2004. Suicide risk to children affirmed by Elizabeth Shogren. <http://www.latimes.com/news/nationworld/nation/la-na-depress14sep14,1,2785032.story?coll=la-home-headlines>
- *Seattle Times*, September 14, 2004. Antidepressants and suicide linked by Shankar Vedantam (*The Washington Post*). http://seattletimes.nwsourc.com/html/nationworld/2002034845_depress14.html
- ABC News, September 13, 2004. Feds warn on antidepressants and children (The Associated Press). http://abcnews.go.com/wire/Living/ap20040913_671.html
- CNN, September 13, 2004. Experts consider antidepressant warnings. <http://www.cnn.com/2004/HEALTH/09/13/anti.depressants.ap/>

How should the potential association between suicidality and depression be interpreted? Will this lead to a quagmire of litigation? Are antidepressants no longer the golden goose eggs of the pharmaceutical world? Should this affect the search for new drugs to treat depression? Because these findings are so new, there is a paucity of peer-reviewed scientific articles to constitute a foundation for a chapter. It is therefore not possible to construct a text based solely on peer-reviewed

references. It would however be inappropriate for this book to ignore this highly crucial topic. In this context, I am making the unorthodox option of basing this chapter on official and public FDA documents and I am also citing from respected news media. The reader would benefit from following these events by reading the following relevant, official FDA documents, in chronological order.

38.2 FDA Documents

38.2.1 FDA Talk Paper – T04-08

On March 22, 2004, The FDA issued a Talk Paper and a Public Health Advisory.
<http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html>
 FDA Issues Public Health Advisory on Cautions for Use of Antidepressants in Adults and Children

The Food and Drug Administration today issued a Public Health Advisory that provides further cautions to physicians, their patients, and families and caregivers of patients about the need to closely monitor both adults and children with depression, especially at the beginning of treatment, or when the doses are changed with either an increase or decrease in the dose.

FDA has been closely reviewing the results of antidepressant studies in children, since June 2003, after an initial report on studies with paroxetine (Paxil), and subsequent reports on studies of other drugs, appeared to suggest an increased risk of suicidal thoughts and actions in the children given antidepressants. There were no suicides in any of the trials. On close examination of the initial reports, it was unclear whether certain behaviors reported in these studies represented actual suicide attempts, or other self-injurious behavior that was not suicide-related.

FDA has initiated a full review of these reported behaviors by experts in such evaluation. However, it is not yet clear whether antidepressants contribute to the emergence of suicidal thinking and behavior. The agency is advising clinicians, patients, families and caregivers of adults and children that they should closely monitor all patients being placed on therapy with these drugs for worsening depression and suicidal thinking, which can occur during the early period of treatment. The agency is also advising that these patients be observed for certain behaviors that are known to be associated with these drugs, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania, and that physicians be particularly vigilant in patients who may have bipolar disorder.

FDA is asking manufacturers to change the labels of 10 drugs to include stronger cautions and warnings about the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening.

The drugs under review include bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine. It should be noted that the only drug that has received approval for use in children with major depressive disorder is fluoxetine (Prozac). Several of these drugs are approved for the treatment of obsessive-compulsive disorder in pediatric patients, i.e. sertraline (Zoloft), fluoxetine (Prozac), and fluvoxamine (Luvox). Luvox is not approved as an antidepressant in the United States.

These interim actions follow recommendations made by FDA's Psychopharmacologic Drugs and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committees, which met on February 2, 2004. The advisory committee members advised FDA that the labeling should draw more attention to the need to monitor patients being treated with certain antidepressants.

FDA has previously noted (in Public Health Advisory and a Talk Paper T03-70 published October 27, 2003) the possible finding of increased suicidal thinking or behavior, but emphasized that it was not clear that the drugs caused such events and additional analyses were being done to allow FDA to seek more definitive answers.

The Public Health Advisory containing the new label warnings and cautions is available online at <http://www.fda.gov/cder/drug/antidepressants/default.htm>.

Later this summer, FDA plans to update the Advisory Committees on the results of the expert analyses and its own analyses of the pediatric suicidality data.

38.2.2

FDA Public Health Advisory

<http://www.fda.gov/cder/drug/antidepressants/AntidepressantPHA.htm>

Subject: Worsening Depression and Suicidality in Patients Being Treated with Antidepressant Medications

Today the Food and Drug Administration (FDA) asked manufacturers of the following antidepressant drugs to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality. The drugs that are the focus of this new Warning are: Prozac (fluoxetine); Zoloft (sertraline); Paxil (paroxetine); Luvox (fluvoxamine); Celexa (citalopram); Lexapro (escitalopram); Wellbutrin (bupropion); Effexor (venlafaxine); Serzone (nefazodone); and Remeron (mirtazapine).

38.2.2.1 Warning Information

- Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases. Although FDA has not concluded that these drugs cause worsening depression or suicidality, health care providers should be aware that worsening of symptoms could be due to the underlying disease or might be a result of drug therapy.

- Health care providers should carefully evaluate patients in whom depression persistently worsens, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms, to determine what intervention, including discontinuing or modifying the current drug therapy, is indicated.
- Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although FDA has not concluded that these symptoms are a precursor to either worsening of depression or the emergence of suicidal impulses, there is concern that patients who experience one or more of these symptoms may be at increased risk for worsening depression or suicidality. Therefore, therapy should be evaluated, and medications may need to be discontinued, when symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
- If a decision is made to discontinue treatment, certain of these medications should be tapered rather than stopped abruptly (see labeling for individual drug products for details).
- Because antidepressants are believed to have the potential for inducing manic episodes in patients with bipolar disorder, there is a concern about using antidepressants alone in this population. Therefore, patients should be adequately screened to determine if they are at risk for bipolar disorder before initiating antidepressant treatment so that they can be appropriately monitored during treatment. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.
- Health care providers should instruct patients, their families and their caregivers to be alert for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality and worsening depression, and to report such symptoms immediately to their health care provider.

38.2.2.2 Background

Among antidepressants, only Prozac (fluoxetine) is approved for the treatment of pediatric major depressive disorder. Prozac (fluoxetine), Zoloft (sertraline), and Luvox (fluvoxamine) are approved for pediatric obsessive compulsive disorder. None of these drugs is approved as monotherapy for use in treating bipolar depression, either in adults or children.

The requested labeling changes are consistent with recommendations made to the Agency at a meeting of the Psychopharmacological Drugs Advisory Committee (PDAC) and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC), held on February 2, 2004. The possibility of suicidality associated with the use of antidepressant drug products in the pediatric population was also the subject of two previous FDA communications (FDA Talk Paper on June 19, 2003, and FDA Public Health Advisory on October 27, 2003).

FDA is continuing to review available clinical trial data for pediatric patients with depression and other psychiatric disorders to try to determine whether there is evidence that some or all antidepressants increase the risk of suicidality. Later

this summer, the FDA plans to update the PDAC and Peds AC about the results of this review.

FDA plans to work closely with each of the nine manufacturers of the antidepressants that are the subject of today's request to continue investigating how to optimize the safe use of these drugs and implement the proposed labeling changes and other safety communications in a timely manner.

The most recent statements from the FDA on the issue of suicidality occurring in the context of antidepressant treatment have focused on children. On August 20, 2004, an FDA talk paper was released, followed on September 16, 2004 by an FDA Statement.

The text of the FDA Talk Paper is given below.

38.2.3

FDA Talk Paper – T04-31

August 20, 2004

FDA Updates Its Review of Antidepressant Drugs in Children
Agency Details Plans to Present Data to Advisory Committees in September and
Seek Advice on Appropriate Regulatory Actions

As part of its commitment to keep the American public fully informed about the status of its review of data concerning the use of antidepressants in pediatric patients, the Food and Drug Administration (FDA) is issuing this update to provide health care providers and patients with the most current information on this topic.

FDA has completed a new analysis of pediatric suicidality (suicidal thoughts and actions) data submitted to the agency and will be posting its analysis on its web site. FDA will also be posting on its web site additional summaries of pediatric efficacy studies from drugs that have been studied in depression in pediatric patients. Although specific new labeling language has yet to be developed, FDA will assure that the labels of the antidepressants used in pediatric patients reflect the most recent information obtained from these studies and analyses.

Next month, on September 13 and 14, 2004, FDA officials will be discussing this issue at a public meeting of its Psychopharmacologic Drugs and Pediatric Advisory Committees, at which time the agency will hear from the public and solicit the advice of the committees on these labeling changes and other possible regulatory actions.

38.2.3.1 Background

FDA has been closely reviewing the results of antidepressant studies in children since June 2003, after an initial report on studies with paroxetine (Paxil) appeared to suggest an increased risk of suicidal thoughts and actions in the children given Paxil, compared to those given placebo. Later reports on studies of other drugs supported the possibility of an increased risk of suicidal thoughts and actions in children taking these drugs. There were no suicides in any of the trials.

FDA has closely examined the studies of the antidepressants because of the potential public health impact of a link between the drugs and suicidality and the importance of these drugs in treating depression and other serious mental health conditions. On close examination of the initial reports of suicidality, it was unclear whether some of the identified suicidal behaviors reported in these studies represented actual suicide attempts or self-injurious behavior that was not suicide-related. FDA therefore arranged with Columbia University suicidality experts to review these reports.

Meanwhile, FDA brought the available information to its Psychopharmacologic Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committees on February 2, 2004. The advisory committee members advised FDA that even before the Columbia analysis was complete, the labeling should draw more attention to the need to monitor patients closely when antidepressant therapy is initiated. Based on this recommendation, FDA asked manufacturers to change the labels of 10 drugs to include stronger cautions and warnings about the need to monitor patients for worsening of depression and the emergence of suicidality, whether such worsening represents an adverse effect of the drug or failure of the drug to prevent such worsening. The new warning language has now been added to the labels for seven of these products. Sponsors for the other three drugs have agreed to adopt the language.

38.2.3.2 The “Columbia” Study

Because of concerns about whether the varied events identified by sponsors under the broad category of “possibly suicide-related” could all reasonably be considered to represent suicidality, FDA asked Columbia University to assemble an international panel of pediatric suicidality experts to undertake a blinded review of the reported behaviors using a rigorous classification system. The Columbia group submitted its completed review to FDA last month.

FDA has developed its analysis of the pediatric suicidality data, based on case classifications provided by Columbia University, and will be posting the analysis on its web site. While there are findings among these data suggestive of an increased risk of suicidality for some of these drugs, there remain inconsistencies in the results, both across trials for individual drugs and across drugs. Thus, an overall interpretation of these findings represents a substantial challenge.

38.2.3.3 The September FDA Advisory Committee Meeting

FDA's next step, planned for some time, will be to update the Psychopharmacologic Drugs and the Pediatric Advisory Committees about the results of these reviews and to seek assistance from the committees in interpreting the data and in considering what additional regulatory actions may be needed to promote the safe use of these drugs.

As a public health agency, FDA must weigh the possibility of an increased risk of suicidality in young patients taking these drugs against the known risk of suicide in patients whose depression goes untreated.

FDA will be bringing the following issues and draft questions to the committees for their input:

- Please comment on our approach to classification of the possible cases of suicidality (suicidal thinking and/or behaviors) and our analyses of the resulting data from the 23 pediatric trials involving nine antidepressant drugs.
- Do the suicidality data from these trials support the conclusion that any or all of these drugs increase the risk of suicidality in pediatric patients?
- If the answer to the previous question is yes, to which of these nine drugs does this increased risk of suicidality apply? Please discuss, for example, whether the increased risk applies to all antidepressants, only certain classes of antidepressants, or only certain antidepressants.
- If there is a class suicidality risk, or a suicidality risk that is limited to certain drugs in this class, how should this information be reflected in the labeling of each of the products? What, if any, additional regulatory actions should the Agency take?
- Please discuss what additional research is needed to further delineate the risks and benefits of these drugs in pediatric patients with psychiatric illness.

The meeting will be held in Bethesda, Maryland on September 13 and 14, 2004. So that all interested parties will have ample opportunity to review the information to be discussed next month, FDA will be posting information on its website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and <http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1.htm>.

Less than 1 month later, the FDA held the meeting describe above, which resulted in the following recommendations.

38.2.3.4 FDA Statement on Recommendations of the Psychopharmacologic Drugs and Pediatric Advisory Committees

September 16, 2004;

<http://www.fda.gov/bbs/topics/news/2004/NEW01116.html>

The Food and Drug Administration (FDA) generally supports the recommendations that were recently made to the Agency by the Psychopharmacologic Drugs and Pediatric Advisory Committees regarding reports of an increased risk of suicidality (suicidal thoughts and actions) associated with the use of certain antidepressants in pediatric patients. FDA has begun working expeditiously to adopt new labeling to enhance the warnings associated with the use of antidepressants and to bolster the information provided to patients when these drugs are dispensed.

In summary, the members of the advisory committees:

- Endorsed FDA's approach to classifying and analyzing the suicidal events and behaviors observed in controlled clinical trials and expressed their view that the new analyses increased their confidence in the results;

- Concluded that the finding of an increased risk of suicidality in pediatric patients applied to all the drugs studied (Prozac, Zoloft, Remeron, Paxil, Effexor, Celexa, Wellbutrin, Luvox and Serzone) in controlled clinical trials;
- Recommended that any warning related to an increased risk of suicidality in pediatric patients should be applied to all antidepressant drugs, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single medication from an increased risk;
- Reached a split decision (15 – yes; 8 – no) regarding recommending a “black-box” warning related to an increased risk for suicidality in pediatric patients for all antidepressant drugs;
- Endorsed a patient information sheet (“Medication Guide”) for this class of drugs to be provided to the patient or their caregiver with every prescription;
- Recommended that the products not be contraindicated in this country because the Committees thought access to these therapies was important for those who could benefit; and
- Recommended that the results of controlled pediatric trials of depression be included in the labeling for antidepressant drugs.

38.3

Black Box Warning

On October 15, 2004, the FDA issued a Public Health Advisory announcing a multipronged strategy to warn the public about the increased risk of suicidality in children and adolescents treated with antidepressants. The most noteworthy component of that strategy was a directive that manufacturers of all antidepressant medications add a “black box” warning that describes the increased risk of suicidality in children and adolescents taking antidepressants and notes what uses the drugs have been approved or not approved for in these patients. A “black box” warning is the most serious warning placed in the labeling of a prescription medication. Advertisements that serve to remind health care professionals of a product’s availability (so-called “reminder ads”) are not allowed for products with “black box” warnings. Until now, only ten drug products approved for children contained a black box warning about their use in children. The new warning language does not prohibit the use of antidepressants in children and adolescents. Rather, it warns of the risk of suicidality and encourages prescribers to balance this risk with clinical need.

In this Advisory, the FDA re-states that Prozac is currently the only medication approved to treat depression in children and adolescents.

38.4**Comments on FDA Documents**

In a *Wall Street Journal* article (September 16, 2004), Thomas B. Newman, a professor at the University of California, San Francisco, and member of the FDA Advisory Panel described above, was cited as stating “We have very strong evidence of harm, and not very good evidence of efficacy”.

Elizabeth Shogren wrote in *The Los Angeles Times* (September 14, 2004) that concerns about a possible link between the drugs and suicide were raised in the media and by some psychiatrists in 1990. The FDA convened an advisory panel on the topic but no warnings were issued. Anecdotal evidence of such a link continued to accumulate, and in December 2003 the United Kingdom Medicines and Healthcare Products Regulatory Agency effectively prohibited physicians from prescribing a range of antidepressants to children, citing an increased risk of suicide. Dr Andrew Mosholder, an FDA researcher, produced an earlier internal analysis showing a connection between the drugs and suicidal behavior in children, but his superiors prohibited him from presenting his findings at a February FDA advisory committee meeting on the same topic. However, following formal studies that confirmed the Agency’s earlier observations, Dr Tarek Hammad, the FDA’s senior medical reviewer, stated this month that 2 to 3% of the children treated with antidepressants in the most recent study experienced increased suicidal behavior or thought. This has resulted in the FDA statement of September 16, 2004 (*vide supra*).

38.5**Discussion**

The topic of depression treatment in children is covered in this book in the chapter by Cynthia Pfeffer, which went to press prior to the recent controversy and FDA Statement. Briefly, in the United States (and United Kingdom), fluoxetine is the only drug officially approved for the treatment of depression in children, but it has now been shown to be associated with increased suicidality. Consequently, for the use of fluoxetine in children, one could argue that there is a cost–benefit ratio that must be individually assessed by the physician. In other words, for a particular patient does the potential benefit of treatment outweigh the risk caused by potential treatment-induced suicidality? This equation becomes more complicated for all other antidepressants, which have not been approved for pediatric use (but which can be prescribed to children off-label). Is it ethical to prescribe in off-label-fashion drugs which can induce suicidality in the absence of well-documented potential benefit?

The critical issues in this clinically complex situation are as follows:

1. One of the key features of the underlying disease, depression, is suicidality, which is included in the official diagnostic criteria.
2. Symptoms of the underlying disease, including suicidality, wax and wane over time.

3. At the onset of drug therapy, one of the earliest signs of improvement is increased energy and decreased psychomotor retardation.
4. Improvement in symptoms of low self-esteem, guilt, worthlessness, and despair can take several weeks to occur.
5. Increased suicidality may therefore be an inherent element in antidepressant treatment, particularly during the time window, early in treatment, when the drugs increase the level of activity but have not yet reduced negative affect, depression, and despair.
6. In addition to the points cited above, emerging data suggest that antidepressant treatment with specific drugs can enhance suicidality over and above that which is directly related to the underlying disorder, major depression.

Treatment is consequently a matter of careful medical judgment, requiring expertise, close follow-up, and monitoring of patients. While over time in the 1980s, the economic burden of depression seemed to be on the increase [6], in the 1990s the treatment rate of depression increased by over 50%, but its economic burden rose by only 7%. The economic burden of depression remained relatively stable between 1990 and 2000, despite a dramatic increase in the proportion of depression sufferers who received treatment [7]. It could therefore be presumed that such treatment was beneficial and that the benefits of treatment offset the costs of treating 50% more patients by the end of the 1990s than by the beginning of that decade. It is unquestionable that depressed patients treated with antidepressants can and do experience dramatic improvement in their lives. However, antidepressants, once associated with the terms “cosmetic psychopharmacology” [8], and “lifestyle drugs” [9], should be considered medically important drugs that are used to treat a life-threatening disorder [10], which is itself associated with suicidality, and which can cause serious adverse reactions.

What should not be forgotten in the current debate on suicidality during antidepressant treatment is that depression itself is the major cause of suicide. In the United States in 2002, suicide was the 11th most frequent cause of death, being the 5th in the age group 5–14 years, the third in the age group 15–24 years, and the fourth in the age group 25–44 years (see Table 38.1). It has been estimated that 60–70% of acutely depressed patients experience suicidal ideation, and that

Table 38.1 Suicide as cause of death

Age group (years)	Position of “suicide” in the list of most frequent causes of death among the various age groups	Actual number of suicides
All	11	30,646
5–14	5	259
15–24	3	3,932
25–44	4	11,501
45–64	8	9,517

Source [11].

10–15% of depressed patients commit suicide [12]. Depression has been estimated to be present in at least 50% of all suicides in adults [13, 14]; in children that rate has been reported to be 76% [15]. This is directly relevant to the issue of whether antidepressants should be used in children. Treatments that are known to be effective for depression should be seriously considered to treat a disorder that has been associated with such a high rate of suicide.

To address the issue of association between antidepressant treatment and completed suicides, Andersen et al. studied consecutive suicides in the period of April 1, 1991–December 31, 1995 in the Danish county of Funen [16]. There were 390 cases of suicide in which there was complete documentation for prescription data for the year prior to death. Of those, only 17% had more than 10 days of treatment with antidepressants or psychiatric hospitalization during the last 30 days before suicide and 9% had presented a prescription for antipsychotics in the month before suicide. Isaacson et al. conducted toxicological screening in 5281 suicides committed in Sweden in the period 1992–1994 [17]. They detected antidepressants in 12.4% of the men and 26.2% of the women (7.2 and 14.2%, respectively, of those under 30 years of age). They concluded that depression appeared to be under-treated in those individuals committing suicide, especially in men and in subjects under the age of 30 years. In two separate articles, the same group studied the presence of antidepressants in samples from suicide victims in Sweden and in San Diego, California, USA. In Sweden, 7000 cases of unnatural death with results from forensic toxicological screening in the period 1990–1991, including 3400 (85%) of the 4000 cases of suicide, were studied [18]. The presence of antidepressants was detected in 542 subjects or less than 16% of the 3400 cases of suicide. In San Diego, out of a study group of 247 cases in whom it was possible to perform toxicological analyses, only 12% of suicide victims with a diagnosis of major depression were positive for antidepressants [19]. These authors conclude that most depressed patients who commit suicide were not taking antidepressants immediately before death, and that therapeutic failure may be a greater problem with antidepressants than toxicity.

38.6

Conclusions

The current controversy on suicidality associated with antidepressant use has positive aspects such as alerting physicians and patients to the fact that treatment of depression requires considerable specialized clinical expertise and close monitoring. However, it should be kept in mind that most suicide victims suffer from major depression and that in the vast majority of cases their suicide is the result of untreated or inadequately treated depression, and not an adverse reaction to antidepressants. Suicide prevention in depression should therefore be addressed with expert treatment.

Note added in proofs: After this chapter went to press, the author wrote a full review on this topic; see: Licinio, J. & Wong, M.-L.: Antidepressants, depression, and suicidality: A critical appraisal. *Nature Reviews Drug Discovery* 2005 [in press].

Acknowledgements

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References

- 1 LAPID, M. I., RUMMANS, T. A., Evaluation and management of geriatric depression in primary care. *Mayo. Clin. Proc.* **2003**, 78, 1423–1429.
- 2 MACGILLIVRAY, S., ARROLL, B., HATCHER, S., OGSTON, S., REID, I., SULLIVAN, F., et al., Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ* **2003**, 326, 1014.
- 3 MANNING, J. S., Difficult-to-treat depressions: a primary care perspective. *J. Clin. Psychiatry* **2003**, 64 (Suppl. 1), 24–31.
- 4 REMICK, R. A., Diagnosis and management of depression in primary care: a clinical update and review. *CMAJ* **2002**, 167, 1253–1260.
- 5 NORFLEET, M. A., Responding to society's needs: prescription privileges for psychologists. *J. Clin. Psychol.* **2002**, 58, 599–610.
- 6 GREENBERG, P. E., STIGLIN, L. E., FINKELSTEIN, S. N., BERNDT, E. R., The economic burden of depression in 1990. *J. Clin. Psychiatry* **1993**, 54, 405–418.
- 7 GREENBERG, P. E., KESSLER, R. C., BIRNBAUM, H. G., LEONG, S. A., LOWE, S. W., BERGLUND, P. A., et al., The economic burden of depression in the United States: how did it change between 1990 and 2000? *J. Clin. Psychiatry* **2003**, 64, 1465–1475.
- 8 KRAMER, P. D., *Listening to Prozac*. New York: Penguin Books, **1998**.
- 9 ATKINSON, T., Lifestyle drug market booming. *Nature Med.* **2002**, 8, 909.
- 10 LICINIO, J., WONG, M.-L., Depression and obesity treatments are life-saving. *Nature Med.* **2002**, 8, 1336.
- 11 KOCHANNEK, K. D., SMITH, B. L., Deaths: Preliminary data for **2002**. *National Vital Statistics Reports (CDC)* **2004**, 52 (13), 1–48.
- 12 MOLLER, H. J., Suicide, suicidality and suicide prevention in affective disorders. *Acta Psychiatr. Scand. Suppl.* **2003**, (418), 73–80.
- 13 HENRIKSSON, M. M., ARO, H. M., MARITTUNEN, M. J., HEIKKINEN, M. E., ISOMETSA, E. T., KUOPPASALMI, K. I., et al., Mental disorders and comorbidity in suicide. *Am. J. Psychiatry* **1993**, 150, 935–940.
- 14 BALAZS, J., LECRUBIER, Y., CSISZER, N., KOSZTAK, J., BITTER, L., Prevalence and comorbidity of affective disorders in persons making suicide attempts in Hungary: importance of the first depressive episodes and of bipolar II diagnoses. *J. Affect Disord.* **2003**, 76, 113–119.
- 15 SHAFII, M., STELTZ-LENARSKY, J., DERRICK, A. M., BECKNER, C., WHITTINGHILL, J. R., Comorbidity of mental disorders in the post-mortem diagnosis of completed suicide in children and adolescents. *J. Affect Disord.* **1988**, 15, 227–233.
- 16 ANDERSEN, U. A., ANDERSEN, M., ROSHOLM, J. U., GRAM, L. F., Psychopharmacological treatment and psychiatric morbidity in 390 cases with special focus on affective disorders. *Acta Psychiatr. Scand.* **2001**, 104, 458–465.
- 17 ISAACSON, G., HOLMGREN, P., DRUID, H., BERGMAN, U., Psychotropics and suicide prevention. Implications from toxicological screening of 5281 suicides in Sweden 1992–1994. *Br. J. Psychiatry* **1999**, 174, 259–265.
- 18 ISACSSON, G., HOLMGREN, P., WASSERMAN, D., BERGMAN, U., Use of antidepressants among people committing suicide in Sweden. *BMJ* **1994**, 308, 506–509.
- 19 ISAACSON, G., BERGMAN, U., RICH, C. L., Antidepressants, depression and suicide: an analysis of the San Diego study. *J. Affect Disord.* **1994**, 32, 277–286.

39

Depression in Developing Countries*Maurício Silva de Lima and Bernardo Garcia de Oliveira Soares***Abstract**

It is important to evaluate the status of depression in developing countries in order to establish the main factors associated with this highly prevalent disorder. Establishing a target population who are more susceptible to developing depression is a major task for those who have to plan the distribution of resources for the prevention and treatment of highly prevalent and severe diseases, such as depression. Factors important in the modification of the prevalence/incidence of depression in underdeveloped countries are as follows: improvement of general social and health conditions, and attainment of social equality. In this chapter, we review 26 studies (25 cross-sectional studies, and 1 case-control study); we have focused on population-based studies because they provide more reliable estimates of the prevalence/incidence of major depression and its associated factors. These studies assessed a total of 45,967 subjects, and they showed that depression rates range from 3% (in a Brazilian city) to 44.4% (in a Pakistani village) in developing countries. These differences can be partially explained by social conditions and the use of diverse instruments to measure the presence of psychiatric disorders. The main factors associated with depression were found to be female gender, old age, poor education, low income, poor social support and the occurrence of stressful life events.

39.1**Introduction**

In 1990, unipolar major depression was identified as the fourth main cause of burden in the world-ranking of disabling diseases [1]; and it is predicted that by 2020, it will be the number one ranking disease in developing countries and will be the third major burden in developed countries [2].

Numerous clinical trials have documented the efficacy of various interventions, particularly pharmacotherapy, for treating depressive disorders. Despite these data

and major educational and research initiatives to improve both recognition and treatment of depression, this disorder continues to be an elusive and vexing problem in primary care [3]. The scenario in developing countries may be even worse, since the correlation of low socio-economic status, poor access to health care and mental disorders has been established in epidemiological studies [4]. Well-designed research projects conducted in developing countries have provided evidence that depression deserves special attention and must be considered a priority in mental health policy [5]. One study in Zimbabwe established that one-quarter of the people attending primary care clinics suffered from depression, up to 40% were still ill after 12 months, and the incidence of new episodes was 16% [6]. The prevalence of depression and its correlates in adolescents ($n = 463$) was assessed in a cross-sectional study conducted in primary care clinics in a Southern Brazilian community [7] and was found to be 26.5%. A striking discovery from this study was the finding that in 99.2% of cases depression had not previously been identified or diagnosed.

Although depression is an important cause of morbidity and mortality worldwide, it has unique ethnic, socio-cultural, and political characteristics that influence both the prevalence and the related risk/prognosis factors. In this chapter, we discuss findings from major population-based surveys assessing the prevalence and associated/risk factors of depression in developing countries. We highlighted those investigations and initiatives that have adopted more rigorous methods of research.

39.2

Definition of Developing Countries

In this chapter, we adopted the World Bank classification [8] to define “developing” countries. We did not select to use a classification based solely on income because there is evidence showing that income inequality is not a reliable indicator of common mental disorders, including depression [3]. In the World Bank classification, the distribution of developing countries is given for each region as follows:

1. East Asia and Pacific ($n = 24$)
2. Europe and Central Asia ($n = 27$)
3. Latin America and the Caribbean ($n = 30$)
4. Middle East and North Africa ($n = 15$)
5. South Asia ($n = 8$)
6. Sub-Saharan Africa ($n = 48$)

39.3

Population-Based Studies Conducted in Developing Countries

We have only included data on the prevalence, incidence, and associated factors of depression from population-based studies that focused on developing countries. We have not considered studies addressing other mental illnesses.

Box 39.1 Search strategy for identification of relevant studies

```
#1 depress* OR dysth* OR (mood disorder) OR (affective disorder)
#2 (common mental) AND (disorder or illness)
#3 population based OR epidemiol* OR case-control OR cohort OR cross-sectional OR
prevalence OR incidence)
#4 (developing OR poor OR low income OR middle income OR third world OR deprivat*)
AND countr*
#5 (#1 OR #2) AND #3 AND #4
```

We carried out electronic searches of MEDLINE (1966 to 2003) and LILACS (1982 to 2003) databases, no restrictions in terms of language or time of publication were used. LILACS (Latin America and the Caribbean) database indexes regional literature from over 640 journals. It contains around 300,000 citations of literature published since 1982 and abstracts are provided in English, Portuguese, and Spanish. The following search strategy was used for both databases with specific and appropriate modifications (see Box 39.1).

This search strategy included terms such as “common mental disorders” as defined in epidemiological research. Such terms include depression, anxiety and somatoform disorders, conditions which share a considerable number of overlapping diagnostic criteria and are often used in population surveys in developing countries [9]. Additional searches were undertaken by cross-checking the references of studies obtained through the electronic search.

Our focus remained on population-based studies that used a suitable method for selecting participants (such as random selection, so that all subjects had the same chance of being included in the sample). Cross-sectional studies were included to provide prevalence estimates; we considered primarily cohort studies but one case-control study was also included in our efforts to determine incidence rates and risk factors related to depressive illness.

The search strategy resulted in 388 references, most of them from MEDLINE (Figure 39.1).

In these 26 studies, 45,967 participants were evaluated. Table 39.1 summarizes the methods used, participants and main results of these studies. Most of the studies are cross-sectional surveys of random samples obtained from urban populations.

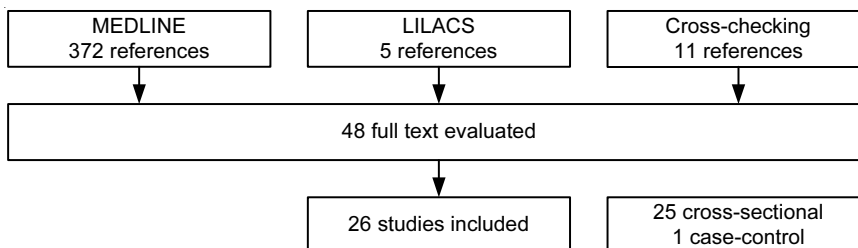
**Figure 39.1** Selection of studies

Table 39.1 Main population-based studies conducted in developing countries

Study	Country/year	Population/methods	Main results
Minor Psychiatric Disorders (MPD) and use of legal drugs in Pelotas, southern Brazil [10]	Brazil/1996	Representative sample of the adult urban population (<i>N</i> = 1277) Instruments: SRQ-20, socio-demographic questionnaire	Prevalence of MPD: 22.3%, higher among the lower social class, elderly, and women
The Brazilian Multicentre Study of Psychiatric Morbidity [11]	Brazil/1997	Representative sample of the adult population living in three urban centres (<i>N</i> = 6476) Instruments: first step, QMPA; second step, sub-sample re-interviewed with the DSM-III checklist	Prevalence of depression ranged from 3 to 10%. Females were more likely to suffer from depression (prevalence ratio: 2.0)
Social class and common mental disorders [12]	Brazil/2001	Representative urban sample of adults in Recife (<i>N</i> = 621) Instruments: first stage, SRQ-20; second stage, Clinical Diagnostic Interview (DSM-III-R criteria)	Prevalence of common mental disorders: males 20.7%, females 45.4%; associated to low educational levels (OR 3.3; <i>p</i> < 0.001) and low income (OR 3.9; <i>p</i> < 0.02).
Gender and minor psychiatric disorders (MPD) [13]	Brazil/1999	Population based case-control study, conducted in three urban centres. <i>N</i> = 266 cases of MPD and 261 controls	Women were more likely to suffer from MPM than men (OR = 3.34; 2.27–4.91). Interaction of gender with age group, suggests an increment in the magnitude of the association among those older than 30 years of age
The Bambuí Study [14]	Brazil/2001	Representative sample of the urban population of Bambuí (<i>N</i> = 1221) Instrument: CIDI	Prevalence of depression: 8.2% (1-month prevalence), 0% (1 year), 15.6% (lifetime) Associated factors: females (OR = 2.4; 95% CI 1.3–4.2), age 45–59 years (OR = 3.5; CI 1.7–7.2), age > 60 years (OR = 4.0; CI 1.9–8.5), unemployment (OR = 2.1; CI 1.2–3.6)
Minor Psychiatric Disorders in Pelotas, southern Brazil [15]	Brazil/2002	Representative sample of the urban population (<i>N</i> = 1967). Instruments: SRQ-20; socio-demographic questionnaire	Prevalence of MPD (28.5%) was higher in the lower social status group and lower income group, aged 40 years or older, and for females with tobacco dependence, non-transmissible chronic disease, and medical consultation

Table 39.1 (continued)

Study	Country/year	Population/methods	Main results
Prevalence of depression and related factors in woman [16]	Chile/1999	Representative sample of adult women of Santiago, aged 15 to 65 years ($N = 1188$) Instruments: ICD-10 Diagnostic Criteria for Research	27% suffered from a depressive disorder (1.9% severe, 12.5% moderate). Related factors: poor education level, conjugal separation, and house keeping
Common Mental disorders in Santiago [17]	Chile/2001	Representative sample of adult population of Santiago ($N = 3870$) Instrument: CIS-R	Prevalence of depressive episode: 5.1% (females 6.9%, males 3.2%)
Chilean Prevalence Study of Psychiatric Disorders [18]	Chile/2002	Representative sample of individuals from four Chilean provinces ($N = 2978$). Instruments: CIDI	Lifetime prevalence of major depressive disorders: 9%; dysthymia: 8% Factors associated with common mental disorders: psych, poor education level, lower social class, increased age, lone parents with children
Psychiatric morbidity in India [19]	India/1979	All families in the rural villages of Gambhirgachi and Paharpur were contacted ($N = 2183$) Instruments: The Household Schedule, The Case Detection Schedule, The Case Record Schedule, and SES	Mental morbidity: 11.7%, depression: 5% Related factors: women, lower age group (29.3%), higher age group (29.5%)
Psychiatric morbidity in India [20]	India/2000	All families of the rural villages Gambhirgachi and Paharpur were contacted ($N = 3488$). Instruments: The Household Schedule, The Case Detection Schedule, The Case Record Schedule, and SES	Mental morbidity 10.5%, depression: 7.4% Related factors: women, lower age group (18%), higher age group (41.7%)
Mental Health and Socio-economic conditions in Sumatera [21]	Indonesia/1992	Representative sample from rural population ($N = 1670$) Instruments: first stage, GHQ; second stage, PSE	GHQ rate: 20%

Table 39.1 (continued)

Study	Country/year	Population/methods	Main results
Anxiety and Depression in Lesotho [22]	Lesotho/1990	Representative sample from a rural population ($N = 356$) Instrument: DIS	Depression: 12.4% (8.8% males, 14.5% females) No association of education with depression or any specific psychiatric diagnosis
Epidemiology of psychiatric disorders in Mexico [23, 24]	Mexico/2002	Representative sample of the adult population of Mexico City ($N = 1932$) Instrument: CIDI	Depression 7.9% (lifetime), 4.5% (12 months); dysthymia 4.4% (lifetime) Associated factor: females
Psychiatric disorders in Hindu Kush [25]	Pakistan/1996	Adult population living in two mountain villages in Chitral, Pakistan, including more than 90% of the total number of households ($N = 558$) Instruments: first phase: BSI; second phase: ICD-10 Diagnostic Criteria for Research.	Depression and/or anxiety disorders: 15% males, 46% females; more prevalent among illiterate subjects, and in families who had experienced bereavement within the previous 12 months
Depression and social stress [26]	Pakistan/2000	Representative sample of the adult population of the village Mandra ($N = 259$). Instruments: first stage, PHQ, SRQ; second stage ($N = 103$): PAS, LEDS	Prevalence of depressive disorder: 44.4% (25.5% males, 57.5% females) Marked independent social difficulty over last 2 years: 83.6% in depressed subjects, 54.2% in controls ($p = 0.001$). Independent factors associated with depression: financial, housing, health, and relationship difficulties
Psychiatric disorders in rural Punjab [27]	Pakistan India/1997	Adult population of the village Susral (97% of the total number of households) $N = 700$ Instruments: first phase: BSI and SRQ; second phase: ICD-10 Diagnostic Criteria for Research	Depression and/or anxiety: 25% males, 66% females; individuals with poor levels of education had a higher prevalence of psychiatric disorders
Psychiatric disorders in Puerto Rico [28]	Puerto Rico/1987	Representative sample of urban population of Puerto Rico ($N = 1513$) Instrument: DIS	Major depressive episode: 4.6% (lifetime); 3.0% (6 months) Dysthymia: 4.7% (lifetime). Associated factors for dysthymia: female gender, urban population

Table 39.1 (continued)

Study	Country/year	Population/methods	Main results
Depression in the elderly [29]	Saudi Arabia/1999	National survey of the elderly population (60 years and over), with two sampling procedures (N = 7970) Instruments: GDS	Depressive symptoms: 39%, severe depressive symptoms: 8.4% Associated factors: poor education, unemployment, divorced or widowed status, old age, female, adverse living conditions, limited privacy, low income, other medical diagnoses, loss of a close relative, living alone, limited participation in recreational activities, perception of poor health and dependence on others for daily activities
Psychiatric morbidity in South Africa [30]	South Africa/1966	Rural population of South Africa (N = 481) Instruments: SRQ, PSE	Prevalence of depression: 27.1% Risk factors: physical ill-health
Minor psychiatric disorders in Africa [31]	South Africa/1998	Random cluster sampling method of the adult population of a province of South Africa (N = 354) Instruments: first stage, SRQ-20; second stage, clinical interviews based on DSM-IV checklists	Prevalence of major depression, 4.8%; dysthymia, 7.3%; and major depression associated with dysthymia, 8.2% Depression was associated with older age (more than 30 years old) Major depression more prevalent among women (16.8 vs. 6.3%) and dysthymia among men (26.1 vs. 13.3%) Depression was associated with: employment (with low salaries), low income, and poor educational achievement
Depression in Korea [32]	South Korea/1998	Nation-wide sample of adult population (N = 3711) Instrument: CES-D	Depression prevalence (severe cases): 6.8% males, 10.4% females Associated factors: women, spousal separation, low income, lower social class, age in 20s
Mental disorders in Khartoum [33]	Sudan/1989	Young subjects (22–35 years old) randomly selected from a suburban area of Khartoum (N = 204) Instruments: SRQ, LES	Depressive illness: 8.4%. Psychiatric morbidity was positively associated with a high score of life events (65.4 vs. 33.8%) and high loneliness score (54.3 vs. 20.5%)

Table 39.1 (continued)

Study	Country/year	Population/methods	Main results
Depression among Taiwanese female homemakers [12]	Taiwan/1995	Random sample of female homemakers from one district of the city Kaohsiung ($N = 85$) Instruments: life events inventory, SSBS, SDS	Prevalence of depression not stated in the paper Age ($p < 0.05$) and social support ($p < 0.01$) were negatively related to depression. Life events were positively related to depression ($p < 0.05$). Education and income were not related to depression
Depression in Uganda [34]	Uganda/1979	Adults in two small Ugandan villages ($N = 206$) Instrument: PSE	Depressive disorders: 14.3% males, 22.6% females
Harare study [35, 36]	Zimbabwe/1997	Random sample of adult women from the city of Harare ($N = 172$) Instruments: first stage, demographic questionnaire, SSMD, LEDS; second stage ($N = 92$), SSI, PSE	Prevalence of depression: 12.2% (last month), 30.8% (last year) Proportion of women becoming depressed in the 6 months following at least one severe event (humiliation, entrapment, death, danger, loss): 26%

QMPA, Adults Psychiatric Morbidity Questionnaire; QMPI, "Cuestionario de Morbilidad Psiquiátrica Infantil"; PERI-D, Psychiatric Epidemiology Research Interview Demoralization Scale; SAMHSA, Substance Abuse and Mental Health Services Administration; CIDI, Composite International Diagnostic Interview; SSBS, Social Support Behavior Scale; SDS, Self-Rating Depression Scale; SSMD, The Shona Screen for Mental Disorders; LEDS, Life Events and Difficulties Schedule; SSI, Shona Symptoms Interview; PSE, Present State Examination; PHQ, Personal Health Questionnaire; SRQ, Self-rating Questionnaire; PAS, Psychiatric Assessment Schedule; LES, Life Events Scale; BSI, Bradford Somatic Inventory; CIS-R, Clinical Interview Schedule-Revised; SES, Socio-Economic Status Schedule, GDS, Geriatric Depression Scale; CES-D, The Center for Epidemiologic Studies Depression Scale; DIS, Diagnostic Interview Schedule.

In general, the prevalence of depression was high (between 10–20%) but notable differences were found. In one of the sites in the Brazilian Multicenter Study, prevalence of depression was 3%. In a representative sample of the adult population of a village in Pakistan, a prevalence of 44.4% was found for depressive disorder. Common factors that were found to be associated with depression are: female gender, old age, poor education and low income, and the occurrence of stressful life events (like divorce).

39.4

Understanding Specific Factors Related to Depression in Developing Countries: A Hierarchical Approach

The prevalence of depression was particularly high in studies conducted in developing countries and there was a wide variation in prevalence rates between different regions. Factors that were most consistently related to the occurrence of depression were female gender, old age, low education, low income, unemployment, and the presence of stressful life events. Variation in prevalence rates may be due not only to the use of different diagnostic assessment tools, but also to the different degrees of social inequalities and specific roles of population subgroups in certain countries. In developing countries, social changes may also contribute to an increase in general psychiatric morbidity and depression in particular.

The main findings of our review are discussed here taking into consideration the hierarchical/conceptual models of disease distribution [37, 38]. Following these concepts, variables linked to the outcome “depression” are distributed in levels

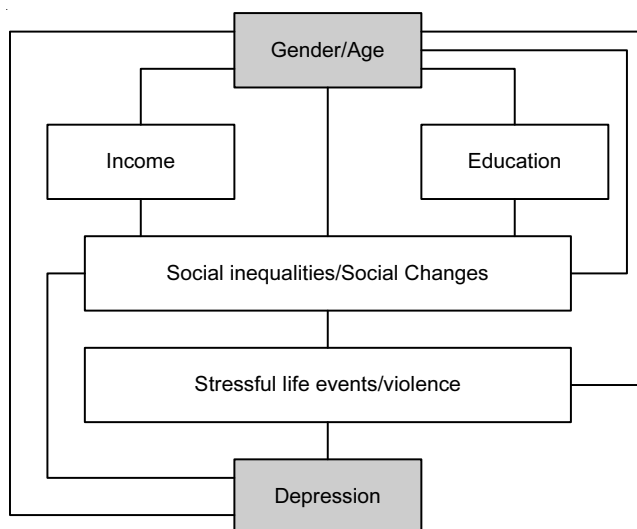


Figure 39.2 A hierarchical model used for understanding the specific factors related to depression in developing countries

according to the strength of their relationship. Gender and age occur at the first level, education and income at the second and social inequality, which is influenced by the above-mentioned variables, is located at the third level, and affects the occurrence of depression either directly or through stressful life events [39]. Although we did not find that lack of social support was among the key factors associated with depression in developing countries, it has been assumed that this plays an important role in the determination of depression.

The adoption of pre-determined hierarchical models is an effective way of analysing epidemiological data considering particular contexts and features of specific populations. The model described above summarizes the models used in surveys conducted in developing countries (see Figure 39.2). The degree of agreement between these models is high, highlighting the importance of social/economic determinants in the distribution of common mental disorders in those countries.

39.4.1

Income

Income has not been consistently described as a risk factor for common mental disorders. In a review and meta-analysis of studies assessing the association between depression and low socio-economic status, Lorant et al. [40] found 51 studies of prevalence, five studies of incidence, and four studies of persistence. Using the method of meta-regression to assess the relevance of covariates, it was found that those with low socio-economic status had a higher chance of becoming depressed (OR 1.81, $p < 0.001$).

In many other investigations, income was not significantly associated with depression. However, there is a strong correlation between income and level of education, which is consistently related to the occurrence of depression (see below). In developing countries, it is possible that those with higher literacy skills may have better access to information and have higher aspirations in terms of progression in society. Therefore, even with a low income, many subjects in developing countries may suffer less from inequalities if they received adequate levels of education.

A review of general population-based studies in developed countries also established that unemployment, poor education levels and low income were significant factors associated with common mental disorders, and occupational social class was the least consistent marker [41].

In the study conducted in Pelotas, Southern Brazil, socio-economic variables and particularly education level, were strongly associated with minor psychiatric disorders. The concept of “focusing” (the proportion of subjects taking psychotropic drugs who have a minor psychiatric disorder (MPD)) and “coverage” (proportion of all those with MPD who were taking psychotropics) were used to analyse the relationship between the use of psychotropics and the presence of MPD. An inverse relationship was observed between level of income and prevalence of MPD, but a positive linear relationship was revealed between income and psychotropic drug consumption [42].

39.4.2

Education

Low socio-economic status is generally associated with high psychiatric morbidity, disability, and poor access to health care. The group with the lowest level of education appears to have poorer coping styles, more stressful life events, and weaker social support, which are all well-known risk factors for psychiatric morbidity. Poor education has been considered as a chronic stressful life event, which can in turn be associated with depression.

In developing countries, welfare support is not available for a high percentage of the population, and access to health care can be difficult or even non-existent. In addition, depression typically presents multiple physical symptoms of chronic duration (Vikram et al., 2001). Patients with low literacy skills may have problems recognising these symptoms as related to depression. Even if they visit a doctor due to the presence of physical symptoms, depression is likely to be unidentified and undiagnosed by general practitioners [43].

39.4.3

Stressful Life Events (SLE)

The role of SLE as a cause of common mental disorders and depression [44–46] has been assessed in a number of studies. There is evidence suggesting that events such as loss of employment, divorce, death of a relative, and having a relative suffering from a chronic disorder are all positively associated to chronic mental disorders (CMD), including depression. The study conducted in Pelotas, however, showed that the relative importance of individual events as determinants of CMD is small (less than 5%), when considering the population-attributable fraction (PAF). The PAF is higher than 50% for education, suggesting that poor educational level can be considered as a chronic stressful event. The reason for SLEs having no major impact on the variation of CMD is probably related to its low prevalence or alternatively, to the high percentage of people with inadequate education levels in the developing countries. Therefore, this factor plays a large role in the development of depression and CMD in general.

39.4.4

Social Changes

According to two studies conducted in the same community in India, the overall rates of mental disorders have not changed in 20 years. However, depression rates have increased from 4.9 to 7.3%. This increase was correlated with the effects of lifestyle changes within that community [23]. This was also observed in China, where increased suicide rates may be explained by the increased prevalence of depressive disorders [47].

39.4.5

Gender

In a paper containing data from five data sets (three based on primary care providers in Goa, India, Harare, Zimbabwe and Santiago, Chile, and two based on community samples in Pelotas and Olinda, Brazil), the role of poverty and female gender as risk factors for depression was assessed. It was found that female gender, along with poor education and poverty, was strongly associated with common mental disorders. Women in developing countries are exposed to a number of stressful and frustrating situations, and it is clear that there is sufficient cause in the current social arrangements among such societies to account for the higher prevalence of depression and other mental disorders among women. The multiple roles played by women, including child-bearing, running the family home, caring for sick relatives, and earning an income are likely to lead to considerable stress [48].

39.4.6

Violence/Insecurity

Violence is an important problem for those living in developing countries. High rates of murder, assault, kidnapping and child abuse are common events in underdeveloped societies. A study conducted in Temuco, Chile [49], showed that psychological aggression was seen among 17.5% of mothers and 6.8% of fathers, and corporal punishment was delivered by 42.3% of mother and 17% of fathers. Of mothers 3% and 1.2% of fathers recognized severe physical abuse. Associated factors included impaired mental health status in mothers, both parents having a previous history of child abuse, parental alcohol abuse and child emotional/behavioral problems.

Similarly, a Peruvian study [50] found that 35.4% of the participants suffered from psychological violence inflicted by their partners, and 17.4% suffered from physical violence. Regarding child violence, 36.2% of parents reported that they had psychologically abused their children.

Other aspects of violence related to poverty, such as crime caused by drug trafficking, may be so common that people consider violent death as part of everyday life events. This has a psychological impact on individuals, contributing to the lack of perspective and increased pessimism, which in turn can act as a trigger for the development of depression.

39.5**Limitations of the Study**

Although we conducted a comprehensive search of epidemiological literature, this review may be affected by publication bias: small studies and studies published in other languages or in non-indexed journals had a lower chance of being included

in this review regardless of our efforts to include all available data. Our conclusions may have lacked specificity regarding depressive disorders, because we decided to also include studies in which common mental disorders were evaluated. However, results from these two types of studies do not differ in terms of factors related to depression.

The variety of diagnostic tools is a limitation for defining a unique prevalence rate. Different diagnostic systems and screening methods were used, which can lead to different results and estimates. It is also true that prevalence rates can vary because of regional factors that determine different degrees of social inequality and social support.

Recall bias is also common in cross-sectional studies, and can affect the events which precede the depressive episode. It is also helpful to consider that countries that are undergoing critical political situations, such as civil war or extreme poverty, have few if any available data, and we would expect that the prevalence of depression may be even higher under those conditions.

39.6 Conclusions

Mental ill health is one of the chronic diseases which appears to be increasing in developing countries [51]. Population-based surveys provide useful estimates of the prevalence of psychiatric disorders, which help in the planning of action regarding this health issue.

Many studies have been conducted in treatment settings, with very specific populations; because these data are difficult to extrapolate to the population as a whole, and because they are not particularly useful for evaluating risk and prognostic factors, they were not considered in this chapter. There is a lack of longitudinal (cohort) studies, which can generate data on the natural history of illness and also data on prognostic factors.

A recent meta-analysis on the impact of socio-economic factors on depression concludes that it is difficult to determine the relevance of social and financial adversities in the origin of depression [40]. Distinct instruments used to diagnose depression and diverse cultural aspects may limit the pooling of data obtained in developing countries in comparison to developed countries, although there is reasonable consistency across studies regarding risk factors. The model proposed in Figure 39.1 aims to explain the complex relationships among a number of variables that play significant roles in the occurrence of depression in developing countries. Such a model seems to be applicable, with local variations, to data obtained in developing countries in general.

Therefore, social factors must be considered as potential targets for intervention in developing countries for the effective prevention, diagnosis and treatment of depression. Elderly people and women seem to be more susceptible to the economic/educational gaps in these countries. The roles/responsibilities of elderly people are inadequately supported by the available resources in these societies.

A problem in the less industrialized world is that depression and anxiety may be difficult to recognize. Symptom presentation is often overwhelmingly somatic and may be associated with physical illness [52].

Considering all the available evidence from epidemiological studies in developing countries, the next step would be to identify cost-effective health interventions for these populations [53]. Quality trials that can inform and guide clinical practice would be the next step towards a better health service in developing countries.

References

- MURRAY, C. J. L., LOPEZ, A. D., Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* **1997**, 349, 1436–1442.
- MURRAY, C. J. L., LOPEZ, A. D., Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* **1997**, 349, 1498–1504.
- CALLAHAN, C. M., HENDRIE, H. C., TIERNEY, W. M., The recognition and treatment of late-life depression: a view from primary care. *Int. J. Psychiatry Med.* **1996**, 26, 155–171.
- ANDRADE, L., CARAVEO-ANDUAGA, J. J., BERGLUND, P., et al., Cross-national comparisons of the prevalences and correlates of mental disorders. *Bull. World Health Organization* **2000**, 78, 413–426.
- PATEL, V., ABAS, M., BROADHEAD, J., TODD, C., REELER, A., Depression in developing countries: lessons from Zimbabwe. *Br. Med. J.* **2001**, 322, 482–484.
- PATEL, V., TODD, C. H., WINSTON, M., GWANZURA, F., SIMMUNYU, E., ACUDA, W., et al., The outcome of common mental disorders in Harari, Zimbabwe. *Br. J. Psychiatry* **1998**, 172, 53–57.
- PALAZZO, L. S., BERIA, J. U., ALONSO-FERNANDEZ, F., TOMASI, E., Depression in adolescence treated at primary care centres: size of a hidden problem of general health. *Atencion Primaria* **2001**, 28, 543–549.
- THE WORLD BANK GROUP. *Data & Statistics – Country Groups*. <http://www.worldbank.org/data/countryclass/classgroups.htm>.
- PATEL, V., KLEINMAN, A., Poverty and common mental disorders in developing countries. *Bull. World Health Organization* **2003**, 81, 609–615.
- LIMA, M. S., HOTOPE, M., MARI, J. J., BERIA, J. U., DE BASTOS, A. B., MANN, A., Psychiatric disorder and the use of benzodiazepines: an example of the inverse care law from Brazil. *Soc. Psychiatry Psychiatr. Epidemiol.* **1999**, 34, 316–322.
- ALMEIDA-FILHO, N., MARI, J. J., COUTINHO, E., FRANCA, J. F., FERNANDES, J., ANDREOLI, S. B., BUSNELLO, E. D., Brazilian multicentre study of psychiatric morbidity. Methodological features and prevalence estimates. *Br. J. Psychiatry* **1997**, 171, 524–529.
- LUDERMIR, A. B., LEWIS, G., Links between social class and common mental disorders in Northeast Brazil. *Soc. Psychiatry Psychiatr. Epidemiol.* **2001**, 36, 101–107.
- COUTINHO, E. D., DE ALMEIDA FILHO, N., MARI, J. J., RODRIGUES, L. C., Gender and minor psychiatric morbidity: results of a case-control study in a developing country. *Int. J. Psychiatry Med.* **1999**, 29, 197–208.
- VORCARO, C. M. R., LIMA-COSTA, M. F. F., BARRETO, M. S., UCHOA, E., Unexpected high prevalence of one-month depression in a small Brazilian community: the Bambuí study. *Acta Psychiatr. Scand.* **2001**, 104, 257–263.
- COSTA, J. S. D., MENEZES, A. M. B., OLINTO, M. T. A., GIGANTE, D. P., MACEDO, S., BRITTO, M. A. P., FUCHS, S. C., Prevalence of minor psychiatric disorders in the City of Pelotas, Brazil. *Revista Brasileira Epidemiol.* **2002**, 5, 164–173.
- ROJAS, G., ARAYA, R., FRITSCH, R., ACUÑA, J., GONZÁLEZ, I., Mujer y depresión en

- Santiago de Chile: resultados preliminares (Depression among women in Santiago, Chile: preliminary results). *Psiquiatria Clin. (Santiago de Chile)* **1999**, 36, 11–17.
- 17 ARAYA, R., ROJAS, G., FRIETICSH, J., et al., Common mental disorders in Santiago, Chile: prevalence and socio-demographic correlates. *Br. J. Psychiatry* **2001**, 178, 228–233.
 - 18 PARADA, B. V., STEVENSON, P. R., SALDIVIA, B. S., KOHN, R., TORRES, P. S., Estudio chileno de prevalencia de patología psiquiátrica: DSM-III-R/CIDI, ECPP (Prevalence of psychiatric disorders in Chile). *Revista Méd. Chile* **2002**, 130, 527–536.
 - 19 NANDI, D. N., BANERJEE, G., BORAL, G. C., GANGULI, H., AJMANY (SACHDEV), S., GHOSH, A., SARKAR, S., Socio-economic status and prevalence of mental disorders in certain rural communities in India. *Acta Psychiatr. Scand.* **1979**, 59, 276–293.
 - 20 NANDI, D., BANERJEE, G., MUKHERJEE, S. P., GHOSH, A., NANDI, P. S., NANDI, S., Psychiatric morbidity of a rural Indian community. Changes over a 20-year interval. *Br. J. Psychiatry* **2000**, 176, 351–356.
 - 21 BAHAR, E., HENDERSON, A. S., MACKINNON, A. J., An epidemiological study of mental health and socioeconomic conditions in Sumatera, Indonesia. *Acta Psychiatr. Scand.* **1992**, 85, 257–263.
 - 22 HOLLIFIELD, M., KATON, W., SPAIN, D., PULE, L., Anxiety and depression in a village in Lesotho, Africa: a comparison with the United States. *Br. J. Psychiatry* **1990**, 156, 343–350.
 - 23 CARAVEO-ANDUAGA, J. J., BERMÚDEZ, E. C., Los trastornos psiquiátricos y el abuso de sustancias en México: panorama epidemiológico. *Salud Mental* **2002**, 25, 9–15.
 - 24 CARAVEO-ANDUAGA, J., COLMENARES, E., SALDIVAR, G., Estudio clínico-epidemiológico de los trastornos depresivos. *Salud Mental* **1999**, 22, 7–17.
 - 25 MUMFORD, D. B., NAZIR, M., JILANI, F. M., BAIG, I. Y., Stress and psychiatric disorder in the Hindu Kush: a community survey of mountain villages in Cintral, Pakistan. *Br. J. Psychiatry* **1996**, 168, 299–307.
 - 26 HUSAIN, N., CREED, F., TOMENSON, B., Depression and social stress in Pakistan. *Psychol. Med.* **2000**, 30, 395–402.
 - 27 MUMFORD, D. B., SAEED, K., AHMAD, I., LATIF, S., MUBBASHAR, M. H., Stress and psychiatric disorder in rural Punjab: a community survey. *Br. J. Psychiatry* **1997**, 170, 473–478.
 - 28 CANINO, G. J., BIRD, H. R., SHROUT, P. E., et al., The prevalence of specific psychiatric disorders in Puerto Rico. *Arch. Gen. Psychiatry* **1987**, 44, 727–735.
 - 29 AL-SHAMMARI, S. A., AL-SUBAIE, A., Prevalence and correlates of depression among Saudi elderly. *Int. J. Geriatr. Psychiatry* **1999**, 14, 739–747.
 - 30 RUMBLE, S., SWARTZ, L., PARRY, C., ZWARENSTEIN, B., Prevalence of psychiatric morbidity in the adult population of a rural South African village. *Psychol. Med.* **1966**, 26, 997–1008.
 - 31 BHAGWANJEE, A., PAREKH, A., PARUK, Z., PETERSEN, I., SUBEDAR, H., Prevalence of minor psychiatric disorders in an adult African rural community in South Africa. *Psychol. Med.* **1998**, 28, 1137–1147.
 - 32 CHO, M. J., NAM, J. J., SUH, G. H., Prevalence of symptoms of depression in a nationwide sample of Korean adults. *Psychiatry Res.* **1998**, 81, 341–352.
 - 33 RAHIM, S. I., CEDERBLAD, M., Epidemiology of mental disorders in young adults of a newly urbanized area in Khartoum, Sudan. *Br. J. Psychiatry* **1989**, 155, 44–47.
 - 34 ORLEY, J., WING, J. K., Psychiatric disorders in two African villages. *Arch. Gen. Psychiatry* **1979**, 36, 513–520.
 - 35 ABAS, M. A., BROADHEAD, J. C., Depression and anxiety among women in an urban setting in Zimbabwe. *Psychol. Med.* **1997**, 27, 59–71.
 - 36 BROADHEAD, J. C., ABAS, M. A., Life events, difficulties and depression among women in an urban setting in Zimbabwe. *Psychol. Med.* **1998**, 28, 29–38.
 - 37 LIMA, M. S., BERIA, J. U., TOMASI, E., CONCEICAO, A. T., MARI, J. J., Stressful life events and minor psychiatric disorders: an estimate of the population-attributable fraction in a Brazilian community-based study. *Int. J. Psychiatry Med.* **1996**, 26, 211–222.
 - 38 PATEL, V., GWANZURA, F., SIMUNYU, E., MANN, A., LLOYD, K., The explanatory

- models and phenomenology of common mental disorder in Harare, Zimbabwe. *Psychol. Med.* **1995**, *25*, 1191–1199.
- 39 LU, L., Life events, social support, and depression among Taiwanese female homemakers. *J. Soc. Psychol.* **1995**, *135*, 185–190.
 - 40 LORANT, V., DELIÈGE, D., EATON, W., ROBERT, A., PHILLIPPOT, P., ANSEASU. Socioeconomic inequalities in depression: a meta-analysis. *Am. J. Epidemiol.* **2003**, *157*, 98–112.
 - 41 FRYERS, T., MELZER, D., JENKINS, R., Social inequalities and the common mental disorders. *Soc. Psychiatry Psychiatr. Epidemiol.* **2003**, *38*, 229–237.
 - 42 LIMA, M. S., HOTOPF, M., MARI, J. J., BÉRIA, J., BASTOS, A. B., MANN, A., Psychiatric disorder and the use of inverse care law from Brazil. *Soc. Psychiatry Psychiatr. Epidemiol.* **1999**, *34*, 316–322.
 - 43 PINI, S., BERARDI, D., RUCCI, P., PICCINELLI, M., NERI, C., TANSELLA, M., FERRARI, G., Identification of psychiatric distress by primary care physicians. *Gen. Hosp. Psychiatry* **1997**, *19*, 411–418.
 - 44 BROWN, G. W., HARRIS, T. O., Aetiology of anxiety and depressive disorders in an inner city population. 1. Early adversity. *Psychol. Med.* **1993**, *23*, 143–154.
 - 45 KENDLER, S. K., KESSLER, R. C., WALTERS, E. E., MACLEAN, C., NEALSE, M. C., HEATH, A. C., EAVES, L. J., Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am. J. Psychiatry* **1995**, *152*, 833–842.
 - 46 PAYKEL, E. S., Contribution of life events to causation of psychiatric illness. *Psychol. Med.* **1978**, *8*, 245–253.
 - 47 PHILLIPS, M. R., LIU, H., ZHANG, Y., Suicide and social change in China. *Culture, Med. Psychiatry* **1999**, *23*, 25–50.
 - 48 PATEL, V., ARAYA, R., LIMA, M. S., LUDERMIR, A., TODD, C., Women, poverty and common mental disorders in four restructuring societies. *Soc. Sci. Med.* **1999**, *49*, 1461–1471.
 - 49 VIZCARRA, L. M. B., CORTÉS, M. J., BUSTO, L., ALARCÓN, M., MUÑOZ, S., Maltrato infantil en la ciudad de Temuco: estudio de prevalencia y factores asociados (Child abuse in Temuco, Chile: prevalence and risk factors). *Rev. Méd. Chile* **2001**, *129*, 1425–1432.
 - 50 ANICAMA, J., VIZCARDO, S., CARRASCO, J., MAYORGA, E., Estudio epidemiológico sobre la violencia y comportamientos asociados en Lima Metropolitana y Callao (Epidemiology study about violence and associated behaviour in Lima and Callao). MINSA 1999 (Ministry of Health).
 - 51 HARPHAM, T., Urbanization and mental health in developing countries: a research role for social scientists, public health professionals and social psychiatrists. *Soc. Sci. Med.* **1994**, *39*, 233–245.
 - 52 ABAS, M., BROADHEAD, J., Mental disorders in the developing countries (editorial). *Br. Med. J.* **2003**, *308*, 1052.
 - 53 PATEL, V., The need for treatment evidence for common mental disorders in developing countries (editorial). *Psychol. Med.* **2000**, *30*, 743–746.

40

Complementary and Alternative Medical Treatment for Depression*Peter B. Bongiorno***Abstract**

As the mainstream medical world is challenged with the dramatic increases in the utilization of complementary and alternative medicine (CAM) therapies, much is unknown regarding how to adequately consider these alternative treatments. There is an emerging body of scientific literature to support the use of the vast array of alternative options. Since these treatments are readily available to the public and CAM professionals, more research to elucidate efficacy and safety is clearly needed. The public has been choosing to use dietary supplements, which has driven the increased utilization of CAM treatments in the past decade. This chapter discusses CAM treatments for major depression, and although the primary focus is on dietary supplements, effective complementary therapies should include treatments which address diet, lifestyle, and psychological factors. It is important to discuss how CAM clinicians ascertain that alternative treatment modalities are appropriate and then ascertain factors/symptoms in depressive illness that are most relevant when choosing from a myriad of treatment options available. It is important to mention that a substantial portion of the public has been utilizing dietary supplements without consulting CAM or non-CAM clinicians.

40.1**Introduction****40.1.1****Definitions**

Familiarity with the following frequently used terms is helpful to understanding this chapter.

Complementary and alternative medicine: The National Center for Alternative and Complementary Medicine (NCCAM) refers to complementary and alternative

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medicine (CAM) as a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine [1]. ‘Complementary’ describes a therapy that is used ‘in addition to’, and ‘alternative’ therapy is one that is used ‘instead of’ conventional therapy. CAM practitioners may be doctors of conventional medicine (see below) or may be doctors of naturopathic medicine (ND), nutritionists, herbalists, Chinese medicine practitioners, chiropractors, energetic healers, and so forth. The NCCAM classifies CAM treatments into seven categories: (1) alternative systems of medical care; (2) bio-electromagnetic therapies; (3) diet, nutrition and lifestyle changes; (4) herbal medicine; (5) manual healing methods; (6) mind–body medicine; and (7) pharmacological and biological therapies. Therefore, CAM therapies may incorporate nutrient therapies, botanical medicines, dietary changes, Ayurvedic medicine, energy healing, hypnosis, acupuncture, spinal manipulation, animal-assisted therapy, physical medicines, and so forth.

Ayurveda: An ancient comprehensive system of medicine that was developed in India over 5000 years ago. It places emphasis on body, mind, and spirit with the goal of restoring the natural harmony of the individual. A patient’s ‘constitution’ can be classified into one of three types (Vata, Pitta, or Kapha); these metabolic body types become the foundation for a specific treatment plan designed to guide the individual back to a state of harmony with his/her environment.

Conventional medicine: Medicine as practiced by holders of medical doctor (MD) or doctor of osteopathy (DO) degrees and by their allied health professionals, such as physical therapists, psychologists, and registered nurses. Other terms for conventional medicine include allopathic, Western, mainstream, orthodox, and regular medicine and biomedicine. Some conventional medical practitioners are also practitioners of CAM [1].

Dietary supplement: A product that is ingested and intended to supplement the diet and, among other requirements, it contains a ‘dietary ingredient’ that was defined by Congress in the Dietary Supplement Health and Education Act (DSHEA) of 1994. The dietary ingredient may include several products, such as vitamins, minerals, herbs or other botanicals, amino acids, and enzymes. Dietary supplements (DS), which can be found in many forms, including tablets, capsules, liquids, and bars, are classified under a special category of ‘foods’; the DSHEA requires that every supplement be labeled as a DS, but these products are not subject to the stringent U.S. Food and Drug Administration (FDA) safety and efficacy testing requirements that are required for drugs. DS are by nature heterogeneous products; therefore, within a particular DS product type, there are many different types of products and many different forms in which the products are made available.

Integrative Medicine: Combination of mainstream medical therapies and CAM therapies [1].

Naturopathic Medicine: Founded upon a holistic philosophy, naturopathic medicine combines safe and effective traditional therapies with the most-current advances in modern medicine. Naturopathic medicine is appropriate for the management of a broad range of health conditions affecting all people of all ages. Naturopathic physicians (ND) are the highest-trained practitioners in the broadest scope of naturopathic medical modalities. In addition to the basic medical sciences and conventional diagnostics, naturopathic education includes therapeutic nutrition, botanical medicine, homeopathy, natural childbirth, classical Chinese medicine, hydrotherapy, naturopathic manipulative therapy, pharmacology, and minor surgery [2].

40.1.2

Complementary and Alternative Medicine Use today

Despite a long history of folk and anecdotal use, CAM modalities have received relatively little attention in the conventional medical world until recently. Modalities such as botanical medicines, lifestyle, nutrition, and acupuncture have silently played a role in the treatment of depressive illness, as they are clearly sought by the public, and the perception has been that their utilization has increased [3, 4].

However, only lately has the medical literature begun to be confronted with the ubiquity with which CAM modalities have been utilized and their possible impact on conventional medical treatments. The Centers for Disease Control (CDC) and Prevention's National Center for Health Statistics recently reported that 62% of adults employed some form of CAM therapy during the past 12 months. Modalities that were most relied on, in order of popularity, included prayer, natural products (nutrient therapies, botanicals), deep breathing, meditation, chiropractic care, yoga, massage, and dietary changes [6]. This corroborates recent data, which finds prayer to be the most popular alternative therapy, as 35% of the population makes use of prayer for their health concerns [5]. CAM was most often used to treat anxiety or depression, back pain or back problems, head or chest colds, neck pain or neck problems, and joint pain or stiffness [6].

Eisenberg's national survey documented that Americans spent \$629 million on CAM treatments in 1997. Out of those surveyed, 42.1% had used some type of alternative treatment. Botanical medicines, massage, vitamins, support and self-help groups, folk remedies, energy healing, and homeopathy were the primary therapies reported with the greatest frequency. Again, depression and anxiety were noted as a primary condition for which those surveyed used CAM applications. Other conditions included back problems, headaches, and chronic medical illness [7]. Thirty-two percent of the men and women surveyed used an alternative therapy to treat a condition for which they were concurrently seeing a physician. Interestingly and importantly, fewer than 40% of these people disclosed to their physician that they were using another type of therapy. This is vital to keep in mind, for in these patients preventable untoward interactions between complementary and conventional therapies may be more likely to occur and progress be unrecognized.

The choice of CAM treatment modality seem to be population-dependent, as age group, specific medical condition, and geographic location may predispose a

particular set of population or CAM practitioners to gravitate toward preferentially employing a particular form of therapy or not to use any at all. Conversely to Eisenberg's work, one study of an elderly population found a decreased incidence of alternative medicine use. Out of 655 elderly living in an urban center, the overall use of at least one alternative medicine was 29.5%; among these, botanical (47%) and acupuncture (34%) were the most frequently cited therapies; 3.7% of the sample used exclusively alternative medicines [8]. The reasons for decreased CAM use in the elderly may include decreased education about these therapies, decreased access, or unwillingness to try unconventional modes of treatment. One study suggests that the use of CAM may be an indicator of the presence of more severe psychological stress among patients [9]; that study revealed that 32% of breast cancer patients used CAM therapy and that a large majority of patients who used spiritual healing had depressive symptoms.

Although there may not be enough information to develop a complete world map of CAM usage at this time, it is clear that the utilization of these therapies varies greatly. For example, a survey of 7485 people in Canberra, Australia, showed that just 2.28% used sole CAM therapies to treat their depression or anxiety, while merely 0.59% used integrated conventional medications with CAM therapies [10].

Literature supporting the use of alternative therapies for mild-to-moderate depression has been coalescing [11]. Favorable reviews regarding the use of CAM is becoming more common as published research finds "the potential for doing good is greater than the potential for doing harm" [12]. Although many of the therapies that are said to benefit depression appear to be safe, it is important to note that serious neuropsychiatric side effects and interactions have been reported [13]. Although many CAM therapies for depression are probably safe and effective for yet-to-be-identified subgroup(s) of depressed individuals, more research is required to understand their mechanisms of actions and to understand whether the placebo effect plays a role in these treatments.

40.1.3

Public Health Impact

Herbal or botanical supplements are taken daily by millions of people, in spite of a paucity of data on their potential mechanisms of action. The DS industry is a multibillion dollar industry that has recently been growing exponentially. The full range of DS products sales has been reported to have reached \$17.1 billion in 2000 [1]. The U.S. FDA published an economic characterization of the DS industry in 1999 [14], and most sources agree that this industry has grown rapidly and will continue to do so in the near future. The estimated retail sales of DS products vary widely, but consumer spending has been reported to have doubled between 1994 and 2000 and continues to grow at more than 10% per year [15]. In addition, the distribution channels have diversified rapidly, as grocery stores, drugstores, and direct selling, mail-order, and online marketers are increasing the range of DS products they carry. Consumer demands have driven larger pharmaceutical companies to enter the market by buying DS firms.

Herbal and botanical supplement sales totaled \$3 billion, for a 28% share of the DS market; their growth rate of 20% from 1995 to 1996 was the highest of all DS products. Since the DSHEA has classified DS as a new category of food, DS have remained largely unregulated, and consequently consumers have been poorly informed about safety and efficacy of alternative treatments. The World Health Organization (WHO) has recognized this problem and has sounded the alarm: in June 23, 2004 it announced new guidelines to promote proper use of alternative medicines (<http://www.who.int/mediacentre/releases/2004/pr44/en/index1.html>) [16]. That WHO Report warned that growing use of alternative medicine poses global health risks and urged governments around the world to intensify oversight of this industry. The NCCAM published a nationwide survey in May 27, 2004, [17] which found that 36% of American adults use some form of alternative medicine or treatment; the number is even higher for other high-income developed countries. In developing nations, up to 80% of the population may rely on traditional or alternative medicine for their primary medical care (WHO).

40.1.4

CAM Research and Practice

In the interest of safety and time efficacy of CAM therapies, emphasis has been placed on the need to hold CAM therapies to the same scientific standards as conventional medicine [18]. It is very important to characterize the possible toxicity of alternative therapies and to evaluate CAM compounds for clinical efficacy; but, as DS are a category of 'food', their clinical efficacy does not need to be proven. The CAM community has been concerned about not losing sight of its own mission, while applying allopathic conventional standards to nonconventional therapeutics, as detailed in the statement below made by Joseph E. Pizzorno, ND, former appointee to the White House Commission on Complementary and Alternative Medicine Policy [19]:

"CAM is about a fundamentally different approach to health and healing that comprehensively addresses promotion of the health of the patient, not simply the temporary relief of the symptoms of disease that characterizes the health-care system today. [We need] to research systems of healing, rather than simply 'green' drugs (for example, substituting a 'natural drug' for a synthetic drug). Comparing the efficacy of St. John's wort to conventional antidepressant medication is of limited value. This is not how CAM is practiced! Worse, it continues the failing medical philosophy of treating the symptom rather than the person, and not addressing the cause(s) of his disease. When I see a patient with depression, I treat that person comprehensively, searching deeply for the fundamental cause of his or her disease. Is there a nutritional deficiency? Has he been exposed to a neurotoxic chemical? Has she disrupted her neurochemical balance by excess sugar consumption? Has he developed inappropriate learned behavior? Correcting these kinds of causes is curative. St. John's wort is not a curative treatment, but rather a symptomatic one –

my last choice, not my first! This is not to dismiss the fact that St. John's wort is a very useful natural therapy in the care of the depressed patient. But this herb by itself does not fully utilize the power of integrative medicine.”

The majority of scientific information available to this field has emerged from conventional medical research that has not utilized a systems-integrated approach toward healing. It is relevant to point out that CAM professionals working with depressed patients try to adopt a multidimensional approach aimed at the perceived main ‘causative’ factors of this condition and not just at symptom relief; thus, they try to deliver what they believe to be the most complete therapy that will have lasting clinical results. This chapter discusses CAM treatment approaches and focuses on DS treatments.

40.2

Treatment Approach

It is paramount to keep in mind the point of view of an integrative health practitioner, who seeks possible ‘causative’ factors of depression for each individual, which are thought to be unique and multifactorial. This integrative thinking recognizes that the alleged ‘causes’ of depression for one individual may be different than those for another patient. The CAM practitioner takes a careful history of the condition in a process that is parallel to the approach taken in conventional medicine. Several medical conditions may be associated with the presentation of major depressive symptoms, which they have been addressed in Chapter 4. The CAM practitioner also recognizes that stabilization of chronic or acute conditions is also helpful to the improvement of depressive symptoms. It is important to note that CAM practitioners will treat only mild-to-moderate cases of depression and refer severe cases and cases with a perceived organic cause to conventional medicine clinicians. CAM professionals pay special attention to lifestyle factors (see Section 40.4), largely based on common sense; some of these factors have not been fully scrutinized in the medical literature.

40.2.1

When CAM Therapies Are Not Appropriate as a First Line of Treatment

In the interests of safety and practicality, pharmaceutical medications should be considered as the first line therapy in any instance in which:

- There is immediate concern of harm to self or harm to others (suicidal ideation, planning, history of harming self and others, threats to do so, and so forth).
- The patient is not able to function in a capacity necessary to perform basic functions such as work to feed or house self or family and/or to take care of another person who relies on the patient for survival in a situation in which no other option exists.

Once the patient has been stabilized with respect to the above conditions, CAM therapies that address lifestyle, psychological/spiritual, as well as nutrient and supplemental therapies may be considered for a longer-term treatment. Preferably, team management by the patient's pharmaceutical prescribing doctor, psychologist, and CAM practitioner(s) will afford the best overall care and enable the comanagement needed to consider discontinuation of medications. This possibility will be more appropriately realized once other lifestyle, psychological, physiological, and nutritional factors are successfully addressed.

Two possible exceptions to the above conditions would be pregnant and breastfeeding women. Incidences of withdrawal effects in newborns have recently prompted the Food and Drug Administration to caution women about the use of antidepressants during the third trimester of pregnancy. Nortriptyline, paroxetine, and sertraline may be preferred choices in breastfeeding women [20]. But overall, since there is a striking lack of clinical evidence about the safety of psychotropic medications during breastfeeding [21], it is advisable to carefully consider the pros and cons of using antidepressants for the duration of breastfeeding. Of course, untreated depression in pregnant and breastfeeding patients can also pose great risk for both the mother and child; therefore, a careful case-by-case evaluation of the pharmaceuticals chosen as well as the specific circumstances of depression is required.

40.2.2

When CAM Therapies Can Be Considered as a First Line of Treatment

A team approach involving a doctor experienced and licensed to prescribe pharmaceutical interventions, a psychologist/therapist, and a CAM practitioner well versed in the use of natural and alternative modalities all working together would combine the best of all worlds regarding optimal patient care. Once a decision is made that the patient does not meet the criteria outlined above that necessitate first-line pharmaceutical intervention, the CAM practitioner should feel comfortable trying alternative and holistically minded modalities, while remaining vigilant to changes in the patient's condition that could lead to him or her meeting the above criteria at a later time.

It is clear that clinical studies conducted primarily in hospital settings have demonstrated efficacy for patients with moderate-to-severe major depression. However, the vast majority of patients treated for depression occur in general-practice settings, where most of these patients do not meet the diagnostic criteria for major depression [22]. From a naturopathic perspective, this is the situation in which CAM practitioners could probably do the most good by intervening with more holistic options, while keeping in mind that antidepressants may be implemented as a final resort if needed.

40.3

CAM Therapies

The list of all available CAM therapy is long and beyond the scope of this chapter. While focusing on treatment alternatives with DS, I try to provide an objective summary of the research available regarding various alternative therapies and attempt to compare them with conventional therapies.

40.3.1

Botanical Medicines

Known as herbs in the mainstream community, the recognition of botanical medicines has grown considerably in the last decade. Eisenberg found that use of herbal medicine rose from 3% to 12% from 1990 to 1997 [7]. Although there are a plethora of botanicals that are used to modify central nervous system function, those listed below represent the ones most studied in the medical literature.

40.3.1.1 *Hypericum perforatum* (St. John's Wort)

As one of the best-studied botanicals of all time, St. John's wort (SJW) is notable for its ability to treat mild-to-moderate depression [23, 24] and is also known to be safe and effective for children [25]. As a result, SJW has become very popular in the U.S., where it is available over the counter. In Germany, physicians prescribe SJW to patients with mild-to-moderate depression [26].

The possible action of SJW stems in part from its hypericin and hypericin-like constituents, which may act on acetylcholinesterase by decreasing the degradation rate of acetylcholine [27]. Sedative actions come from the hypericins, biflavones, and hyperforin. Other reports demonstrate a serotonergic activity [28], by which it can act as a weak serotonin-reuptake inhibitor (SSRI) that leads to fewer side effects [29]. In addition, sigma 1 receptors, which are affected by antidepressant medications in animal studies, may also be affected by SJW [30]. Most likely, the demonstrated efficacy of this botanical in treating depression is through its synergistic effects, orchestrated by the multitude of components in the whole herb working both within and peripheral to the central nervous system.

A meta-analysis of 23 randomized trials which included 1757 outpatients with mainly mild or moderately severe depressive symptoms found that *Hypericum* extracts were significantly superior to placebo and similarly effective as standard antidepressants. Side effects occurred in 19.8% patients on *Hypericum* and 52.8% patients on standard antidepressants [23], and data analysis revealed a dropout rate of 0.8% for SJW and 3.0% for standard antidepressant drugs due to side effects.

Two well publicized clinical studies have suggested that SJW is ineffective in treating depression [31]. One 8-week trial employed suboptimal doses of SJW, using 900 mg d⁻¹ for patients with severe depression. If there was no response, doses were increased to 1200 mg d⁻¹. (In a previous study of severe depression, patients improved significantly on SJW, compared to placebo and the antidepressant drug imipramine, on a dose of 1800 mg d⁻¹ [32, 33].) It is worth mentioning the role of

a possible conflict of interest in that study, given that that trial was funded by a drug company that manufactures antidepressant medications. In light of a previous history of effective SJW trials, it is dubious whether those results accurately reflect the clinical ability of this botanical.

A second 8-week study made a similar suboptimal dosing error and consequently deemed St. John's wort to be ineffective. A valuable note in this study is that the comparison drug sertraline, a drug with a much stronger side-effect profile than *Hypericum*, was not any more effective than SJW or the placebo, which leads to concerns about the overall design of the study [34].

The action of SJW has been well characterized in direct comparisons with leading antidepressant medications [35–37]. In a randomized controlled double-blind trial, 70 patients suffering from mild-to-moderate depression received one tablet of either SJW extract or fluoxetine twice a day for 6 weeks. Patients were rated by the 17-item Hamilton Rating Scale for Depression (HAM-D) and the von Zerssen depression scale (ZDS). HAM-D scores significantly decreased ($p < 0.001$) in the SJW group (50%) and in the fluoxetine group (58%), and ZDS also decreased in both treatments (42% and 52%, respectively). Assessments by physicians and patients indicated considerable improvement with no between-treatment differences [35]. The conclusion of that study is that SJW was therapeutically equivalent to fluoxetine and is therefore a reasonable alternative to synthetic antidepressants. *Hypericum* extract has similarly been tested and showed an efficacy similar to that of sertraline in the treatment of mild-to-moderate depression in a small group of outpatients [36]. Efficacy and tolerability of SJW was also compared with imipramine and was equivalent to that of the drug in treating mild-to-moderate depression. In addition, patients tolerated SJW better than imipramine [37].

In a review of over 3000 depressed patients spanning 34 double-blind trials, the effective dosage level of SJW for mild-to-moderate depression was between 500 and 1000 mg of standardized alcohol extract per day [38]. For patients with preexisting conductive heart dysfunction or elderly patients, high-dose *Hypericum* extract has found to be safer with respect to cardiac function than tricyclic antidepressants [39].

The side-effect profile of SJW extract is minor, especially when compared to the well known side effects of antidepressant medications [40]. Due to its lack of monoamine oxidase (MAO) inhibition, SJW is not considered to interact negatively with MAO-inhibiting drugs or tyramine-containing foods. However, it has been shown important SJW–drug interactions may occur. SJW can reduce the circulating levels of certain drugs [41–44] (Table 40.1). Synergistic therapeutic effects may also lead to complications and unfavorable treatment outcome. SJW is a potent inducer of cytochrome p450 (CYP) enzymes, particularly CYP 3A4 and/or P-glycoprotein, and it may also inhibit or induce other CYPs [45].

Although SJW induces photosensitivity in some patients, this not likely to happen with standard dosages; it has occurred mainly in HIV patients using larger than normal quantities for an antiviral effect [46]. SJW is not recommended for use during pregnancy, because its safety in pregnancy has not been studied. A study of 33 mothers who used SJW while nursing found no significant difference in the

Table 40.1 Saint John's wort (SJW)–drug interactions

1. SJW decreases the blood concentrations of the following agents:	
Anticancer drugs:	irinotecan and its active metabolite SN-38
Anticoagulants:	phenprocoumon and warfarin
Antidepressants:	amitriptyline
Anti-HIV agents:	protease inhibitor indinavir reverse transcriptase inhibitor nevirapine
Antihistamines:	fexofenadine
Bronchodilators:	theophylline
Cardiovascular drugs:	digoxin and simvastatin
Immune suppressants:	cyclosporine and tacrolimus
Opiates:	methadone
Sedatives:	midazolam
2. SJW may cause:	
Serotonin syndrome when coadministered with selective serotonin-reuptake inhibitors (e.g., sertraline, paroxetine)	
Breaththrough bleeding and unplanned pregnancies when used concomitantly with oral contraceptives	
Hypoglycemia when used concomitantly with tolbutamide	
3. SJW does not alter the pharmacokinetics of:	
Anticonvulsants:	carbamazepine
Cardiovascular drugs:	pravastatin
Cough medication:	dextromethorphan
Immunosuppressants:	mycophenolic acid

frequency of maternal report of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life [47].

The most commonly recommended dose of SJW is 300 mg of standardized extract, three times daily, for mild-to-moderate depression [38]. A number of CAM practitioners use the upper therapeutic range, which approaches 1800 mg d⁻¹, for moderate-to-severe illness. Of course, when the CAM practitioner is considering *Hypericum* therapy, he or she should always consider lifestyle, nutrient, and other factors described later in this chapter to work on simultaneously so as to achieve the best results. Symptoms indicating excessive levels of serotonin should also be considered and monitored when using SJW with SSRIs, tryptophan, or 5-HTP.

40.3.1.2 Ginkgo biloba (Ginkgo)

Although SJW is a clear favorite botanical treatment option for depression, ginkgo is known for its antioxidants/free radical scavenging effects, neuroprotective/antiplatelet aggregating actions, beneficial effects against ischemia/reperfusion injury, hypoxia, cerebrovascular and cardiovascular diseases, cognitive deficit and dementia and has been found to normalize stress-elevated alterations in levels of brain catecholamines, serotonin, and plasma corticosterone [48].

Given its reputation for neuroprotective and cerebrovascular effects, ginkgo may be most useful for depressive symptoms associated with and/or resulting from

vascular events. This type of mood disorder, due to a general medical condition, occurs principally the elderly and is caused by acute or chronic damage to the cerebral vascular system.

Although SJW may be best for those under 50 years of age, CAM practitioners may want to work with ginkgo first as a means to treat older patients with a clinical presentation suggestive of major depressive-like episode secondary to cerebrovascular disease. *Ginkgo biloba* extract may be used at a dosage of 80 mg three times a day (24% ginkgo flavonglycosides) [102].

Ginkgo biloba leaf extract is quite low in toxicity – a review of 44 double-blind trials having nearly 10 000 participants showed only mild discomfort of the gastrointestinal tract, headache, or dizziness in a total of 34 cases. In contrast, ginkgo fruit pulp exposure should be avoided, because it can cause severe allergic reaction and gastrointestinal irritation [102].

40.3.1.3 *Lavendula angustifolium* (lavender)

Lavender is used principally as an aromatic essential oil for relaxation. In a single-blind randomized control trial, 80 women who took daily baths with lavender oil experienced improved mood, reduced aggression, and a more positive outlook [49]. Furthermore, the combination of lavender (60 drops d⁻¹ of a lavandula tincture) and imipramine (100 mg d⁻¹) was found to be more effective in the treatment of depression than either treatment alone, according to a double-blind randomized control trial. The findings of this study suggested that taking a moderate amount of lavender may help reduce the amount of tricyclic antidepressants needed to treat depression, leading to fewer side effects [50].

40.3.2

Supplemental Therapies

Both botanical and other alternative therapies are listed in Table 40.2.

40.3.2.1 Chromium

It has been observed that poor glycemic control is correlated with moderate-to-severe depression [51]. Chromium is an essential trace element that is known as a component of the body's glucose tolerance factor and may be a useful means to balance insulin levels. Chromium's mode of operation may also be by alteration of brain serotonin levels [52], as well by increasing insulin sensitivity [53].

A placebo-controlled double-blind pilot study of chromium piccolinate was conducted in 15 patients with atypical types of major depressive disorder, a type of depression that constitutes more than one-fifth of all cases of depression. Ten patients started with a dose of 400 µg, which was increased to 600 µg. The other five patients took a placebo. Seventy percent of the patients on chromium responded positively to the treatment. This study had some unusual results, as none of the placebo patients showed improvement. Other outcomes were consistent with greater effect of chromium. Three patients on chromium failed to show any improvement. Chromium piccolinate was well tolerated, with no attrition due to side effects [54].

Table 40.2 Brief review of natural supplements for depression

Botanical	Dosage	Possible Mechanism	Side Effects and Contraindications
<i>Hypericum perforatum</i> (St. John's wort)	300–600 mg of the extract TID	Reduces the degradation rate of acetylcholine, sedative actions, weak serotonergic activity, sigma 1 receptor blockade	Minor side effect profile, but interactions can change the bioavailability of many drugs (Table 40.1); photosensitivity at very high doses
<i>Ginkgo biloba</i>	80 mg TID	Antioxidant, cerebrovascular protection, etc.	Rare mild gastrointestinal complaints from the extract; fruit is toxic
Supplement	Dosage	Possible Mechanism	Side Effects and Contraindications
Chromium	200 µg qd	Glucose balance, serotonin modulation	None known at therapeutic dosages
Fish oil (omega-3 fatty acids)	1 tablespoon of fish oil qd, or 2 g DHA qd	Platelet clotting ability, inhibits sympathoadrenal activation and normalizes membranes	Side effects of mild reflux and gastrointestinal disturbances; consider TT, PTT, and INR monitoring for patients on anticlotting medications.
Folic Acid	0.5–1.0 mg qd	Lowers homocysteine	Contraindicated with methotrexate for cancer treatment or antiseizure medications
Inositol	4–12 g qd	Serotonin and acetylcholinergic modulation	None known at therapeutic dosages
Melatonin	0.5–5 mg hs	Circadian rhythm restoration and antioxidant	Side effects of some waking drowsiness; contraindicated in nocturnal asthmatics
SAME	See dosing schedule in Section 3.2.6	Methylation; may help lower homocysteine levels	Nausea, mild gastrointestinal disturbances, agitation
Selenium	200 µg qd	Antioxidant, helps convert T4 to T3, enhances immunity	Can cause brittle nails in high doses

Table 40.2 (continued)

Botanical	Dosage	Possible Mechanism	Side Effects and Contraindications
L-tryptophan	0.5–1.0 g qd	Serotonin precursor	Side effect of possible serotonin syndrome when used with other SSRIs or St. John's Wort
5-HTP	100–200 mg TID	Serotonin precursor	Possible serotonin syndrome when used with other SSRIs or St. John's wort
Vitamin E	400 IU qd	Antioxidant	None known at therapeutic dose
Zinc	25 mg qd	Neurologic and immune modulator	Long-term supplementation may deplete copper

With no known side effects at the standard dosage of 200 $\mu\text{g d}^{-1}$, chromium could be used as a reasonable treatment choice for depressed patients, especially for those exhibiting blood sugar dysregulation.

40.3.2.2 Fish Oils and Fatty Acids

Two types of omega-3 fatty acids are eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). These are found in seafood, especially in wild salmon, striped bass, mackerel, rainbow trout, halibut, and sardines. There is ample evidence that shows correlations between low seafood consumption and higher rates of depressive illness. For instance, lower DHA content in mother's milk and lower seafood consumption were associated with higher rates of postpartum depression [55]. Conversely, geographic areas where consumption of DHA is high are associated with decreased rates of depression. Individuals with major depression have marked depletions in omega-3 fatty acids (especially DHA) in erythrocyte phospholipids compared with controls. These data suggest that DHA may be associated with depression, and the limited data available on supplementation with DHA or other omega-3 fatty acids seem to support the hypothesis that DHA may have psychotropic effects [56].

Possible mechanisms of action include the ability of omega-3 fatty acids to positively affect the cardiovascular system and adrenal function and to normalize membranes of brain tissues. Omega-3 fats reduce the clotting ability of platelets and so can potentially decrease the incidence of heart attacks and strokes. It thus seems reasonable that the relationship between depressive disorders and cardiovascular disease could be intertwined with omega-3 fatty acid deficiency and elevated homocysteine levels [57]. Omega-3 fatty acids acts mechanistically on the central nervous system by inhibiting sympathoadrenal activation elicited by mental stress [58]. Finally, one hypothesis is that omega-3 fatty acids can normalize the altered membrane microstructure and neurotransmission in patients with depression [59].

These altered structures are thought to be a contributing factor in depressive pathogenesis.

A number of studies support the use of fish oil for depression as well as for bipolar disorder [60]. Furthermore, there is evidence that fish oil may benefit people who fail to respond to standard medications. A study of 70 patients with persistent depression despite ongoing treatment with an adequate dose of a standard antidepressant were found to benefit from 1 g d⁻¹ of ethyl-eicosapentaenoate. Strong beneficial effects were indicated by using the HAMD, Montgomery–Asberg Depression Rating Scale, and Beck Depression Inventory to monitor depression, anxiety, sleep, lassitude, libido, and suicidality [61].

In other studies, the benefit was not as clear. In one study, employing DHA for postpartum depression, supplementation of approximately 200 mg d⁻¹ for 4 months after delivery prevented the usual decline in plasma phospholipid docosahexaenoic acid content in women who breastfeed. However promising this may be, this supplementation did not influence self ratings of depression or diagnostic measures of depression or information processing [62]. A second randomized control trial involved 36 depressed patients who were randomly assigned to receive 2 g d⁻¹ DHA or placebo for 6 weeks. In this work, response rates were 27.8% in the DHA group and 23.5% in the placebo group, numbers that did not achieve statistical significance [63].

Some studies have also evaluated the use of a fatty acid supplement in addition to a conventional antidepressant regimen. One randomized controlled double-blind trial of 22 patients with major depressive disorder found significant benefits from the addition of omega-3 fatty acid compared with placebo. These benefits were apparent by the third week of treatment [64].

Although fish oil is quite safe [65], some people taking fish oil dietary supplements may experience nausea, loose stools, and ‘fishy’ breath from high doses. Because of a possible concern of excess antiplatelet activity when used in combination with anticoagulating drugs, it seems to be best to monitor thrombin time, prothrombin time, and INR closely if the patient is on an anticoagulating medication. Also of note, CAM practitioners should prescribe only high-quality pharmaceutical-grade fish oils, because the lower-quality versions may have an increased liability to rancidity and may contain higher amounts of toxins and impurities.

40.3.2.3 Folate

Although its effects in depression are not fully elucidated, folate may modulate serotonergic or catecholaminergic functions [67] and may decrease plasma homocysteine levels [66]. Observed deficiencies in these have been correlated with depressive symptoms in bulimia nervosa [67]. The relationships among levels of folate, vitamin B12, and homocysteine and response to fluoxetine (20 mg d⁻¹ for 8 weeks) treatment have been examined in 213 outpatients with major depressive disorder [68]. Subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine. There might be a correlation between low folate levels and poorer response to antidepressant treatment; thus, folate levels may be considered in the evaluation of depressed

patients who do not respond to antidepressant treatment. Daily use of folic acid (500 µg) can greatly improve the therapeutic effects of fluoxetine, probably by decreasing levels of homocysteine [69]. It seems that higher levels of folic acid were required in men to optimally decrease folic acid levels.

The chemotherapeutic drug methotrexate interferes with folate metabolism and leads to toxicity; thus, folate supplementation may reduce methotrexate's efficacy during cancer treatment [70]. However, supplementation with folate (1 mg d⁻¹) has been found to have hepatoprotective effects in patients using methotrexate to treat rheumatoid arthritis (RA). These patients required slightly higher doses of the drug but had lower liver enzymes [71]. Folate has also been reported to reduce the effectiveness of several anticonvulsants, potentially leading to seizures [70].

In summary, it is useful to check folate levels in depressed patients. Given the safety profile of folate, a therapeutic trial using physiologic doses may be an option for the CAM practitioner.

40.3.2.4 Inositol hexaphosphate (IP6)

An abundant component of plant seeds, inositol is an isomer of glucose that is a precursor in the phosphatidylinositol cycle and a source of two second messengers: diacylglycerol and inositol triphosphate, which may be used for cancer treatment [72]. Animal studies have reported that inositol is effective in relieving symptoms of depression [73]. The antidepressant effect of inositol may involve serotonin receptors and acetylcholine mechanisms [74]. Thus, it is possible that the effects of reuptake antidepressant drugs and the effects of inositol may have a common pathway [75]. Inositol (12 g) was found to be more effective than placebo at week 4 in a double-blind study of 29 patients [76], but other studies have shown little or no benefit. A recent study by Taylor et al. failed to report clear therapeutic benefits in four short-term trials of double-blind design that included a total of 141 patients. These trials showed that patients had good tolerability to inositol [77]. Sodium-IP6 given to 35 patients at a dose of 8.8 g d⁻¹ in divided doses for several months resulted in no apparent toxicity [78].

40.3.2.5 Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine), the main secretory product of the pineal gland in the brain, is known to have powerful antioxidant effects and is typically used to coordinate circadian rhythms in people with insomnia and jet lag. It has also been utilized in the treatment of cancer. Low melatonin levels have been observed in bulimia, neuralgia, and in women with fibromyalgia. The time of the nocturnal melatonin peak secretion was significantly delayed in depressive subjects compared to healthy controls [79], although both groups showed no significant difference in the mean level of melatonin. Interestingly, in patients with major depression, positive response to antidepressants correlated with an increase in their melatonin profiles, but only patients suffering from delayed sleep phase syndrome were successfully treated with melatonin [80].

A reasonable dose of melatonin may be 0.5–5 mg, 20 min before bed. Typical dosages for cancer treatment are often in the 20 mg range [81]. Although side effects

are rare, melatonin should be given at a time of day consistent with the sleep-wake cycle (20 min before bedtime). A potential concern in the use of melatonin is that elevated melatonin levels have been associated with exacerbations of nocturnal asthma [82].

40.3.2.6 S-Adenyosyl-L-methionine (SAmE)

SAmE is a naturally occurring molecule derived from L-methionine, which acts as a methyl donor and is involved in the synthesis of various neurotransmitters in the brain [83]. This molecule has been found to be safe and effective in the treatment of mild and moderate depression [83, 84]. In a meta-analysis of 47 studies of people with mild-to-moderate depression, SAmE produced a significant improvement in the HAMD score. SAmE treatment was significantly better than placebo and worked as well as conventional drug therapy [85].

One uncontrolled trial administered SAmE in doses of 800 to 3600 mg d⁻¹ for a period of 10 weeks in 13 depressed patients with Parkinson's disease; 11 patients completed the study, and 10 had at least a 50% improvement in HAMD. Only one patient did not improve, two patients terminated participation in the study prematurely because of increased anxiety, one patient experienced mild nausea, and another two patients developed mild diarrhea, which resolved spontaneously.

Because oral SAmE may cause nausea, a incremental regimen has been suggested, with a starting dose of 200 mg twice daily for the first day, which is increased to 400 mg twice daily on day 3, then to 400 mg three times daily on day 10, and finally to the full dose of 400 mg four times daily [102]. Little research has been done using SAmE to treat severe depression, so it is unknown whether SAmE would have the same benefits as seen in mild-to-moderate depression.

40.3.2.7 Selenium

Selenium is a mineral known for its capacity as an antioxidant, as a cofactor for glutathione peroxidase. Selenium also helps in the conversion of thyroxine to triiodothyronine and can modulate immune function. It has been shown that selenium deficiency encourages depressed mood. Conversely, high dietary or supplementary selenium has been shown to improve mood [86]. Research has consistently reported that low selenium status was associated with significantly increased incidence of depression, anxiety, confusion, and hostility [87]. Even more, when alcoholism and depression occur together in an individual, there is an increased risk for suicide.

Given the propensity for low selenium status in alcoholic patients and the relationship between selenium levels and mood disorder, selenium supplementation is warranted in an attempt to ameliorate the untoward comorbid psychological and physical profile of patients with alcohol abuse or dependence and may also be of value even in the nonalcoholic depressed individual.

Large doses may cause brittle nails, and one fatality has been reported after the accidental ingestion of 31 mg. Overall, selenium is historically quite safe when taken in prescribed doses, and in high-selenium areas of the country, intake as high as 724 µg d⁻¹ was considered safe [88, 89].

40.3.2.8 L-Tryptophan and 5-Hydroxytryptophan (5-HTP)

Tryptophan is a well known amino acid precursor of serotonin (5-hydroxytryptamine). Plasma tryptophan also has antioxidant activity [90]. Research shows that tryptophan is significantly lower in major depressed subjects than in normal controls [91]. Low serum levels of 5-hydroxytryptophan may increase the risk of a suicide attempts in patients who are depressed.

As SSRIs are known to block the reuptake of serotonin, their desired therapeutic effect is through enhancing levels of serotonin in the brain. Supplementing with tryptophan and 5-HTP allows the body to convert more of these amino acids to tryptophan. Some CAM practitioner believe that using tryptophan or 5-HTP is a better method of achieving the same goal, for it allows the body to have more control over this process, which may mitigate side effects that contribute to the side-effect profile of SSRIs.

When considering whether to use tryptophan or 5-HTP, 5-HTP would probably be the better supplement choice. Also known to help in depression [92], 5-HTP has been shown to be more effective at crossing the blood–brain barrier, and oral dosing results in greater conversion to serotonin than dosing with tryptophan (70% vs. 3%, respectively) [102].

When considering serotonin abnormalities in a depressed patient from a naturopathic standpoint, it is important to consider the role and health of the digestive tract. Evidence linking digestive dysfunction, abnormal serotonin levels, and psychiatric illness is emerging. One study demonstrated that 20% of patients with functional bowel disorders also have psychiatric comorbidities [93]. Effectively treating digestive dysfunction may rebalance tryptophan and serotonin levels, thus working to alleviate depressive illness. The naturopathic notion of ‘treating the gut’ may be of use in treating primary mechanisms of depression.

When dosed accordingly, tryptophan appears to be quite safe and effective. The possibility of eosinophilia myalgia syndrome almost 15 years ago caused concern in the United States after a few individuals fell ill after consuming contaminated batches of the supplement [94]. Probably more salient would be words of caution about ‘serotonin syndrome’, which is a situation in which SSRI and natural therapies known to increase serotonin levels are used in combination. This syndrome can be characterized by severe agitation, nausea, and confusion. However, with careful dosing of SSRI drugs and tryptophan, supplementation may provide a side-effect free and useful integrative approach to depression. A randomized controlled trial of 8-week treatment with 20 mg of fluoxetine in combination with 2 g of tryptophan daily in 30 patients with major depression found that this combined treatment appeared to be a safe and that it had both a rapid antidepressant effect and a protective effect on slow-wave sleep, with no need for monitoring of drug levels [95].

In patients who do not require first-line pharmaceutical therapy (see Section 4.1), it may be best for the CAM healthcare provider to choose a prescription-grade high-quality tryptophan or 5-HTP. Since more research is needed to optimize dosing schedule and amounts, it may be best to start with 500 mg d⁻¹ of tryptophan and work up to a dose of 2 g d⁻¹ if needed. Doses of 5-HTP can start at 100 mg three times a day and work up to 200 mg three times a day. At this time it is not known

whether 5-HTP can be dosed with fluoxetine, and any attempt to use them in an integrative fashion should begin cautiously. One recent meta-analysis of tryptophan and 5-HTP studies found few of high quality and merit. Out of 108 studies, only two studies (one of 5-HT and one of L-tryptophan) with a total of 64 patients met sufficient quality criteria to be included. These studies suggested that 5-HTP and L-tryptophan are better than placebo at alleviating depression [96]. But more quality research on a larger number of individuals is clearly needed.

40.3.2.9 Vitamin E

Depression has been associated with decreased antioxidant capacity and increased lipid peroxidation [97]. In a study evaluating 26 healthy volunteers and 42 depressed patients, patients with major depression had significantly lower serum vitamin E concentrations than healthy controls [98]. Given the relative safety of vitamin E supplementation and the possible benefits to both the cardiovascular system and to decreasing oxidative damage, it is reasonable to supplement patients having major depression with 400 IU of vitamin E d⁻¹.

40.3.2.10 Zinc

Known as a mineral cofactor, zinc is responsible for wound healing and immune- and nervous-system modulation. It has been postulated that zinc may act as an antagonist of the NMDA glutamate receptor [99]. In general, unipolar depression is connected with low blood zinc levels that are known to increase during antidepressant therapy [100]. One double blind placebo-controlled pilot study of zinc supplementation during antidepressant therapy was conducted with patients who met DSM IV criteria for major depression. A total of 14 patients received either zinc supplementation at 25 mg zinc d⁻¹ or placebo and were concomitantly treated with standard antidepressants [101]. Zinc supplementation significantly reduced both Hamilton Depression and Beck Inventory scores after 6- and 12-week supplementation when compared with placebo treatment. Due to theoretical depletion of copper by zinc treatment, long-term supplementation (greater than two months) with zinc should be balanced with copper supplementation.

40.4

Important Lifestyle Factors Targeted by CAM in Depressed Persons

40.4.1

Diet and the Digestive System

Nutrient deficiencies are common in depressed patients. Impaired digestive function can often claim significant responsibility for these deficiencies. Making matters worse, the Standard American Diet (SAD) fails to provide the high-quality nutrients necessary for metabolic processes (such as folic acid, B vitamins), for antioxidant protection (such as vitamins E and C), and for providing the necessary amino acid precursors for neurotransmitters (such as the amino acid tryptophan).

High quality and varied types of vegetables and fruits, as well as adequate fiber and protein sources, are crucial to the physical and mental health of any individual. It seems reasonable to assume that systems under stress, like that of the depressed patient, would require these even more; but these assumptions have not been fully characterized or studied. Related to this, the patient must also attempt to eat in a quiet environment and learn to chew food well for good digestion. Given that a large percentage of adults skip meals or eat in the car, this alone can be quite a lofty goal for the depression sufferer and the CAM practitioner.

40.4.2

Tobacco, Alcohol, and Recreational Drugs

Comorbid substance abuse is detailed addressed in Chapter 13 of this book. Cigarette smoking also leads to a relative deficiency in vitamin C [102]. As lipid oxidation is increased in depressive illness [97], this becomes a crucial health issue. Depressive symptoms, smoking, and sedentary behavior are independent predictors of mortality. Results indicate that smoking and/or sedentary behavior may partially mediate the relation between depressive symptoms and mortality [103].

Alcohol can lead to increased adrenal cortisol and is known to disrupt sleep architecture. Chronic alcohol ingestion also depletes a number of vitamins and nutrient cofactors, as well as causing precipitous changes in blood sugar. Recreational drug use (e.g., of cannabis) is known to increase the occurrence of depressive symptoms [104].

40.4.3

Sleep

Regular sleep is of paramount importance to good health. Given the poorly characterized yet global effects of circadian rhythm on overall hormonal regulation, it is reasonable to consider instituting lifestyle changes that support circadian rhythm function. Changing to an earlier bedtime, implementing support for regular sleep patterns (minimizing nighttime light, eating a diet adequate in protein, maintaining a reasonable eating schedule, balancing blood sugar, supplementing with melatonin, etc.), and assuring exposure to morning sunlight may have far-reaching effects on depressive illness. More specifically, certain types of depression may be even better amenable to certain therapies. For instance, one observational study noted that exposure to morning sunlight, a mainstay for treating seasonal affective disorder, can have therapeutic effects in bipolar depression but not in unipolar illness [105].

40.4.4

Exercise

Throughout history, many societies, ancient and modern, have used exercise as a means of preventing disease and promoting health and well-being [106]. Exercise

may be the most beneficial form of depression therapy [102]. Known to elevate mood [107], exercise is also known to balance blood sugar, raise levels of good cholesterol, and improve cardiac function. There is ample evidence that exercise is beneficial to mental health, for it reduces anxiety, depression, and negative mood and improves self-esteem and cognitive functioning [106]. In a randomized controlled trial, 156 adults with major depression were assigned to a 4-month course of aerobic exercise, sertraline therapy, or a combination of exercise and sertraline. After four months patients in all three groups exhibited significant improvement; But after 10 months, subjects in the exercise group had significantly lower relapse rates ($p = 0.01$) than subjects in the medication group. Additionally, exercising on one's own during the follow-up period was associated with a reduced probability of depression diagnosis at the end of that period ($p = 0.0009$) [108]. In another randomized controlled trial, 156 patients at least 50 years old were given exercise or antidepressant medications. That study found that initially, a quicker improvement was found in the antidepressant group. But after 16 weeks of treatment, exercise was equally effective in reducing depression among older patients with major depression [109]. Finally, in a 2-year follow up study of post-MI patients with depression, those who performed regular exercise were shown to have less than half the risk of fatal cardiac events than patients who did not [110].

40.4.5

Other Lifestyle Factors and Further Considerations

Low socioeconomic status and social isolation can contribute to depressed mood and should be addressed for solutions when possible.

The nature-cure notion of getting enough sunlight also seems to be playing out in the medical literature as more information regarding the role of vitamin D and mood is emerging. Since research demonstrates that dosages of 100 µg vitamin D (4000 IU d⁻¹) in depressed patients tend to improve well-being [111], it makes sense for the CAM practitioner to ensure that patients who tend to get inadequate amounts of sunlight begin to get outside and enjoy the sun. Of course, those at higher risk for melanoma and other skin cancer should be more cautious and may consider using a vitamin D supplement.

In summary, modification of the above lifestyle factors plays a fundamental role in addressing the symptoms and underlying presumed causative aspects of depressed mood. It is important for the CAM practitioner to ferret all these out and to spend time with the patient devising an individualized plan to positively adjust these factors. It is often helpful to keep in mind several factors when implementing long-term healthful lifestyle changes, including patient education to clarify the purpose of the suggested treatment, being realistic as to what factors the patient is willing and able to change at that time, and meeting the patient where they are. As the art of CAM medicine dictates, it is up to the individual practitioner to use his or her knowledge of treatment modalities, clinical experience, intuition, and consideration of patient preferences when deciding on which options would be most efficacious for the individual patient.

Other CAM therapies relevant to the treatment of major depression include psychological support, such as the emotional freedom technique (EFT) [112, 113], neurolinguistic programming (NLP) [114, 115], and eye movement desensitization and reprocessing (EMDR); acupuncture [116, 117]; and energetic healing therapy/Reiki [118]. Biofeedback, guided imagery, and massage therapy have also been reported to transiently help with pain and anxiety [119–123].

40.5 Conclusions

Depression is a multifactorial disease that is governed by a complex system modulated by lifestyle, dietary, psychological, spiritual, nutritional, and physiological aspects. Although the term 'depression' is used as a diagnosis, the CAM practitioner perceives this condition to be vastly different for each patient and as a result, the CAM practitioner tries to understand the multiplicity of factors that can be contributing to the patient's condition and then applies that knowledge in a synergistic way most in line with the probable causes of illness. In this way, the CAM clinician tries a double approach: to help the patient's immediate mood problems and then, more importantly, to give long-term healing its best chance of occurring by ministering to the underlying causes of depression. Unfortunately, a large portion of the public uses DS without consulting a CAM or non-CAM practitioner.

References

- 1 The National Center for Complementary and Alternative Medicine Clearinghouse website: <http://nccam.nih.gov/health/whatiscam/#sup1> (Accessed July 19, 2004).
- 2 The American Association of Naturopathic Physicians website: http://www.naturopathic.org/naturopathic_medicine/whatis.html (Accessed July 19, 2004).
- 3 KESSLER, R. C., SOUKUP, J., DAVIS, R. B., FOSTER, D. F., WILKEY, S. A., VAN ROMPAY, M. I., EISENBERG, D. M., The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am. J. Psychiatry* **2001**, *158*, 289–294.
- 4 UNUTZER, J., KLAP, R., STURM, R., YOUNG, A. S., MARION, T., SHATKIN, J., WELLS, K. B., Mental disorders and the use of alternative medicine: results from a national survey. *Am. J. Psychiatry* **2000**, *157*, 1851–1857.
- 5 McCAFFREY, A. M., EISENBERG, D. M., LEGEDZA, A. T., DAVIS, R. B., PHILLIPS, R. S., Prayer for health concerns: results of a national survey on prevalence and patterns of use. *Arch. Intern. Med.* **2004**, *164*, 858–862.
- 6 BARNES, P. M., POWELL-GRINER, E., MCFANN, K., NAHIN, R. L., Complementary and alternative medicine use among adults: United States, 2002. *Adv. Data* **2004**, *343*, 1–19.
- 7 D. M. EISENBERG, R. B. DAVIS, S. L. ETTNER, M. S. APPEL, S. WILKEY, VAN ROMPAY, M., et al., Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* **1998**, *280*, 1569–1575.
- 8 DELLO BUONO, M., URCIUOLI, O., MARIETTA, P., PADOANI, W., DE LEO, D., Alternative medicine in a sample of 655 community-dwelling elderly. *J. Psychosom. Res.* **2001**, *50*, 147–154.

- 9 MONTAZERI, A., SAJADIAN, A., KAVIANI, A., HAJI-MAHMOODI, M., EBRAHIMI, M., Depression and the use of complementary medicine among breast cancer patients. *Eur. J. Cancer Supplements* **2004**, 2, 112.
- 10 PARSLow, R. A., Jorm AF Use of prescription medications and complementary and alternative medicines to treat depressive and anxiety symptoms: results from a community sample. *J. Affective Disorder* **2004**, 82, 77–84.
- 11 No authors listed. Update on dietary supplements for depression. *Harv. Women's Health Watch* **2004**, 11 (7), 6–7.
- 12 ERNST, E., The risk–benefit profile of commonly used herbal therapies: ginkgo, St. John's wort, ginseng, Echinacea, saw palmetto and kava. *Ann. Intern. Med.* **2002**, 136, 42–53.
- 13 PIES, R., Adverse neuropsychiatric reactions to herbal and over-the-counter 'antidepressants'. *J. Clin. Psychiatry* **2000**, 61, 815–820.
- 14 Economic Characterization of the Dietary Supplement Industry Final Report: U. S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, March **1999**.
- 15 GLOBAL MARKETS II, *Nutrition Business Journal* **1998**.
- 16 Guidelines on Developing Consumer Information on Proper Use of Traditional, Complementary and Alternative Medicine. Geneva, Switzerland: World Health Organization, **2004**.
- 17 BARNES, P., POWELL-GRINER, E., MCFANN, K., NAHIN, R., Complementary and Alternative Medicine Use Among Adults: United States, **2002**. CDC Advance Data Report #343 2004.
- 18 VICKERS, A. J., Message to complementary and alternative medicine: evidence is a better friend than power. *BMC Complement Altern. Med.* **2001**, 1, 1. Epub 2001 May 01.
- 19 PIZZORNO, J., Editorial: building community. *Integrative Medicine* **2004**, 3, 7.
- 20 WEISSMAN, A. M., LEVY, B. T., HARTZ, A. J., BENTLER, S., DONOHUE, M., ELLINGROD, V. L., WISNER, K. L., Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. *Am. J. Psychiatry* **2004**, 161, 1066–1078.
- 21 WEIR, K. M., BEAL, M. W., Complementary therapies as adjuncts in the treatment of post-partum depression. *J. Midwifery Women's Health* **2004**, March–April, 96–104.
- 22 [No authors listed] Mild depression in general practice: time for a rethink? *Drug Ther. Bull.* **2003**, 41 (8), 60–64.
- 23 LINDE, K., RAMIREZ, G., MULROW, C. D., PAULS, A., WEIDENHAMMER, W., MELCHART, D., St John's wort for depression: an overview and meta-analysis of randomised clinical trials. *BMJ* **1996**, 313, 253–258.
- 24 BROWN, D., St. John's wort effectively treats mild to moderate depression in large French trial. *Herbalgram* **2003**, 57, 26–28.
- 25 HUBNER, W. D., KIRSTE, T., Experience with St John's Wort (*Hypericum perforatum*) in children under 12 years with symptoms of depression and psychovegetative disturbances. *Phytother. Res.* **2001**, 15, 367–370.
- 26 BUTTERWECK, V., Mechanism of action of St John's wort in depression: what is known? *CNS Drugs* **2003**, 17, 539–562.
- 27 RE, L., CORNELI, C., STURANI, E., PAOLUCCI, G., ROSSINI, F., SONIA LEÓN, O., MARTÍNEZ, G., BORDICCHIA, M., TOMASSETTI, Q., Effects of *Hypericum* extract on the acetylcholine release: a loose patch clamp approach. *Pharmacol. Res.* **2003**, 48, 55–60.
- 28 HELGASON, C. M., WIESELER FRANK, J. L., JOHNSON, D. R., FRANK, M. G., HENDRICKS, S. E., The effects of St. John's Wort (*Hypericum perforatum*) on NK cell activity in vitro. *Immunopharmacology* **2000**, 46, 247–251.
- 29 MORELLI, V., ZOOROB, R. J., Alternative therapies: depression, diabetes, obesity. *Am. Fam. Physician* **2000**, 62, 1051–1060.
- 30 NODA, Y., KAMEI, H., NABESHIMA, T., Sigma-receptor ligands and anti-stress actions. *Nippon Yakurigaku Zasshi* **1999**, 114, 43–49.
- 31 SHELTON, R. C., KELLER, M. B., GELENBERG, A., DUNNER, D. L., HIRSCHFELD, R., THASE, M. E., RUSSELL, J., LYDIARD, R. B., CRITS-CRISTOPH, P., GALLOP, R., TODD, L., HELLERSTEIN, D., GOODNICK, P., KEITNER, G., STAHL, S. M., HALBREICH, U., Effectiveness of

- St. John's wort in major depression: a randomized controlled trial. *JAMA* **2001**, *285*, 1978–1986.
- 32 VORBACH, E. U., ARNOLDT, K. H., HUBNER, W. D., Efficacy and tolerability of St. John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD-10. *Pharmacopsychiatry* **1997**, *30*, S81–S85.
 - 33 MILLER, A. L., Vitamin C causes cancer! St. John's wort useless for depression! *Altern. Med. Rev.* **2001**, *6*, 353–354.
 - 34 HYPERICUM DEPRESSION TRIAL STUDY GROUP. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* **2002**, *10*, 287, 1807–1814.
 - 35 BEHNKE, K., JENSEN, G. S., GRAUBAUM, H. J., GRUENWALD, J., *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression. *Adv. Ther.* **2002**, *19*, 43–52.
 - 36 BRENNER, R., AZBEL, V., MADHUSOODANAN, S., PAWLOWSKA, M., Comparison of an extract of *Hypericum* (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. *Clin. Ther.* **2000**, *22*, 411–419.
 - 37 WOELK, H., Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. *BMJ* **2000**, *321*, 536–539.
 - 38 SCHULZ, V., Clinical trials with *Hypericum* extracts in patients with depression: results, comparisons, conclusions for therapy with antidepressant drugs. *Phytomedicine* **2002**, *9*, 468–474.
 - 39 CZEKALLA, J., GASTPAR, M., HUBNER, W. D., JAGER, D., The effect of *Hypericum* extract on cardiac conduction as seen in the electrocardiogram compared to that of imipramine. *Pharmacopsychiatry* **1997**, *30* Suppl. 2, 86–88.
 - 40 HENRY, J. A., ALEXANDER, C. A., SENER, E. K., Relative mortality from overdose of antidepressants. *Br. Med. J.* **1995**, *310*, 221–224.
 - 41 IZZO, A. A., Drug interactions with St. John's wort (*Hypericum perforatum*): a review of the clinical evidence. *Int. J. Clin. Pharmacol. Ther.* **2004**, *42*, 139–148.
 - 42 TANNERGREN, C., ENGMAN, H., KNUTSON, L., HEDELAND, M., BONDESSON, U., LENNERNAS, H., St John's wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. *Clin. Pharmacol. Ther.* **2004**, *75*, 298–309.
 - 43 HALL, S. D., WANG, Z., HUANG, S. M., HAMMAN, M. A., VASAVADA, N., ADIGUN, A. Q., HILLIGOSS, J. K., MILLER, M., GORSKI, J. C., The interaction between St. John's wort and an oral contraceptive. *Clin. Pharmacol. Ther.* **2003**, *74*, 525–535.
 - 44 PEEBLES, K. A., BAKER, R. K., KURZ, E. U., SCHNEIDER, B. J., KROLL, D. J., Catalytic inhibition of human DNA topoisomerase II by hypericin, a naphthodianthrone from St. John's wort (*Hypericum perforatum*). *Biochem. Pharmacol.* **2001**, *62*, 1059–1070.
 - 45 ZHOU, S., CHAN, E., PAN, S. Q., HUANG, M., LEE, E. J., Pharmacokinetic interactions of drugs with St. John's wort. *J. Psychopharmacol.* **2004**, *18*, 262–276.
 - 46 GULICK, R., LUI, H., ANDERSON, R., et al., Human hypericisim: a photosensitivity reaction to hypericin (St. John's wort). *Int. Conf. AIDS* **1992**, *8*, B90 (abstract no. PoB 3018)
 - 47 LEE, A., MINHAS, R., MATSUDA, N., LAM, M., ITO, S., The safety of St. John's wort (*Hypericum perforatum*) during breastfeeding. *J. Clin. Psychiatry* **2003**, *64*, 966–968.
 - 48 SHAH, Z. A., SHARMA, P., VOHORA, S. B., *Ginkgo biloba* normalises stress-elevated alterations in brain catecholamines, serotonin and plasma corticosterone levels. *Eur. Neuropsychopharm.* **2003**, *13*, 321–325.
 - 49 MORRIS, N., The effects of lavender (*Lavandula angustifolium*) baths on psychological well-being: two exploratory randomised control trials. *Complement Ther. Med.* **2002**, *10*, 223–228.
 - 50 AKHONDZADEH, S., KASHANI, L., FOTOUHI, A., JARVANDI, S., MOBASERI, M., MOIN, M., KHANI, M., JAMSHIDI, A. H., BAGHALIAN, K., TAGHIZADEH, M., Comparison of *Lavandula angustifolia* Mill. tincture and imipramine in the treatment of mild to moderate depression: a double-blind, randomized trial. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2003**, *27*, 123–127.
 - 51 POWWER, F., SNOEK, F. J., Association between symptoms of depression and

- glycaemic control may be unstable across gender. *Diabet. Med.* **2001**, *18*, 595–598.
- 52 ATTENBURROW, M. J., ODONTIADIS, J., MURRAY, B. J., COWEN, P. J., FRANKLIN, M., Chromium treatment decreases the sensitivity of 5HT_{2A} receptors. *Psychopharmacology* **2002**, *159*, 432–436.
 - 53 ANDERSON, R. A., Chromium, glucose intolerance and diabetes. *J. Am. Coll. Nutrition* **1998**, *17*, 548–555.
 - 54 DAVIDSON, J. R., ABRAHAM, K., CONNOR, K. M., MCLEOD, M. N., Effectiveness of chromium in atypical depression: a placebo-controlled trial. *Biol. Psychiatry* **2003**, *53*, 261–264.
 - 55 HIBBELN, R., Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J. Affect Disord.* **2002**, *69*, 15–29.
 - 56 MISCHOULON, D., FAVA, M., Docosahexaenoic acid and omega-3 fatty acids in depression. *Psychiatr. Clin. North Am.* **2000**, *23*, 785–794.
 - 57 SEVERUS, W. E., LITTMAN AB STOLL, A. L., Omega-3 fatty acids, homocystiene, and the increased risk of cardiovascular mortality in major depression. *Harvard Rev. Psychiatry* **2001**, *9*, 280–293.
 - 58 DELARUE, J., MATZINGER, O., BINNERT, C., SCHNEITER, P., CHIOLERO, R., TAPPY, L., Fish oil prevents the adrenal activation elicited by mental stress in healthy men. *Diabetes Metab.* **2003**, *29*, 289–295.
 - 59 SU, K. P., HUANG, S. Y., CHIU, C. C., SHEN, W. W., Omega-3 fatty acids in major depressive disorder: a preliminary double-blind, placebo-controlled trial. *Eur. Neuropsychopharmacol.* **2003**, *13*, 267–271.
 - 60 FREEMAN, M. P., Omega-3 fatty acids in psychiatry: a review. *Ann. Clin. Psychiatry* **2000**, *12*, 159–165.
 - 61 PEET, M., HORROBIN, D. F., A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Archives of General Psychiatry* **2002**, *59*, 913–919.
 - 62 LLORENTE, A. M., Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am. J. Obstet. Gynecol.* **2003**, *188*, 1348–1353.
 - 63 MARANGELL, L. B., MARTINEZ, J. M., ZBOYAN, H. A., KERTZ, B., KIM, H. F., PURYEAR, L. J., A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am. J. Psychiatry* **2003**, *160*, 996–998.
 - 64 NEMETS, B., STAHL, Z., BELMAKER, R. H., Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry* **2002**, *159*, 477–479.
 - 65 KROES, R., SCHAEFER, E. J., SQUIRE, R. A., WILLIAMS, G. M., A review of the safety of DHA45-oil. *Food Chem. Toxicol.* **2003**, *41*, 1433–1446.
 - 66 SLOT, O., Changes in plasma homocysteine in arthritis patients starting treatment with low-dose methotrexate subsequently supplemented with folic acid. *Scand. J. Rheumatol.* **2001**, *30*, 305–307.
 - 67 GENDALL, K. A., BULIK, C. M., JOYCE, P. R., Visceral protein and hematological status of women with bulimia nervosa and depressed controls. *Physiol. Behav.* **1999**, *66*, 159–163.
 - 68 FAVA, M., BORUS, J. S., ALPERT, J. E., NIERENBERG, A. A., ROSENBAUM, J. F., BOTTIGLIERI, T., Folate, vitamin B12, and homocysteine in major depressive disorder. *Am. J. Psychiatry* **1997**, *154*, 426–428.
 - 69 COPPEN, A., BAILEY, J., Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. *J. Affect Disord.* **2000**, *60*, 121–130.
 - 70 FUGH-BERMAN, A., COTT, J. M., Dietary supplements and natural products as psychotherapeutic agents. *Psychosomatic Med.* **1999**, *61*, 712–728.
 - 71 VAN EDE, A. E., LAAN, R. F., ROOD, M. J., HUIZINGA, T. W., VAN DE LAAR, M. A., VAN DENDEREN, C. J., WESTGEEST, T. A., ROMME, T. C., DE ROOIJ, D. J., JACOBS, M. J., DE BOO, T. M., VAN DER WILT, G. J., SEVERENS, J. L., HARTMAN, M., KRABBE, P. F., DIJKMANS, B. A., BREEDVELD, F. C., VAN DE PUTTE, L. B., Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* **2001**, *44*, 1515–1524.

- 72 VUCENIK, I., SHAMSUDDIN, A. M., Cancer inhibition by inositol hexaphosphate (IP6) and inositol: from laboratory to clinic. *J. Nutr.* **2003**, 133 (11 Suppl. 1), 3778S–3784S.
- 73 EINAT, H., KARBOVSKI, H., KORIK, J., TSALAH, D., BELMAKER, R. H., Inositol reduces depressive-like behaviors in two different animal models of depression. *Psychopharmacology* **1999**, 144, 158–162.
- 74 BRINK, C. B., VILJOEN, S. L., DE KOCK, S. E., STEIN, D. J., HARVEY, B. H., Effects of myoinositol versus fluoxetine and imipramine pretreatments on serotonin 5HT_{2A} and muscarinic acetylcholine receptors in human neuroblastoma cells. *Metab. Brain Dis.* **2004**, 19, 51–70.
- 75 EINAT, H., CLENET, F., SHALDUBINA, A., BELMAKER, R. H., BOURIN, M., The antidepressant activity of inositol in the forced swim test involves 5-HT(2) receptors. *Behav. Brain Res.* **2001**, 118, 77–83.
- 76 LEVINE, J., Controlled trials of inositol in psychiatry. *Eur. Neuropsychopharmacol.* **1997**, 7, 147–155.
- 77 TAYLOR, M., WILDER, H., BHAGWAGAR, Z., GEDDES, J., Inositol for depressive disorders. *Cochrane Database Syst. Rev.* **2004**, 2, CD004049.
- 78 HENNEMAN, P. H., BENEDICT, P. H., FORBES, A. P., DUDLEY, H. R., Idiopathic hypercalcuria. *N. Eng. J. Med.* **1958**, 17, 802–807.
- 79 CRASSON, M., KJIRI, S., COLIN, A., KJIRI, K., L'HERMITE-BALERIAUX, M., ANSSEAU, M., LEGROS, J. J., Serum melatonin and urinary 6-sulfatoxymelatonin in major depression. *Psychoneuroendocrinology* **2004**, 29, 1–12.
- 80 ROHR, U. D., Herold J Melatonin deficiencies in women. *Maturitas* **2002**, 41 (15), Suppl. 1, 85–104.
- 81 LISSONI, P., CHILELLI, M., VILLA, S., CERIZZA, L., TANCINI, G., Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. *J. Pineal Res.* **2003**, 35, 12–15.
- 82 SUTHERLAND, E. R., ELLISON, M. C., KRAFT, M., MARTIN, R. J., Elevated serum melatonin is associated with the nocturnal worsening of asthma. *J. Allergy Clin. Immunol.* **2003**, 112, 513–517.
- 83 MISCHOULON, D., FAVA, M., Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am. J. Clin. Nutr.* **2002**, 76, 1158S–61S.
- 84 NGUYEN, M., GREGAN, A., S-adenosyl-methionine and depression. *Aust. Fam. Physician* **2002**, 31, 339–343.
- 85 Agency for Healthcare Research and Quality, the United States Department of Health and Human Services **2002**, 64, 1–3.
- 86 FINLEY, J. W., PENLAND, J. G., Adequacy or deprivation of dietary selenium in healthy men: clinical and psychological findings. *Trace Elem. Exp. Med.* **1998**, 11–27.
- 87 SHER, L., Role of selenium depletion in the etiopathogenesis of depression in patient with alcoholism. *Med. Hypotheses* **2002**, 59, 330–333.
- 88 LONGNECKER, M. P., Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. *Am. J. Clin. Nutr.* **1991**, 53, 1288–1294.
- 89 GABY, A. R., Nutrient Therapeutics. Published by the author, **2000**, 42–43.
- 90 MAES, M., MELTZER, H. Y., COSYNS, P., SCHOTTE, C., Evidence for the existence of major depression with and without anxiety features. *Psychopathology* **1994**, 27, 1–13.
- 91 MAES, M., VERKERK, R., VANDOOALAECH, E., VAN HUNSEL, F., NEELS, H., WAUTERS, A., DEMEDTS, P., SCHARPE, S., Serotonin-immune interactions in major depression: lower serum tryptophan as a marker of an immune-inflammatory response. *Eur. Arch. Psychiatry Clin. Neurosci.* **1997**, 247, 154–161.
- 92 BYERLEY, W. F., JUDD, L. L., REIMHERR, F. W., GROSSER, B. I., 5-Hydroxytryptophan: a review of its antidepressant efficacy and adverse effects. *J. Clin. Psychopharmacol.* **1987**, 7, 127–137.
- 93 AGAZZI, A., DE PONTI, F., DE GIORGIO, R., CANDURA, S. M., ANSELM, L., CERVIO, E., DI NUCCI, A., TONINI, M., Review of the implications of dietary tryptophan intake in patients with irritable bowel syndrome and psychiatric disorders. *Dig. Liver. Dis.* **2003**, 35, 590–595.
- 94 BELONGIA, E. A., HEDBERG, C. W., GLEICH, G. J., WHITE, K. E., MAYENO, A. N., LOEGERING, D. A., et al., An investigation of the cause of the eosinophilia-myalgia syndrome

- associated with tryptophan use. *N. Engl. J. Med.* **1990**, 323, 357–365.
- 95 LEVITAN, R. D., SHEN, J. H., JINDAL, R., DRIVER, H. S., KENNEDY, S. H., SHAPIRO, C. M., Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. *J. Psychiatry Neurosci.* **2000**, 25, 337–346.
 - 96 SHAW, K., TURNER, J., DEL MAR, C., Are tryptophan and 5-hydroxytryptophan effective treatments for depression? A meta-analysis. *Aust. N. Z. J. Psychiatry* **2002**, 36, 488–491.
 - 97 CHRISTOPHE, A., DELANGE, J., NEELS, H., SCHARPE, S., MELTZER, H. Y., Lowered omega 3 polyunsaturated fatty acids in serum phospholipids and cholesterol esters of depressed patients. *Psychiatry Research* **1999**, 85, 275–291.
 - 98 MAES, M., DeVos, N., PIOLI, R., et al., Lower serum vitamin E concentrations in major depression: another marker of lowered antioxidant defenses in that illness. *J. Affect Disord.* **2000**, 58, 241–246.
 - 99 NOWAK, G., SZEWCZYK, B., Mechanism contributing to antidepressant zinc actions. *Pol. J. Pharmacol.* **2002**, 54, 587–592.
 - 100 NOWAK, G., SCHLEGEL-ZAWADZKA, M., Alterations in serum and brain trace element levels after antidepressant treatment. Part I, Zinc. *Biol. Tr. Elem. Res.* **1999**, 67, 85–92.
 - 101 NOWAK, G., SIWEK, M., DUDEK, D., ZIEBA, A., PILC, A., Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. *Pol. J. Pharmacol.* **2003**, 55, 1143–1147.
 - 102 MURRAY, M. T., PIZZORNO, J. E., Affective disorders. In MURRAY, M. T., PIZZORNO, J. E. (Eds.), *Textbook of Natural Medicine*. Second edition. Churchill Livingstone, **1999**, 1040–1053.
 - 103 BRUMMETT, B. H., BABYAK, M. A., SIEGLER, I. C., MARK, D. B., WILLIAMS, R. B., BAREFOOT, J. C., Effect of smoking and sedentary behavior on the association between depressive symptoms and mortality from coronary heart disease. *Am. J. Cardiol.* **2003**, 92, 529–532.
 - 104 BOVASSO, G. B., Cannabis abuse as a risk factor for depressive symptoms. *Am. J. Psychiatry* **2001**, 158, 2033–2037.
 - 105 BENEDETTI, F., COLOMBO, C., BARBINI, B., Campori E Smeraldi E Morning sunlight reduces length of hospitalization in bipolar depression. *J. Affective Disorders* **2001**, 62, 221–223.
 - 106 CALLAGHAN, P., Exercise: a neglected intervention in mental health care? *J. Psychiatr. Ment. Health Nurs.* **2004**, 11, 476–483.
 - 107 WEYERER, S., KUPFER, B., Physical exercise and psychological health. *Sports Med.* **1994**, 17, 108–116.
 - 108 BABYAK, M., BLUMENTHAL, J. A., HERMAN, S., KHATRI, P., DORAISWAMY, M., MOORE, K., CRAIGHEAD, W. E., BALDEWICZ, T. T., KRISHNAN, K. R., Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom. Med.* **2000**, 62, 633–638.
 - 109 BLUMENTHAL, J. A., BABYAK, M. A., MOORE, K. A., CRAIGHEAD, W. E., HERMAN, S., KHATRI, P., WAUGH, R., NAPOLITANO, M. A., FORMAN, L. M., APPELBAUM, M., DORAISWAMY, P. M., KRISHNAN, K. R., Effects of exercise training on older patients with major depression. *Arch. Intern. Med.* **1999**, 159, 2349–2356.
 - 110 BLUMENTHAL, J. A., BABYAK, M. A., CARNEY, R. M., HUBER, M., SAAB, P. G., BURG, M. M., SHEPS, D., POWELL, L., TAYLOR, C. B., KAUFMANN, P. G., Exercise, depression, and mortality after myocardial infarction in the ENRICHD trial. *Med. Sci. Sports Exerc.* **2004**, 36, 746–755.
 - 111 VIETH, R., KIMBALL, S., HU, A., WALFISH, P. G., Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. *Nutr. J.* **2004**, 3, 8.
 - 112 Emotional Freedom Technique website. www.emofree.com (accessed on July 18, 2004).
 - 113 WELLS, S., POLGLASE, K., ANDREWS, H. B., CARRINGTON, P., BAKER, A. H., Evaluation of a meridian-based intervention, Emotional Freedom Techniques (EFT), for reducing specific phobias of small animals. *J. Clin. Psychol.* **2003**, 59, 943–966.
 - 114 HOSSACK, A., STANDIDGE, K., Using an imaginary scrapbook for neurolinguistic

- programming in the aftermath of a clinical depression: a case history. *Gerontologist* **1993**, 33, 265–268.
- 115 FIELD, E. S., Neurolinguistic programming as an adjunct to other psychotherapeutic/hypnotherapeutic interventions. *Am. J. Clin. Hypn.* **1990**, 32, 174–182.
- 116 TAO, D. J., Research on the reduction of anxiety and depression with acupuncture. *Am. J. Acupuncture* **1993**, 21, 327–329.
- 117 EICH, H., AGELINK, M. W., LEHMANN, E., LEMMER, W., KLIESER, E., Acupuncture in patients with minor depressive episodes and generalized anxiety: results of an experimental study. *Fortschr. Neurol. Psychiatr.* **2000**, 68, 137–144.
- 118 SHORE, A. G., Long-term effects of energetic healing on symptoms of psychological depression and self-perceived stress. *Altern. Ther. Health Med.* **2004**, 10, 42–48.
- 119 BAKKE, A. C., PURTZER M, Z., NEWTON, P., The effect of hypnotic-guided imagery on psychological well-being and immune function in patients with prior breast cancer. *J. Psychosom. Res.* **2002**, 53, 1131–1137.
- 120 ZELTZER, L. K., TSAO, J. C. I., STELLING, C., POWERS, M., LEVY, S., WATERHOUSE, M., A Phase I Study on the feasibility and acceptability of an acupuncture/hypnosis intervention for chronic pediatric pain. *J. Pain Symptom Manag.* **2002**, 24, 437–446.
- 121 FRASER, J., KERR, J. R., Psychophysiological benefits of back massage on elderly institutionalised patients. *J. Adv. Nurs.* **1993**, 18, 238–245.
- 122 FERRELL-TORRY, A. T., GLICK, O. J., The use of therapeutic massage as a nursing intervention to modify anxiety and the perception of cancer pain. *Cancer Nurs.* **1993**, 16, 93–101.
- 123 FIELD, T., GRIZZLE, N., SCAFIDI, F., SCHANBERG, S., Massage and relaxation therapies' effects on depressed adolescent mothers. *Adolescence* **1996**, 31, 903–911.

41

The Experience of Depression

Susan Blauner, Catherine Bond, Philip J. Burguières, Ma-Li Wong, Julio Licinio, and Deborah L. Flores

Abstract

This book has covered the field of depression research in great detail. We would like to finish with three narratives from people who experienced episodes of major depression. The six co-authors of this chapter include three psychiatrists and three individuals who have experienced the course of major depression. Our aim has been to provide a shift from the academic, research and biological perspectives to the personal. The ultimate goal of depression research is to improve the lives of those suffering from this disorder. We provide here descriptions of how individual lives are affected by chronic depression.

41.1**Introduction**

Major depressive disorder is an illness that affects about 20 million adults in the U.S. in any given year, which is about 10% of the American population [1]. Up to 21% of women and 13% of men experience a depressive episode in their lifetime [2]. It may occur as a single episode or recurrent episodes. The course of the illness varies, but it may last for years. Although most patients recover, three out of four have recurrences throughout their lives, and many have residual symptoms between episodes. It has been estimated that the economic cost of depression in the U.S. exceeded about \$100 billion in 2001 [3].

So what exactly is major depressive disorder? The American Psychiatric Association [4] defines it as follows:

Five (or more) of the following symptoms have been present for two consecutive weeks and represent change from previous function: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

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1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day
3. Significant appetite and/or weight changes, nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue and loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt, which may be delusional, nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death, recurrent suicidal ideation with or without a plan; or a suicide attempt

These symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. They should not be related to bereavement or effects from substances or medical illnesses.

Everyone has experienced feeling sad or down at some point in their lives. However, it is when these sad feelings begin to dominate a person's life, affecting their jobs and interpersonal relationships that one enters the threshold of major depressive disorder. Symptoms of depression may be precipitated by a stressful event such as the loss of a job or a serious medical illness. However, many people develop depression without any obvious precipitant. In addition to psychological symptoms, there are somatic manifestations, such as alterations in sleep, appetite, and sexual function. It may become more difficult to make day-to-day decisions, due to lack of concentration. Depression can also bring about a mixture of feelings and thoughts that may result in that person becoming more withdrawn and isolated or very anxious and agitated. This can be wrongly interpreted as weakness or a character flaw. People with this illness cannot 'snap out of it'. With appropriate treatment, major depressive disorder can be alleviated.

The monoamine hypothesis has been a predominant theory for the cause of depression. It states that monoaminergic dysfunction by unknown pathogenic mechanisms results in decreased monoamines (such as serotonin and norepinephrine) in the brain that is likely associated in the development of major depression. Antidepressant medications target these monoamines so as to increase their levels in the synaptic cleft, thus ameliorating depressive symptoms in many cases.

Evidence suggests that there are significant genetic influences in the cause of recurrent major depressive disorders. Genetic heterogeneity is likely and may involve inheritance of a single dominant gene with variable penetrance or polygenic inheritance. The heritability of major depression is likely to be in the range of 31%–42% or higher [5]. However, environmental influences are also very important and may account for the variability in the development of this illness. If an individual who is genetically vulnerable (e.g., a parent has a diagnosis of major depression) is exposed to a stressful life event, a depressive episode may be precipitated [6]. Because

of the etiological complexity of this disease, a specific gene has not yet been identified, but the genetics of depression continues to be investigated extensively.

Psychological theories have been proposed to explain major depressive disorder. Some of these include Sigmund Freud's *Mourning and Melancholia*, which suggests that the principal disturbance is a fixation in the oral developmental stage caused by a loss (real or perceived), which leads to a susceptibility later in life to interpersonal loss. According to this theory, depression is a result of the disruption of reassurance and sufficient support, which leads to low self-esteem and increased self-doubt and ultimately depression [7]. Heinz Kohut and colleagues [8] proposed that depression is the result of a parent's repeated failure to meet the needs of a developing child so that a positive sense of self is never established. It is probably safe to say that major depressive disorder has biological as well as psychological aspects to its development. Whether one plays a greater role over the other in activating the disease may be patient-specific.

Major depressive disorder is a highly treatable illness, but for which the therapeutic outcome is variable. There are over 20 FDA-approved medications that are effective in the treatment of depression. The likelihood that a patient will respond to a specific drug is 40%–70%. In fact, although 85%–90% of patients eventually respond to antidepressant medication, between 30% and 40% of patients fail to respond to the first antidepressant administered [9]. Since the average period for full efficacy response to an antidepressant medication is about six weeks, it can be very frustrating for a depressed patient to have to endure multiple medication trials. The rate of initial treatment failure is worrisome, because patients who fail their first antidepressant trial are at increased risk for never getting adequate treatment [10]. Elderly patients as a group may be at the greatest risk for failure to respond to the initial medication selected and appear to have greater risk of reemergent depression once remission is achieved [11].

This chapter introduces you to three people who have experienced recurrent depressive symptoms. Even though there are similarities, the individual experiences vary considerably, as detailed below.

41.2 Experience 1

It is the spring of 1990 and I am in the sixth month of my tenure as CEO for a Fortune 100 company. The company has serious ongoing problems 20 years in the making. My personality has adopted, accepted, taken hold, and is obsessive about these problems nearly 24 hours a day seven days a week.

My mind seems to have taken on a life of its own distant from my physical body; but the effects on my body are evident. I have many sleepless nights, and the smallest of things agitates me. I want out but am stuck, because I have never quit anything in my life (suffering through the curse of a cruel high school football coach to the trauma of being in the Navy during Vietnam). I can't quit so the pressure continues to build up.

In a movie with my family I have what I later find was a 'panic attack' ... It is a feeling of incredible anxiety. My heart feels like it will come out of my body, I want to scream, I want this feeling to go away.

Within a few weeks I am totally exhausted and pass out in my office. I had my first encounter with the 911 people; two days in the hospital and every test in the book and I am declared 'well'. The nice doctor tells me I need a vacation.

Within another few weeks I am in the office of a female psychiatrist, my first visit, and she decides to hospitalize me, which I refuse. She says I am suffering from clinical depression and need therapy, medication, etc. I have a position in the community and can't accept much of what she says. She is a woman of presence, beautifully dressed, and I am in a hospital gown. She speaks down to me. (If there is something amiss in my brain why have I had to take off my underwear?) Finally we agree I will take a 'magic pill'. It is called Prozac.

Within two days of being on a low dose of Prozac I am in a state where I want to jump off a bridge. My anxiety level has risen to the breaking point. It is a negative excitement that words find hard to describe. We go through a series of drugs over the next few weeks with similar results. I start to learn and to study ... 'there is not a magic pill' ... This is at the beginning of a process which will soon lead to me leaving my job (I quit) ... and being well for six years.

I get another great job, but little do I know that I have not gotten to the root cause of my depression, which recurs like a firestorm in 1996. This time I am hospitalized and start the hard road to a real recovery. ...

It is May of 1996. My son is about to graduate from high school and has been accepted at a fine private university; my daughter has a job as an investment analyst with Merrill Lynch and is ready to start an MBA program; my wife has been battling breast cancer since 1990 and is winning; and my company has just doubled in size with a major acquisition.

What is wrong with this picture?

I am just about at the bottom of a second clinical depression. Can this be happening to me again after five years of 'good' mental health? The symptoms are all there, but brutally worse than five years ago. I am not sleeping at all; I'm certain that the world would be better off without me; I simply cannot force myself to exercise; and my mind has become a force within itself obsessing over and over for hours on end about the most miserable of outcomes.

Multiple tries of various medications have given me no relief; in fact, seemingly made things worse. Therapy is somewhat helpful ... What do I do? My wife is exasperated.

In June, out of sheer desperation, I start my search for the 'magic' answer. Surely there is someone, somewhere ... I read information sent by a friend about the best mental health facilities in the U.S. My doctor cannot find an adequate place in Texas. I call a few places.

With tremendous trepidation I fly to a major mental health facility in the Midwest with some modest hope. Will I ever see home again? ... I am placed in a program called "Professionals in Crisis"; a synonym for clinical depression.

What? There is no one to greet me ... care for me ... the staff is mixed ... some want control ... medication is 'forced' into me ... I see my doctor for ten minutes each morning ... I'm left alone. There are some planned activities – group meetings held two days a week for one hour ... Acting out our lives (psychodrama) ... one day, one hour at a time, ... no physical activity, ... no faith-based programs. I'm getting worse, if that's possible ...

I'm in the same building, but separated by a hall from substance-abuse patients. They are a more fun group than the depressed group I'm with ... If I were an alcoholic, maybe I'd have more fun ... At least ...

Time is heavy ... Main weekend activity is a visit to the zoo in a van ... maybe a movie with the group. Medication is making me worse. Doctors (one exception) are very standoffish. I can't take it anymore ... I'm doomed ...

My wife, Cheryl, stays for a time at a nearby hotel and visits me daily. I don't know how she does it. I feel badly for putting her through this. Maybe it would be better if she went back to Houston and left me here ... I don't know ... I just don't know ...

I meet three special people – a doctor from Tennessee, a businessman from Florida, and a young lady from Wisconsin. We help and comfort each other – my only solace.

After three months at \$1000 per day plus extra cost for any doctor session, I give up ... I feel just as bad ... The doctors also *seem* to give up ... I go back to Houston. My wife says I'm better. I'm not sure ...

A two-year, incredibly difficult journey has now begun where I find my way out of clinical depression by *totally* changing the way I live my life ... It is so tough ... I try to live just one day at a time ... Friends are helpful beyond comprehension. My company (board of directors) allows me to maintain my dignity.

My family teaches me. They provide unending love and support. From Cheryl I learn about commitment; she never loses her faith in me. From my daughter Emily I get strength and constant dedication. From my son Martial I learn that life is to be enjoyed.

Through fate I run into John Sage who has suffered two episodes of clinical depression, and he becomes my mentor. He was an All-American football player at Louisiana State University (these people aren't supposed to get depressed!). We journey together ... We meet at least weekly and speak daily. We talk a lot about our faith. I feel I am becoming stronger ...

It's spring of '98 – I can see some light ... hope ...

41.3 Experience 2

For me, depression is like trying to do what I need to do while slogging through a muddy swamp. The smallest thing is an effort. Combined with the hopelessness I feel when I'm depressed, I often ask myself "Why bother?" "What's the use?"

The worst depression I ever had lasted a year and a half and ended with me trying to kill myself. I was forty-two and had had a hysterectomy the year before. Most of my prior life I was energetic and optimistic. I described myself as a 'happy workaholic'. I was constantly on the go, promoting my training business and my private practice as a marriage and family therapist.

I had been depressed before, but never like this. It felt as if the entire world had turned gray, including me. Food lost its taste. My friendships felt empty. At first I thought the problem might have been caused by a hormone imbalance. On reflection, the hysterectomy and aftermath may have triggered the depression, but what I experienced was the absolute bottom of a series of mood swings that had been occurring all of my adult life.

I experienced most of the common symptoms. I was always tired and tried to sleep to escape the horrible feeling that life was no longer worth living. A nagging voice kept repeating, "Kill yourself. It's easier." I stopped eating and lost a lot of weight in a short period of time.

Instead of going for help, I tried to tough it out. I kept telling myself that the depression would lift. After all, I had been depressed before and had always 'come out of it' on my own. Gradually, I became so depressed that I began to seriously consider suicide. I became convinced that the world would be better off without me, that I was a worthless person, unlovable and unloved.

I finally took a bottle of sleeping pills that had been given to me by a psychiatrist, whom I knew from my work as a therapist. I was discovered in time by my son and taken to the emergency room. Then I was sent to a psychiatric hospital, where I was diagnosed with bipolar disorder. I was deeply ashamed of being 'mentally ill' and rejected the diagnosis and prescribed medication.

It took me several years and several hospitalizations to eventually come to terms with my diagnosis. I think the turning point came when I went to a psychiatrist complaining of depression, got an antidepressant, took it, and ended up in a hospital with an acute manic episode. I learned the hard way that I needed to acknowledge my diagnosis and to take medication that is appropriate to my condition. That, combined with psychotherapy, helped me turn my life around, and for the past six years I have been in recovery. During that time I suffered one serious depressive episode and dealt with it in therapy. I work full time for a program that is run by and for people with serious mental illness. I have friends and an active social life, and I stay in touch with my son through weekly phone calls and occasional visits.

41.4

Experience 3

I have lived with chronic depression for over 20 years. Even now, I am amazed that a chemical/electrical imbalance in my body can generate such temporary chaos. However, *temporary* does not exist in an actively depressed mind. Along with the malaise, self-devaluation, physical and emotional exhaustion, mental confusion, sleep disturbance, eating disturbance, spiritual disconnection, and hopelessness,

I get the paralyzing message that I'm always this way and always will be. Ironically, when the depression lifts, I somehow think it will never happen again.

My Story

On May 5, 1980 my mother died of ovarian cancer. I was fourteen. Prior to 1980 I had experienced other psychological trauma, but this devastating loss was the 'straw' that broke my metaphorical back.

... Throughout high school I translated my depression into promiscuity, martyrdom, outrageous clothing, indifference, fatigue, and thoughts of self-destruction. My grief became a form of self-definition ...

... The depression went untreated until I took myself to therapy during my freshman year of college. Since that time I've seen eight different therapists, five psychiatrists for medication consults, tried four different antidepressants, and I've been hospitalized three times for overdoses. My diagnosis also includes post-traumatic stress disorder and borderline personality disorder, making treatment all the more challenging and at times nearly impossible ...

I've tried several antidepressants since 1991: Prozac, Pamelor, Remeron, Serzone. I began with Prozac, and returned to it in 1998 after my last overdose.

Early in 2002, I increased my Prozac dosage from twenty milligrams per day to thirty, because I had entered an extremely stressful time. There were no thirty-milligram pills available, so my doctor wrote a prescription for 45 twenty-milligram capsules that I used in a pattern of forty, twenty, forty, twenty.

In August I tried to refill the prescription and the pharmacy told me I could no longer get 45 pills; my insurance wouldn't cover it. I told them to just give me 30, and I would figure out a way to make up the rest (via samples). Two weeks later I felt like I was living in a vat of molasses. To mount a stairway was a Herculean effort. I was on an emotional edge. My thinking became unclear. One day this thought went through my head, "You never tried *drowning*. Why don't you take your kayak out into Nantucket Sound tonight and capsize?"

I got home and called my doctor. While on the phone I picked up the pill bottle and saw that the pharmacy had given me thirty *ten-milligram* capsules, with the instruction to take three a day. For two weeks I had been taking ten, twenty, ten, twenty. My blood level of Prozac was lower than ever.

After a week or so of trying to sort this out between the pharmacy and my physician, my doctor finally wrote a prescription for 30 forty-milligram capsules. Once my blood levels rose that August, the symptoms subsided and suicidal thoughts disappeared. Although a harrowing experience, it showed without a doubt that I needed to be on medication. I will take meds for the rest of my life if necessary.

For the last 13 years I worked with Sylvia, the therapist who helped save my life. With her guidance and support, I examined the way I processed the world, developed new coping skills, changed my behavior and thought patterns, and built a strong foundation on which to flourish. After a gradual decrease in office visits, I stopped seeing Sylvia in April of 2003. For my own benefit I am going to stress the magnitude of that last sentence: *I stopped seeing Sylvia in April of 2003.*

From the Inside

November 8, 1985

I feel like I've slid down a tunnel again, but it's like being on a water slide and there's nowhere to brake myself. Why have I lost interest so?! ... For one week I felt in control, like my life was piecing itself together again. Now I'm back where I started. God, when am I ever going to be happy? Why must I be tortured so?

April 28, 1990

I want to be eliminated. I don't want to have to think about a job or place to live or what I want to do. I'd rather die. ... I wish I could enjoy being alive. I wish I could look forward to the future, rather than dread it. I feel like I have no dream to follow, like I'm lost in a whirlpool, stuck in the center, going down deeper and deeper. I hate this.

July 1992

... I don't believe that God or anyone else has the power to get rid of this self-loathing. I truly believe it is a falsehood when I am feeling well. That is the disguise. This is my true state of being ... [God] just trick[s] everyone into believing it will get better, but there's always that undercurrent of pain – no matter what ... I don't believe in people and I don't believe in me ... I don't deserve to breathe the air or take up space on earth.

February 5, 1995

I feel like a wasted person.

All of the journal entries above show the intense gloom of depression. The following list of traits, thoughts, and/or behaviors are also typical of my experience with depression, though I no longer experience all of these during every episode.

- *Eating/food.* This is usually the first thing to go when I become depressed. I can't figure out what to eat; I don't want to eat. The whole process of preparation, cooking, cleanup, and storage feels paralyzing and insurmountable. It's easier to sleep and ignore the hunger.
- *Personal hygiene.* This is the next to go. I stop caring about my physical appearance. My brain tells me I'm not worth it and no one cares. I don't care. The experience of water hitting my body during a shower becomes almost painful. I start wearing dirty clothes because it is too overwhelming to wash anything. Extreme example: throughout the 1990s, I would have days like this – dress for work/school, sludge through the day, get home, go straight to bed/sleep in my clothes, get up to eat or use the bathroom, go back to bed, get up the next morning, go to work/school in the same clothes. I didn't have the mental energy to wash or change.
- *Sleeping.* One of the only respites for me during depression is to sleep. Extreme example: sleep throughout the day and stay up through the night. This happened after I transferred to the University of Vermont (UVM) in 1985. I went from a 4.0

at my previous college (straight As) to 1.81 at UVM. Even now, I can sleep for 16 hours a day and still be tired and lethargic.

- *Crying.* My brain gets so overloaded that the slightest stress can push me over the emotional edge and bring a flood of tears. I used to spend chunks of time crying in bed: cry for a while, get tired from crying, fall asleep, wake up, start crying again, etc. Extreme examples: at work I used to get so overwhelmed that I'd go into the bathroom and cry for 20 minutes. In a 1987 college art class I felt so overwhelmed about drawing a tree that I started crying and couldn't stop; I left the class in tears.
- *Lack of mental clarity.* This is perhaps the most frustrating agent of any present-day depression. Having to 'work' to think clearly. Memory problems. Feeling as though my head is stuck inside a heavy, weighted box; holding it up takes effort. Mental 'filters' stop working properly: I have trouble tuning out extra noise, I become hypersensitive to noise, clutter, general stimulation. At times I don't understand what people say – their words don't make sense.
- *Dissociation/hopelessness.* All of the above contribute to an experience of disconnection and hopelessness during a depressed episode. The hopelessness and disconnection then make it harder to take steps to ease the symptoms, which fuel the sense of disconnection. I lose my emotional and spiritual connection to life. Nothing that I have ever accomplished means anything. I fall into black-and-white thinking and in the moment of misery my blinders get thicker and thicker. Suicidal thoughts may or may not enter the picture. I perceive myself as a failure, not good enough, worthless, unloved. I cannot *feel* the experience of love from myself or anyone else. Ironically, when I do feel someone's love in moments like this, I start to cry. During these episodes I feel very young and want to be nurtured.
- *Suicidal thoughts.* These occur in the presence of extreme psychological pain, or 'psych-ache'. Fueled by emotional triggers, a long-standing bout of depression, or the complex weave of behavior disorders, suicidal thoughts became an obsession and an addiction. I have a *long* history with suicidal thoughts, beginning at age 14. I've been hospitalized three times for overdoses: 1991, 1992, and 1998.

On Loving Depression

Depression is caused by a chemical imbalance in my brain. I didn't ask for it, didn't cause it, and the only way to cure it is by living the life I've created. There is no need to banish myself for having depression. No need to criticize myself when my mood sinks low.

I used to approach depression as an enemy. I eventually named it The Grim Reaper and learned how to 'push' it out of my mind. When I couldn't get rid of it, I learned how to keep myself safe. ... I'm realizing that it may be with me for the rest of my life.

... Depression remains a vulnerability that I waltz with, but it no longer defines who I am. It is an Achilles heel, a limp, not a trademark ...

41.5

Closing Remarks

There are three entirely different perspectives from people experiencing symptoms of depression. These experiences are recollections that were written by the patients themselves in hope of helping others understand major depressive disorder. Therefore, these histories provide unusual personal accounts, which relate the patients' viewpoint of their own problems, without the analytical interpretation of a therapist or psychiatrist. The interpretation of these accounts is limited by our inability to obtain more details, which would usually be feasible if one was conducting an interview.

In *experience 1*, Mr. Burgieres is a highly insightful and successful businessman. He describes himself as an accomplished CEO in a Fortune 100 company. His initial experience with depressive symptoms appeared to be associated with ruminative thoughts and anxieties regarding his business, to the point that he was physically exhausted and required hospitalization. It is unclear if his precipitating stressor included the highly demanding job, but it is likely that it was related to the events connected with his wife's diagnosis of breast cancer. Mr. Burgieres does not describe how he or his family coped with his wife's serious medical condition and treatment. Those were certainly stressful and difficult events for his nuclear family. He does not mention his wife's illness until later in his account. He also does not describe any details about his family or social life in the first part of his history. When Mr. Burgieres had recurrent depressive episodes it appeared that he was not aware of any precipitating stressors, but he later gave the background supporting history that his children were growing up and had reached an age that they had already left or were leaving home and his wife had been battling breast cancer for six years. Mr. Burgieres may have intellectualized his fears of losing his supportive family, which may have been a contributing precipitator to a full-blown depressive episode. Intellectualization is a common defense mechanism used to help cope with difficult situations that provoke emotions such as fear and anxiety. It reduces the fear and anxiety by repressing the emotions connected with the situation. Unfortunately, the emotions cannot be repressed indefinitely for most people.

It seems that at some level Mr. Burgieres was aware of the changes that he needed to make to better his life. Before his illness, his identity seemed to have been predominantly reflected by his personal successes with his jobs and his financial accomplishments. Later he realized that he needed more personal growth and support from his family and friends to be able to cope with difficult life situations and to overcome his depression. Medications and therapies were helpful, and with the support of his family, his work, and peers who had similar experiences with depression, he has been able to break the cycle of depression and live a more stable and healthy life.

In *experience 2*, Ms. Bonds attempted suicide by overdosing with medications after suffering from a severe depressive episode that had lasted for almost two years. It seems that she had previous depressive episodes that resolved spontaneously. Her symptoms included lethargy, anorexia, hopeless/helpless thoughts,

and recurrent thoughts of wanting to escape everything by death. She was later diagnosed with bipolar disorder, which was confirmed by a medication-induced manic episode. Interestingly, Ms. Bonds related her worst depressive episode after having a hysterectomy. She felt she may have been suffering from a 'hormonal imbalance'. We do not know the details regarding her surgery, whether or not she had an oophorectomy, or whether she was receiving hormone replacement therapy after surgery. In any case, it has been well documented that hormonal changes such as those experienced during the peri and post menopausal period can precipitate depressive and psychotic episodes in vulnerable individuals [12, 13]. It is very likely that Ms. Bonds has a genetic predisposition for an affective disorder, which was triggered by hormonal changes. The etiology of bipolar disorder is multifactorial; nevertheless, there appears to be a genetic component, similar to that in major depressive disorder, that increases an individual's chance of suffering from this disorder.

Ms. Bonds describes the struggle and the shame of recognizing her illness after many years of denial and multiple hospitalizations. When she finally came to terms with it, she was treated with appropriate medications, psychotherapy, and social support, which has helped her become an independent and functional person in today's society. Despite all this however, she has had one relapse of depression – but is better able to cope with it now that she is more accepting of her illness.

In *experience 3*, Ms. Blauner reported a long history of suffering from depression since she was 14 years old. Some of her depressive symptoms included decreased concentration, increased crying spells, hypersomnia, and suicidal thoughts, with three suicide attempts by overdosing with medications. She was also diagnosed with posttraumatic stress disorder (PTSD) and borderline personality disorder. It is very common for patients suffering from depression to have comorbid illnesses such as an anxiety disorder and/or a personality disorder. Treatment becomes more difficult because of the complexity of these overlapping illnesses. It is sometimes nearly impossible to decipher the chronology of each disorder when several diagnoses co-exist. In Ms. Blauner's case, although we don't know the specifics regarding her psychiatric history, it appears that she may have suffered a traumatic experience as a child that may have been an integral component in the development of PTSD and borderline personality disorder. Subsequent depressive symptoms (which are very common in both illnesses) may have started thereafter. Treatment for a patient with only unipolar major depression is not necessarily the same as treatment for someone, who suffers from co-morbid depression, PTSD, and borderline personality disorder. She was given antidepressants, which were helpful, but she also needed psychotherapy specific for her early traumatic experiences and to help her cope with the effects of her PTSD.

All three patients described their initial feelings of denial and at times shame when they were diagnosed with depression. They also reported their frustrations with multiple failed medication and long therapy trials. In the end, they have come to terms with their disorder and accepted their illness and are able to maintain a functional lifestyle with proper treatment and support.

References

- 1 ROBINS, L. N., Psychiatric Disorders in America. In REGIER, D. A. (Ed.), *The Epidemiologic Catchment Area Study*. New York: The Free Press, 1990.
- 2 BLAZER, D. G., et al., The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am. J. Psychiatry* 1994, 151, 979–986.
- 3 PINCUS, H. A., PETTIT, A. R., The societal costs of chronic major depression. *J. Clin. Psychiatry* 2001, 62, Suppl. 6, 5–9.
- 4 ASSOCIATION, A. P., Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington DC: American Psychiatric Association, 1994.
- 5 SULLIVAN, P. F., NEALE, M. C., KENDLER, K. S., Genetic epidemiology of major depression: review and meta-analysis. *Am. J. Psychiatry* 2000, 157, 1552–1562.
- 6 KENDLER, K. S., et al., Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am. J. Psychiatry* 1995, 152, 833–842.
- 7 FREUD, S., Mourning and Melancholia. Vol. 11. London: Penguin Books, 1917.
- 8 BAKER, H. S., BAKER, M. N., Heinz Kohut's self psychology: an overview. *Am. J. Psychiatry* 1987, 144, 1–9.
- 9 BALDESSARINI, R. J., Current status of antidepressants: clinical pharmacology and therapy. *J. Clin. Psychiatry* 1989, 50, 117–126.
- 10 KATZELNICK, D., et al., Predictors of adequate dose and duration of antidepressant medication for depression in an HMO, in New Clinical Drug Evaluation Unit. Boca Raton, 37th meeting, FL, 1997.
- 11 HINRICHSEN, G. A., Recovery and relapse from major depressive disorder in the elderly. *Am. J. Psychiatry* 1992, 149, 1575–1579.
- 12 LEHMANN, S. W., Psychiatric disorders in older women. *Int. Rev. Psychiatry* 2003, 15, 269–279.
- 13 MACQUEEN, G., CHOKKA, P., Special issues in the management of depression in women. *Can. J. Psychiatry* 2004, 49 (3 Suppl. 1), 27S–40S.

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