Current Schizophrenia

Second Edition

Editors
Martin Lambert
Dieter Naber

CURRENT

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Dedication

This book is dedicated to Anna Joelle and Gabriele.

Contents

Author biographies

Martin Lambert performed his psychiatric training at the Department of Psychiatry and Psychotherapy at the University Medical Centre in Hamburg, Germany. During his training, Dr Lambert spent 2 years at the Early Psychosis Prevention and Intervention Centre (EPPIC) as a Research Fellow of the University of Melbourne. He is an Associate Professor of Psychiatry at the University of Hamburg where he heads the Psychosis Centre in which the Psychosis Early Detection and Intervention Centre (PEDIC) is based. Dr Lambert's current research interests include the pharmacological treatment of schizophrenic and patients with first-episode psychosis and, especially, aspects of integrated care, remission and recovery, quality of life and subjective wellbeing. He is also involved, in cooperation with the ORYGEN Youth Health and Research Centre in Melbourne, in research focused on the treatment and outcome of first-episode psychosis and first-episode bipolar disorders. During his time in Australia, he worked as co-editor of the *Australia and New Zealand Guidelines for the Treatment of Schizophrenia*. He has been editor and author of several books about schizophrenia and has published articles in various research fields in schizophrenia and first-episode psychosis.

Dieter Naber has been Director of the Psychiatric University Hospital in Hamburg, Germany, since 1995. After studying medicine in Göttingen and Bonn, Germany, Professor Naber worked at the Psychiatric Hospital of the University of Munich, Germany from 1977 to 1995 as a ward doctor then senior physician. In 1987, he gained a postdoctoral lecturing qualification with his lecture 'The etiological and therapeutic significance of endorphins in endogenous psychosis'. Professor Naber carried out research work during two periods at the National Institute of Mental Health, in 1978–1980 and again in 1984–1985. His current research concentrates on neuroleptic long-term treatment, efficacy and side effects of second-generation neuroleptics, and the subjective effects of neuroleptics.

Eóin Killackey is a Senior Research Fellow and Clinical Psychologist at ORYGEN Research Centre and the Department of Psychology at the University of Melbourne. He completed his doctorate at Deakin University in 2000. He has worked as a clinical psychologist in adolescent and adult public mental health settings. His research is primarily in the area of psychological and pychosocial interventions in first-episode psychosis, specifically functional recovery in first-episode psychosis with particular emphasis on vocational rehabilitation.

He is also interested in evidence-based interventions in mental health and barriers to their implementations. He is a founder of the International First Episode Vocational Recovery group and was recently awarded the ASPR Organon Prize for 2008.

Pat McGorry is currently Professor/Director of the ORYGEN Youth Health and Research Centre, which is linked to the University of Melbourne and the North Western Mental Health in Melbourne, Australia. He has contributed significantly to research in the area of early psychosis over the past 16 years. During this time, he has played an integral role in the development of service structures and treatments specifically targeting the needs of young people with emerging or first-episode psychosis. In the past 2 years, he has published over 50 articles and chapters. Professor McGorry is currently the President of the International Early Psychosis Association and an Executive Board Member of the International Society for Psychological Treatments in Schizophrenia and Related Psychosis. He is also a member of the organizing committee of the World Psychiatric Association Section on Schizophrenia, the Advisory Board of the University of California, Los Angeles (UCLA) Center for the Assessment and Prevention of Prodromal States (CAPPS), the editorial board of *Schizophrenia Research* and the advisory editorial board of the *Journal of Psychiatrie*, *Sciences Humaines*, *Neurosciences*.

Dan Lubman is a Consultant Psychiatrist and Associate Professor at the ORYGEN Research Centre, University of Melbourne, where he heads a clinical research unit that investigates problematic substance abuse and co-occurring mental health issues in young people. This includes a number of pharmacological and psychological treatment trials in psychosis and depression, as well as neuropsychological and neuroimaging studies examining the neurobiology of addiction. His work includes studies investigating comorbidity within primary care, drug treatment and mental health settings, as well as the development of treatment programmes for young people with co-occurring mental health and substance abuse issues. Dr Lubman is Chair of the Royal Australian and New Zealand College of Psychiatrists' Section of Addiction Psychiatry, which is responsible for overseeing drug and alcohol training and policy for the College. He is an advisory board member of Addiction Neuroscience Network Australia, the National Cannabis Prevention and Information Centre, and the National Drug Research Institute. He has lectured widely on the neurobiology of addiction, as well as issues related to dual diagnosis and substance abuse in young people.

Steffen Moritz is an active researcher in the fields of neuropsychology and cognition with a main focus on schizophrenia and obsessive–compulsive disorders. After achieving his masters in psychology in 1997, he became a research assistant at the Psychiatric University Hospital of Hamburg, Germany. Under the supervision of Professor Naber, Dr Moritz is in charge of the clinical neurocognitive unit of the hospital. After achieving his PhD in 1999 and working as a senior research fellow, Dr Moritz has gone on to be Associate Professor. As well as schizophrenia and obsessive–compulsive disorder, his active areas of research are depression and post-traumatic stress disorder. Together with Dr Todd S. Woodward from Vancouver, he has developed a metacognitive training programme for schizophrenia patients, which is now available in five different languages.

Ingo Schäfer studied medicine and public health at the Universities of Tübingen, Bordeaux, Lausanne and Hamburg, and the Hamburg University of Applied Sciences. He received his doctoral degree from the University of Hamburg in 2002. Since 2001 he has been working as a research fellow and clinical lecturer at the Department of Psychiatry and Psychotherapy and the Centre for Interdisciplinary Addiction Research at the University Medical Centre Hamburg–Eppendorf. He is associate lecturer for public mental health at the Hamburg University of Applied Sciences. His clinical and research interests are the treatment of patients with comorbid substance abuse and psychiatric disorders, trauma-related disorders and treatment-resistant schizophrenia. In the last 10 years, he has continuously been involved in research on the consequences of psychological trauma in different populations and is leading various projects in that domain.

Tim Lambert is Professor and Chair of Psychological Medicine at the Concord Medical School at the University of Sydney, Australia. He also holds an appointment as the head of Schizophrenia Treatment and Outcomes Research at the Brain and Mind Research Institute in Sydney. He fulfills clinical duties for the Sydney South West Area Health Service in Sydney at Concord Centre for Mental Health, involving three 'centre activities' – Cardiometabolic Health in Psychosis; Centre of Excellence in Adherence; and Multidimensional Incomplete Recovery (treatment resistance). Professor Lambert has a portfolio of interests spanning clinical psychosis research, outcomes research, training and education. Among these his current interests focus on services research (pharmacoepidemiology); the clinical pharmacology of (i) depot antipsychotics (first- and second-generation) and (ii) the second-generation

antipsychotics (with particular reference to aspects of risk–benefit analyses, the applied clinical pharmacology of antipsychotic switching); physical comorbidity of the psychotic disorders (focusing on metabolic syndrome); and incomplete recovery (treatment-resistant schizophrenia), among others. He has been a principal in the development of a number of clinical practice guidelines, treatment algorithms and consensus documents (the Australian guidelines for schizophrenia – RANZCP Schizophrenia CPG – and Diabetes and the Antipsychotic Disorders, among others). At present he is chairing the Australian consensus development group for TRS. His unit utilizes its evaluation and research activities to produce educational and training materials for mental health workers. Its CD-ROM, DVD and other new media products are used in many parts of the world. Professor Lambert is a regularly invited lecturer, clinical trainer and industry consultant throughout Asia, Australasia, Europe and North America. He is a member of a number of international and national advisory boards concerned with antipsychotic treatments.

Philippe Conus is Médecin Adjoint in the Department of Psychiatry, Centre Hospitalier Universitaire Vaudois in Lausanne, Privat Dozent at the University of Lausanne, Switzerland and Senior Lecturer at the University of Melbourne, Australia. He completed his training for both internal medicine and psychiatry in Lausanne. From 2000 to 2003, he worked as Consultant Psychiatrist in the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne where he developed a specialized programme for early intervention in affective psychoses and a clinical research project on first-episode mania. Since returning to Switzerland he has been leading an inpatient unit that specializes in schizophrenia spectrum disorders and a specialized integrated early intervention programme for psychosis (Treatment and Intervention in the early Phase of Psychosis – TIPP). His research interests cover clinical intervention in early psychosis and early phase of bipolar disorders, as well as neurobiological mechanisms involved in the development of schizophrenia, and pharmacogenetic determinants of side effects of second-generation antipsychotics.

Preface

It is with pride and pleasure that we have produced the second edition of *Current Schizophrenia*. In line with the first edition, this publication provides valuable information and guidance for those who are involved in the care of people who have schizophrenia and their relatives. The primary intention of the book is again to provide a tool that is helpful in the treatment and care of individuals with schizophrenia and easy to use in daily clinical practice.

Many experts have devoted numerous hours to this project. Special thanks go to Dr Eóin Killackey, Associate Professor Dan Lubman, Associate Professor Steffen Moritz, Dr Ingo Schäfer, Associate Professor Philippe Conus and Associate Professor Tim Lambert, who have been directly involved in writing and/or reviewing various parts of the book. In addition, Pat McGorry has participated indirectly through his work on the *Australia and New Zealand Guidelines for the Treatment of Schizophrenia*.

It is exciting to see that awareness of schizophrenia has improved and continues to grow, hopefully at a rapid pace. This is important for obtaining support for research and, of course, for those who suffer and their families. Better understanding throughout society in general will help all of those affected by schizophrenia, bringing them empathy and compassion, and maybe even saving some lives. All of the contributors to this book hope that it will help with some of the issues and challenges that schizophrenia presents, and improve the quality of life of patients and their relatives. In the interest of furthering the knowledge of schizophrenia, the authors welcome any constructive criticism and comments on the contents of this book.

Chapter 1

Introduction

Advances in pharmacotherapy and psychosocial interventions continue to improve the success of schizophrenia treatment. Early detection and intervention in people with, or at risk of, psychosis give patients and their families hope for a better course of illness and an improved outcome. The interdisciplinary approach, combining pharmacotherapy and psychosocial interventions, markedly increases the chance of long-lasting remission and recovery. However, a cure for schizophrenia has yet to be found. Research, particularly in the past decade, has revealed some of the biological and genetic facets of the origins of schizophrenia, and this has contributed to the better quality treatment that is now available.

This book aims to provide a short but detailed overview of current standards of care in schizophrenia. It takes into consideration several treatment recommendations proposed in published guidelines for schizophrenia, eg the National Institute for Health and Clinical Excellence (NICE) guidelines, and the American (APA), Canadian (CPA) and Australian guidelines for schizophrenia (RANZCP; see Schizophrenia guidelines in Further reading, page 147) . A major problem with guidelines such as these is the difficulties encountered in translating them into daily clinical practice. Therefore, the fundamental aim of this book is to present the guidelines as clearly as possible in the context of relevant clinical treatment issues. The book does this with the help of figures that provide the clinician with algorithms and summaries of the most important information required for the practical treatment and theoretical understanding of schizophrenia.

The book is divided into three main chapters: Current topics, Organization of care and Quick reference. Chapter 2 (Current topics) brings together issues of recent interest and includes sections on treatment of special populations and clinical problems. Chapter 2 has been expanded considerably. In addition to the pre-existing sections on first-episode psychosis, suicidality and cognitive dysfunctions in schizophrenia, there are now sections on non-adherence and service disengagement, on comorbid substance abuse disorders, childhood trauma, and on new antipsychotics and new antipsychotic formulations.

Chapter 3 (Organization of care and treatment) provides reviews of the most important treatment recommendations in schizophrenia, including the following:

- Acute and long-term treatment guidelines in first- and multiple-episode patients, including detailed pharmacological and psychosocial treatment recommendations
- Guidelines for the pharmacological and psychosocial management in special clinical situations, ie behavioural emergencies and treatment-resistant schizophrenia
- The management of important psychopharmacological side effects
- The most recommended psychosocial interventions.

Chapter 4 (Quick reference) provides short overviews of the epidemiology, aetiology and course of schizophrenia, as well as short reviews of clinical presentation and diagnosis.

At the end of the book there is a section on Resources, which includes websites that provide further information for clinicians, patients and relatives, a section on useful assessment scales, which gives an overview of the most important measurement scales in schizophrenia and, finally, Further reading, which brings together the key references. To facilitate easy access, Further reading is sorted alphabetically by topic.

Chapter 2

Current topics

2.1 First-episode psychosis

Eóin Killackey

First-episode psychosis (FEP) presents a great opportunity to provide good quality interventions, positively engage the patient in treatment of the psychosis and minimize the secondary disability that can stem from psychosis. Recently published guidelines by the International Early Psychosis Association have informed the following summary of the interventions for FEP.

Two important dimensions of interventions for FEP are the timing of the intervention (and therefore the duration of untreated psychosis – DUP) and the quality of the intervention (the sustained provision of comprehensive phase-specific treatment). Although beyond the scope of this book, situations in which there is identification and treatment of people at risk of psychosis have resulted in the reduction of the DUP to zero.

Often, as a result of both the nature of onset of psychosis and resource issues in mental health-care systems, there are prolonged delays in initiating effective treatment for FEP. Although there was previously some debate, prolonged DUP is now known to be independently associated with poorer response and outcome. The clinical staging model being applied to mental illnesses suggests that identification of patients in the earliest phases of psychotic disorders allows for more optimal treatment, and is likely to reduce the burden of disease while it is active. Any improvements in long-term outcome should be seen as a bonus, rather than as a prerequisite for improving clinical standards during early illness.

The FEP tends to be more responsive to treatment than subsequent episodes; later phases of illness and syndromes, and therefore diagnoses, tend to be unstable and may evolve over time. The umbrella term 'psychosis' accommodates this syndromal flux and comorbidity, and allows treatment to be commenced for all prominent syndromes before a stable diagnosis, such as schizophrenia, can be

or has to be applied. Thus, whether core schizophrenia can be diagnosed is not crucial for effective treatment in FEP. A notable example is that cannabis use is common in FEP but its presence can cause confusion and delay in treating the psychotic episode. Significant cannabis use appears to be a risk factor for the onset of schizophrenia, as well as an aggravating factor for the subsequent course. It is crucially important, therefore, that there is no split between substance abuse and mental health services. Rather, a unified approach is called for. Figure 2.1 gives the recommendations for treatment of FEP.

As stated, FEP is a prime opportunity for intervention. The earlier and more appropriately this intervention begins the better. An optimal and sustained intervention at this point has the greatest possibility of reducing the secondary disability wrought by psychosis. In addition, it increases the probability of better quality-of-life outcomes for the patient. To achieve these goals, an optimistic framework focused on recovery is required, rather than a mindset that concentrates on chronicity and disability. Good practice in this area is to stay abreast of the development of pharmaceutical and psychological therapies targeted at FEP, incorporate evidence-based guidelines developed around FEP into clinical practice, and convey optimism and hope to those experiencing FEP and to their families and friends.

2.2 Cognitive dysfunctions in schizophrenia

Steffen Moritz

Many patients with schizophrenia display severe neurocognitive dysfunction in a wide variety of domains, most notable memory and executive functioning. These dysfunctions are in most cases present at the first exacerbation but, unlike Kraepelin's initial observations at the end of the nineteenth century do not necessarily progress during the course of the illness, beyond age-related decrement. Although neurocognitive deficits are not obligatory for diagnosis, the necessity for their identification and treatment in schizophrenia is increasingly acknowledged.

In the past decade, a large body of empirical evidence has been accumulated showing that cognitive disturbances are important determinants of functional outcome variables such as social relationships and work status. For example, in a meta-analysis, it was demonstrated that memory dysfunction is a particularly strong predictor of functional outcome in schizophrenia. In addition, there is increasing recognition of the impact of neuropsychological dysfunction on a number of treatment-related variables, such as insight and coping skills.

Recommendations for treatment of first-episode psychosis (FEP)

- Strategies to improve the treatment of FEP include better mental health literacy, more informed primary care, and greater responsiveness of public and private psychiatry to cases that are potentially FEP. Community-wide education systems should be developed to improve understanding of how psychotic disorders emerge in a previously healthy person, and to inform people how to seek and obtain effective advice, treatment and support.
- A high index of suspicion and a low threshold for expert assessment should be set for an FEP.
- Proactive retention of patients should be the aim of specialist mental health services throughout the first 3–5 years of illness, combining developmental (youth) and phase-specific perspectives. Otherwise, entry and retention within specialist mental health services are often based on a reactive, crisis-oriented model in which patients must reach a threshold of behavioural disturbance, risk, disability or chronicity before they are retained. This model is a poor use of resources and creates unnecessary trauma, demoralization and therapeutic nihilism in patients, families and clinicians.
- Initial treatment should be provided in an outpatient or home setting, if possible. This can minimize the trauma, disruption and anxiety of the patient and family, who are usually poorly informed about mental illness and have fears and prejudices about inpatient psychiatric care. Inpatient care is required if there is a significant risk of self-harm or aggression, if the level of support in the community is insufficient or if the crisis is too great for the family to manage, even with home-based support.
- Inpatient care should be provided in the least restrictive environment. Optimal inpatient units should be streamed by phase of illness and developmental stage, and be relatively small in size and staffed adequately, so that one-to-one nursing of highly distressed, suicidal or agitated young people is possible, without locking sections of the unit or secluding the patient, unless this is absolutely necessary. The use of traditional psychiatric 'intensive care', a pragmatic intervention that lacks a solid evidence base, is especially traumatic for these patients. Where streaming is not possible, a special section may be created in a general acute unit for young recent-onset patients.
- Pharmacological treatments should be introduced with great care in medication-naïve patients, to do the least harm while aiming for the maximum benefit. Appropriate strategies include graded introduction, with careful explanation, of low-dose antipsychotic medication, plus antimanic or antidepressant medication, where indicated. Skilled nursing care, a safe and supportive environment, and regular and liberal doses of benzodiazepines are essential to relieve distress, insomnia and behavioural disturbances secondary to psychosis, while antipsychotic medication takes effect.
- First-line use of second-generation antipsychotic medication is recommended on the basis of better tolerability and reduced risk of tardive dyskinesia. In the longer term, the risk–benefit ratio may change for some patients, eg if weight gain or sexual side effects associated with the second-generation agents develop. First-generation antipsychotic medications may then be one of the options considered.
- Initial assessment should include a baseline computed tomography (CT) scan, neurocognitive screen, neurological examination for movement disorder, electrocardiogram (ECG), body massw index (BMI) and fasting serum glucose.

Figure 2.1 Recommendations for treatment of first-episode psychosis (FEP) ***(continued overfeaf)***

Recommendations for treatment of first-episode psychosis (FEP) (*continued*)

- Psychosocial interventions, especially cognitive–behavioural therapy (CBT), are an important component of early treatment, providing a humane basis for continuing care, preventing and resolving secondary consequences of the illness, and promoting recovery. CBT may also be helpful for comorbid substance abuse, mood and anxiety disorders, and improving treatment adherence.
- Families and, whenever possible and appropriate, other members of patients' social networks should be supported actively and educated progressively about the nature of the problem, the treatment and the expected outcomes. If there are frequent relapses or slow, early recovery, a more intensive and prolonged supportive intervention for families is required.
- If recovery is slow and remission does not occur despite sustained adherence to two antipsychotic medications (at least one of which is a second-generation antipsychotic) for 6 weeks each, early use of clozapine and intensive CBT should be considered seriously.
- If suicide risk is prominent or persistent, early use of clozapine should also be considered.

Figure 2.1 Recommendations for treatment of a first episode of psychosis (FEP) *Continued*

Neurocognitive dysfunction may also exert a negative impact on compliance with medication. For example, several psychotropic agents, especially benzodiazepines and anticholinergic medications, the latter often being prescribed when giving conventional neuroleptics, are known to have potential adverse effects on neurocognition in some patients. When such side effects remain unnoticed, drug discontinuation may occur, especially if the patient considers that the adverse side effects outweigh the benefits of drug treatment.

Evaluation of negative medication effects is also essential given that many patients are already cognitively impaired before treatment, so that neurocognitive resources cannot be assumed to be sufficient for effective psychotherapeutic or psychoeducational treatment. Memory problems and dysfunctions in abstract logical thinking may severely limit the outcome of insight-based psychotherapeutic interventions. A compromised capacity to store information, as evidenced by many psychiatric patients, as well as older patients with or without mental illness, may also lead to forgetfulness about taking medication and the purpose and contents of psychotherapy, forgetting about the latter being a further risk factor for non-compliance.

Once neurocognitive problems have been detected, there are a number of strategies that can be used to deal with such dysfunctions in psychiatric patients. With regard to memory problems, clinicians should repeat essential information regularly, check from time to time that patients are indeed grasping the core aspects of therapy, give the most essential information in written form (especially medication and dosage) and, when appropriate, involve relatives

in the session so that they can remind patients in their own homes. Patients with decreased vigilance benefit from more frequent but shorter therapeutic sessions. In addition there is evidence that cognitive remediation programmes are efficacious for some patients. The administration of second-generation antipschotics may ameliorate some neurocognitive symptoms, or at least may not aggrevate neurocognitive dysfunctions. However, in view of conflicting new evidence on the neurocognitive effects of atypical antipsychotics, a seemingly closed discussion has been reopened. Clinicians may want to evaluate whether medications that are potentially harmful to memory, such as benzodiazepines and anticholinergic agents, are still necessary or could at least be diminished in dosage. In any case, the presence of memory and other neurocognitive problems should not be disregarded as a minor problem given their possible impact on compliance with medication, insight, treatment and functional outcome. In addition, cognitive dysfunctions may cause increased stress at work or school, because many jobs necessitate intact selective attention, vigilance and memory. To compensate for neurocognitive problems, the impaired patient must devote more effort to a task than individuals whose cognitive functioning is normal. However, this causes stress, a major risk factor for renewed exacerbation of psychiatric symptoms according to the largely acknowledged vulnerability–stress model of psychiatric illness. This creates a vicious circle when job demands are not suited to the patient's cognitive abilities.

2.2.1 Cognitive biases and metacognitive training in schizophrenia

In addition to neurocognitive impairment, cognitive biases (or cognitive distortions) are increasingly being investigated. This line of research encompasses a wide variety of response styles, such as jumping to conclusions (eg hasty decision-making), deficits in theory of mind (failure to empathize with others and to deduce motifs), a bias against disconfirmatory evidence, overconfidence in errors, negative self-schemata and monocausal attributional styles (Fig. 2.2). There is evidence that these styles are related to the emergence and maintenance of psychotic symptoms, especially delusions, in concert with other factors. Importantly, these cognitive distortions seem to precede psychotic breakdown and the patient is not fully aware of them, ie many patients lack metacognitive insight into these problems. Hence, a training programme, entitled metacognitive training (MCT), has been developed (Fig. 2.2). Its eight modules aim to raise the patient's awareness of these distortions and to prompt the patient to critically reflect on, complement and change his or her current repertoire of problem solving. Thus, its main purpose is to change the 'cognitive infrastructure' of delusional ideation. As psychosis is rarely an instantaneous incident, changing

Metacognitive training: summary of modules

Module	Target domain	Description of core exercises
1. Attribution: blaming and taking credit	Self-serving bias versus depressive attributional style	Different causes of positive and negative events are examined, eg 'friend was talking behind your back'; dominant interpretation: 'friend is not trustworthy' (blaming others); alternatives: 'I have done something bad' (blaming self), 'she is preparing a surprise party for my birthday' (circumstances). Explanations that take into account various causes should be preferred over mono-causal ones. Negative consequences of self-serving attribution are repeatedly highlighted
2. Jumping to conclusions: I	Jumping to conclusions/ liberal acceptance/ bias against disconfirmatory evidence	Motifs contributing to hasty decision-making are discussed and disadvantages stressed. Fragmented pictures are shown that eventually display objects: premature decisions often lead to errors, emphasizing benefits of cautious data gathering. Ambiguous pictures are displayed: a quick survey leads to omission of details, demonstrating that first impressions often reveal only half the truth
3. Changing beliefs	Bias against disconfirmatory evidence	Cartoon sequences are shown in reverse order, which increasingly disambiguate a complex scenario. After each picture, patients are asked to (re-)rate the plausibility of four interpretations. With some pictures, the initially most likely interpretation prevails, but with others patients are 'led up the garden path'. Exercises demonstrate value of withholding strong judgements until sufficient evidence is collected. Encourages maintenance of open attitude towards counter-arguments and alternative views
4. To empathize: I	Theory of mind first order	Facial expression and other cues are discussed for relevance to social reasoning. Pictures of human faces are presented: the group guesses what the depicted character(s) may feel. The correct solution often violates a first intuition, demonstrating that relying on facial expression alone can be misleading. In part 2, cartoon strips are shown that must be either completed or brought into correct order demonstrating that social interference requires multiple cues
5. Memory	Overconfidence in errors	Factors that foster/impair memory acquisition are discussed first, eg common false memories are presented. Then complex scenes (eg beach) are displayed with two typical elements removed (eg towel, ball). Owing to logical inference, 'gist'-based recollection and liberal acceptance, many patients falsely recognize 'lure' items in a later recognition trial. Exercises highlight constructive rather than passive nature of memory. Teaches differentiation between false and correct memories by means of the 'vividness heuristic'

Figure 2.2 Metacognitive training: summary of modules ***(continued opposite)***

Metacognitive training: summary of modules (*continued*)

Module	Target domain	Description of core exercises
6. To empathize: II	Theory of mind second order/ need for closure	Different aspects guiding theory of mind are discussed with respect to both their heuristic value and fallibility for social decision-making. Cartoon sequences are then presented, and the perspective of one of the protagonists is considered, which involves discounting knowledge available to observer but not available to protagonist. For most sequences, no definitive solutions can be inferred, which is unsatisfactory for patients with an enhanced need for closure
7. Jumping to conclusions: II	Jumping to conclusions/ liberal acceptance	As in module 2, disadvantages of quick decision-making are outlined with regard to events related and unrelated to psychosis. In exercises, paintings are displayed; the correct title must be deduced from four response options. On superficial inspection, many pictures tempt false responses
8. Mood and self-esteem	Mood and self-esteem	First, depressive symptoms, causes and treatment options are discussed. Then, typical depressive cognitive patterns in response to common events are presented (eg over-generalization, selective abstraction); the group is asked to come up with more constructive and positive ones. Conveys some strategies to help patients to transform negative self-schemata and elevate mood

Figure 2.2 Metacognitive training: summary of modules (*continued*)

the appraisal of one's cognitions and social environment may act prophylactically on psychotic symptoms. The modules are administered in the framework of a group intervention programme. Several studies assert the feasibility of this approach as well as its efficacy. The MCT can be downloaded cost free in several languages via www.uke.de/mkt.

2.3 Suicidality in schizophrenia

Suicide is the most frequent cause of death in patients with schizophrenia. Estimates of completed suicides by patients with schizophrenia range from 4% to 13%, similar to the range seen in affective disorders. This is approximately four times higher than in the period 1913–60, which has been interpreted as suggesting that the suicide rate has risen markedly since the onset of deinstitutionalization. However, recent re-evaluation of previous studies has concluded that the suicide rate is in fact lower, at approximately 5%, and that this rate is 7–10 times higher than in the general population. Fifty per cent of individuals with schizophrenia either consider or attempt suicide. In the prodromal and/or untreated psychotic phase before first treatment contact, 5–15% of patients

with schizophrenia attempt suicide. The high proportion of suicide attempts that result in death can be explained by the high autoaggression of the attempts.

In general, it can be assumed that psychoreactive and social consequences of schizophrenia are the primary causes of suicidal behaviour, especially when accompanied by a depressive affect. There are various risk factors for suicide attempts and completed suicide in schizophrenia; some of them are similar to those in the general population, and others are specific to the disorder itself (Fig. 2.3). Most patients fulfil several of these risk factors concurrently, so there are certain risk constellations that are especially predictive for suicidal behaviour. For example, a high risk was found for single, unemployed males with severe forms of schizophrenia, previous suicide attempt(s), and concurrent depressive episode and/or substance abuse disorder. In summary, the main factors to be taken into account when assessing risk of suicidal behaviour in patients with schizophrenia are previous suicide attempts, recent or past affective symptoms or syndromes, recent suicidal thoughts, threats or behaviour, poor adherence to treatment, fears of the impact of illness on patient's life and substance abuse.

Prevention of suicidal behaviour and suicide is likely to result from ongoing community and professional education, early detection and early intervention, as well as active treatment of the underlying causes. The last mainly includes treatment of affective symptoms and syndromes, improving adherence to

Risk factors for suicidal behaviour

- Previous suicide attempts and actual suicidal ideation and plans
- Recent depressive episode and/or lifetime major depressive episode(s), especially in combination with hopelessness
- Long duration of untreated psychosis (DUP), possibly also long duration of untreated illness (DUI)
- Severe forms of the disorder, paranoid subtype with suspiciousness and agitation in the absence of negative symptoms, impulsivity
- Comorbidity: substance abuse disorder, obsessive–compulsive disorder
- Poor adherence to treatment
- Socially isolated single males, no support, no occupation, homelessness, present life events
- Relatively higher premorbid functioning before onset of psychosis (higher education), relatively higher cognitive functioning including intelligence and self expectations, greater insight into illness, but also problem-solving deficits
- In first 10 years of illness, frequent short hospitalizations in previous year, first 6 months after discharge from hospital
- Repeated unsuccessful antipsychotic treatment attempts with side effects (especially akathisia)

Figure 2.3 Risk factors for suicidal behaviour

treatment, use of medication that may have special anti-suicidal effects, and ongoing special vigilance when patients have a number of risk factors, especially if the impact of the disease on the patient's functional level and quality of life is significant.

The optimal management of suicidality in schizophrenia involves early detection and regular assessment of suicidal ideation, immediate and effective interventions to ensure safety, selection of psychosocial interventions based on the patient's needs, and pharmacotherapy directed primarily at psychotic and depressive symptoms (Fig. 2.4). Pharmacological treatment for suicidality should consist of additional supportive medication to alleviate the emotional pressures. This alleviation can be achieved with sedative or anxiolytic drugs, such as benzodiazepines or antipsychotic drugs or, particularly in the long term, clozapine. Patients for whom clozapine is appropriate are those who have made serious suicide attempts on other medications, and are likely to follow the generally accepted guidelines for taking clozapine. If patients refuse clozapine or are unable to tolerate it, there is no evidence to assist in making the choice among the other antipsychotic drugs. Another of the second-generation antipsychotic drugs would be superior to a first-generation agent, based on their greater tolerability, enhanced effect on depression and possible lower risk of non-compliance. The pharmacotherapy of the underlying disorder should also be re-evaluated with respect to efficacy and tolerability.

2.4 Non-adherence in schizophrenia

Adherence can be defined as 'the extent to which a person's behaviour coincides with the medical advice that he or she has received'. In patients with schizophrenia, non-adherence has to be separated into non-adherence with either the medication or the complete treatment regimen. The latter, so-called 'service disengagement', is defined as complete drop-out from a psychiatric service despite ongoing need of treatment.

Rates of non-adherence to antipsychotic medications range from 20% to 89%; the median non-adherence rate was reported to be 55% within 1 year, and even higher risks were reported for FEP patients. Within the three different categories of adherence most patients are partially adherent: full (30%), partial (45%), non (25%). In epidemiological cohorts without informed consent bias, approximately 20% of patients are complete refusers of (long-term) medication. Rates of service disengagement range from 20% to 30% within 1 year of treatment in a specialised first-episode service; disengagement rates in non-specialised services with no assertive community treatment are possibly near to 50% within 1 year. There is a large overlap between both non-adherence

Recommendations for the management of suicidal behaviour in schizophrenia	
Early detection and regular assessment	Risk of suicide/suicidal behaviour is significant, matching affective disorders. Be alert to subtle hints of suicidality, particularly in high-risk periods. Suicide in schizophrenia is often not impulsive as is commonly believed
Assessment of risk factors and risk constellations	Vital in management of suicidal behaviour. Includes, for example, initial assessment of duration/severity of suicide intent, previous suicidal ideation/attempt, mediating factors (both risk and protective factors; see Fig. 2.3), phase/severity of psychotic (eg command hallucinations) and associated symptoms (eg agitation), degree of subjective distress, level of affective disturbance, access to lethal means, supervision/support available, potential for treatment non-adherence or service disengagement, and patient's initial response to clinical interventions proposed. Check that patient has not made recent attempt that might require immediate treatment
Ensure immediate safety	Provide constant supervision and remove any potential means to self-harm until appropriate intervention has been decided upon
Decide on appropriate management plan	Determine who will be primary clinician and facilitate establishment of therapeutic alliance between patient and that clinician throughout high-risk period Liaise with patients' other treating clinicians, check interventions immediately available, consult with senior clinical staff if high suicide risk is determined. Liaise with carers about recent/past history of factors that might indicate increased suicide risk. Determine degree of supervision needed to minimize likelihood of a suicide attempt, balancing degree of suicide intent, willingness to comply, variability of mental state and reliability of the least restrictive options available. Decide on necessary treatments, negotiate options with the patient, eg hospitalization
Initiate management plan	**Supervision:** provide adequate level of supervision by staff/carers with clear instructions on risk, required degree of monitoring and frequency of clinical reviews, required responses if deterioration is observed, eg who/how to consult if problems arise **Safety:** remove access to means of self-harm, eg razors, knives, cords, guns, medications, poisons. Limit exposure to immediate stressors; if necessary, provide containment within safe setting, eg hospital, with clear instructions to carers about limitations on patient's freedom **Personal contact and counselling:** provide initial counselling and treatment while establishing rapport, understanding and trust; explore cognitions that influence level of suicidality; encourage understanding that suicide ideation is a transient though painful phenomenon related to illness factors, by instilling hope in recovery through treatment or therapeutic options; negotiate a suicide contract. **Initiate treatments:** reduce associated distress due to psychosis/suicidal ideation with anxiolytics (eg benzodiazepines) and/or antipsychotics. Attempt to influence psychosocial factors that might reduce suicidality, eg practical assistance with homelessness, access to social milieu

Figure 2.4 Recommendations for the management of suicidal behaviour in schizophrenia. ***(continued opposite)*** (Adapted from Power 1999; Mamo 2007.)

Recommendations for the management of suicidal behaviour in schizophrenia (*continued*)	
Provide optimal pharmacological treatment	Medication(s) to treat suicidality should fulfil four criteria: 1. Eliminate positive symptoms 2. Enhance quality of life through improved of depressive symptoms, anxiety and social functioning 3. Be free of extrapyramidal symptoms 4. Decrease substance use Clozapine has substantial effect on attempted suicide and completed suicide and should be considered in patients showing significant suicidal behaviour. Other second-generation antipsychotic drugs may be useful if clozapine contraindicated or otherwise undesirable
Review management	Regularly review and negotiate interventions above with patient, carers and other clinicians involved. Ensure clear lines of clinical accountability and decision-making

Figure 2.4 Recommendations for the management of suicidal behaviour in schizophrenia. (*continued*).

categories: approximately 50% of complete medication refusers subsequently become service disengaged.

Deviation from maintenance antipsychotic therapy and service disengagement place patients at risk for exacerbation of psychosis, and thereby at risk for symptomatic and functional illness deterioration and increased risk for suicidal attempts and completed suicide. The risk for relapse is approximately three to five times higher within a 5-year illness period when antipsychotic drug therapy is discontinued. Furthermore, within 4 weeks of non-adherence the risk of relapse is increased almost fourfold. Partial adherence, as opposed to agreed dosage reduction, is related to a comparable risk of relapse, especially in patients who are not in remission with respect to positive symptoms. The consequences of non-compliance-induced relapses are manifold; among others there is often:

- a need for higher antipsychotic dosages with higher side effect rates and subsequently a higher risk of further non-adherence
- a delay in reaching symptomatic remission, with a consequent need for prolonged inpatient treatment
- a high risk of development of incomplete remission within each relapse, with continuous positive and increasing negative symptoms, and deterioration of functioning.

Understanding the reasons for and causes of non-adherence in schizophrenia is a logical step towards improving management of this vast problem. However, there is a range of theories and concepts of non-adherence, a variety of relevant risk factors, and the known problem that professionals, carers and patients

do not have shared understanding of which of these factors are important in patients' behaviour with respect to therapy.

The literature describes numerous factors that contribute to non-adherence. According to one review there are factors that are consistently associated with non-adherence and factors that have shown mixed results or that were not consistently associated (Fig. 2.5). The factors consistently associated with medication non-adherence comprise most importantly a lack of development of insight during treatment, external factors such as insufficient patient support and the factors listed in Fig. 2.5. The few studies on service disengagement have identified lack of family support, persistent substance abuse during treatment, a lower severity of illness at service entry and lack of assertive treatment as risk factors.

These categories are helpful in providing an overview of the most relevant adherence factors. However, in clinical practice most patients fulfil several of these factors, the factors themselves fluctuate over time and they interfere with each other. For example, attitude towards medication interferes with medication side effects and both can change over time, the negative influence of comorbid substance use on antipsychotic response reduces the subjective efficacy–tolerability ratio, etc. Further complexity arises as a result of the fact that adherence attitudes and behaviours are related but are not necessarily the same: some patients like and take medication, others do not like medications

Risk factors related to non-adherence

Consistently associated with non-adherence
- No development of insight during treatment
- Negative attitudes towards medication and treatment in general
- No development of a positive therapeutic alliance during treatment
- Poor subjective wellbeing under pharmacological treatment (= subjective cost–benefit ratio of medication efficacy in relation to side effects)
- Poor aftercare planning and environment
- Shorter duration of illness
- Persistent comorbid substance use disorder during treatment

Mixed findings or not consistently associated with non-adherence
- Age, gender, ethnicity, marital status, education level
- Medication regimen complexity
- Cognitive impairment
- Type and route of medication
- Severity of symptoms
- Family involvement
- Presence of mood symptoms
- Higher antipsychotic dose

Figure 2.5 Risk factors related to non-adherence. (Data from Lacro et al 2002; Kikkert et al 2006.)

and do not take them, and others do not like but take medications. The outcome of this is that there is no single adherence intervention but rather a range of interventions, which should be matched to the specific challenges of the individual patient and have to be continuously adapted. Accordingly, there are several important aspects of treatment that have to be considered when planning a mixed-modality intervention (Fig. 2.6), including:

- **A positive therapeutic alliance:** interventions to improve adherence start with the first contact with the patient (and relatives), and the quality of first contact is of major importance for the development of a positive therapeutic alliance and thereby for close collaboration during ongoing treatment.
- **Shared decision-making** is an important part of this collaboration (Fig. 2.6)
- **A preventive approach** is also important in dealing with non-adherence, and assessment for this should start when the patient is reasonably stabilized (Fig. 2.6)
- **Compliance therapy** may be appropriate if the patient's insight or attitudes towards treatment are the main problem (Fig. 2.6)
- **Cognitive–motivational addiction therapy** should be encouraged if there is a comorbid substance abuse disorder
- **Optimization of the pharmacological therapy** should be the doctor's goal if the patient's subjective wellbeing has not improved with the current medication regimen; the doctor should actively discuss the reasons for such lack of improvement, eg subjective side effects, and adjust therapy accordingly (Fig. 2.6).

2.5 Co-occurring substance abuse in schizophrenia

Dan Lubman

Co-occurring substance use disorders, often termed 'dual diagnosis' or 'comorbidity', are a serious and common issue among patients with schizophrenia, but frequently remain under-recognised and poorly addressed. Up to 90% of people with schizophrenia smoke cigarettes, whereas between 40% and 60% use other substances. Co-occurring substance use disorders (excluding tobacco smoking) appear to be more prevalent (up to 75%) among young people with FEP, as well as among those who are homeless or have come to the attention of the criminal justice system. The most frequently abused substances are cannabis, alcohol and psychostimulants, mirroring patterns of use evident within the general population, although abuse of more than one substance is relatively common. Most patients start using before the onset of psychosis (with regular cigarette use typically starting first); however, this most probably reflects the typical temporal order of onset of both disorders, rather than demonstrating that substance abuse is a critical aetiological factor.

Treatment principles to improve adherence and reduce service disengagement in schizophrenia	
Assess risk factors and risk constellations	Preventive approach important in dealing with treatment non-adherence. Overall short- and long-term risk of non-adherence and service disengagement is so high that assessment of individual risk factors and constellations is vital to management. Within three to four sessions, detailed analysis of individual non-adherence risk factors gives good overview of interventions needed for individual risk profile; treatment plan is devised accordingly
Regularly review risk factors and treatment adaptation	Important because most patients have several risk factors, which fluctuate over time and interfere with each other. In every medication visit include brief screening question about compliance, asked in non-threatening and uncritical manner. Routinely assess attitudes to medication, regardless of patient's actual compliance behaviour
Adapt organization of care	Adapt to individual risk constellation of non-adherence. A helpful service requirement is assertive community treatment: team of experts who help improve adherence, reduce service disengagement and, in case of relapse, reduce duration between relapse and re-start of treatment
Monitor medication adherence regularly	Monitoring is vital because risk of partial/full non-adherence is high and clinician's judgement of adherence is often insufficient even when patient known well. No evidence-based methodology to monitor oral medication adherence exists; therapeutic plasma level monitoring probably most valid method but there is a high individual variability, so assess baseline levels during a period in which medication taking is monitored. Daily monitoring by home-based carer is necessary for some patients. Consider long-acting injectable formulations
Decide on individually adapted adherence interventions	Interventions targeted specifically at non-adherence more likely to be effective than more broadly based ones. Usually mixed modality interventions are needed. Repeated non-adherence necessitates depot medication or continuous medication intake monitoring
	Consider the following interventions: Family and individual psychoeducation: can reduce relapse rate by approximately 20%. Nature of illness, and reasons for taking medication, are explained to patient and family

Community-based intervention: employs strategies such as assertive community treatment or intensive case management

Motivational interviewing: exploit patients' own desires, wishes, goals, to motivate taking of medication

Cognitive–motivational addiction therapy: for patients with comorbid substance use disorder, regardless of whether consuming at present or only in the past

Compliance therapy: a brief intervention based on four to six sessions of motivational interviewing to target treatment adherence in psychotic disorders. Focuses on insight and attitude to treatment

Shared-decision making: doctor communicates information about illness, treatment options and recommendations. Patient and doctor jointly select treatment

Peer to peer: involvement of experienced and well-trained patients in the care of other patients is increasingly common. Positive attitude of peer moderator is probably due to credibility conferred by personally and successfully dealing with own illness

Family to family: experienced, well-trained family moderators give psychoeducation and describe experiences to other families to enhance their knowledge

Second-generation antipsychotics (SGAs): it has been postulated that adherence to medication is better with SGAs. Studies to date have produced mixed results, but it is clear that antipsychotic medication can be fully effective only as part of a broader management plan

Long-acting injectable antipsychotics: may improve adherence by assuring delivery. If patient misses injection, clinician is immediately aware of non-adherence. Injections also encourage regular contacts with treatment team. Other advantages: avoidance of first-pass metabolism with more stable plasma levels, lower effective dose with less dose-dependent side effects, prolonged efficacy in cases of non-adherence, allowing timely intervention before relapse

Mixed modality interventions: includes a number of the above strategies

Figure 2.6 Treatment principles to improve adherence and reduce service disengagement in schizophrenia. (According to Weiden 2007; Schimmelmann et al. 2005.)

A number of hypotheses have been proposed to explain the high rate of co-occurring substance use among people with psychosis, including the following:

- Psychosis increases risk for substance use
- Substance abuse increases risk for psychosis
- Common factors increase risk for both disorders.

The 'self-medication' hypothesis proposes that individuals with psychosis are more prone to substance abuse because they selectively abuse particular substances in order to 'treat' specific symptoms of their psychotic illness. Despite the intrinsic appeal of this model, supporting evidence is limited, and factors associated with substance abuse in the general community also apply to those with psychosis (eg cost, availability, use for intoxication and relaxation, peer group use and acceptance). Nevertheless, people with psychosis do consistently report abusing substances to relieve feelings of dysphoria, anxiety and boredom, and it is likely that some patients continue to abuse substances to help cope with a range of psychosocial problems (eg family conflict, trauma, financial problems, lack of vocational opportunities, social anxiety).

The hypothesis that substance abuse is a risk factor for psychosis has received support from a number of recent longitudinal cohort and population-based studies. Regular cannabis use appears to be associated with an approximately twofold increase in the relative risk of developing schizophrenia or other psychosis outcomes. However, although cannabis use (particularly adolescent-onset and heavy use) is a risk factor for later psychosis, the incidence of schizophrenia does not appear to be increasing despite elevated rates of cannabis use in the general community. This suggests that the relationship between cannabis use and psychosis is particularly complex, and further studies examining the interaction of genotype, developmental processes and cannabinoid exposure are required.

An alternative hypothesis for the high rate of co-occurring substance abuse disorders among individuals with psychosis is the possibility that common underlying biological, personality or environmental factors increase vulnerability for both disorders. For example, both disorders are associated with dysfunction within the brain's reward system, as well as frontal executive deficits, whereas certain personality traits (eg sensation seeking, impulsivity and negative affect) have been implicated in the aetiology of co-occurring psychosis and substance use disorders. Certain personality traits (eg antisocial personality disorder) as well as environmental experiences (eg trauma, family conflict, poverty and social difficulties) also increase risk for both disorders.

Cigarette smoking is associated with considerable morbidity and mortality among people with schizophrenia, yet interventions are not routinely offered to

this population despite evidence for their effectiveness. Smoking also places a substantial financial burden on such individuals, who spend a large proportion of their weekly income on cigarettes. Abuse of other substances has a significant impact on both treatment course and outcome, and many patients do poorly in standard treatment settings. Indeed, co-occurring substance use disorders are associated with lower rates of remission, frequent use of health-care services and increased rates of relapse and hospitalization, blood-borne virus infections (e.g. human immunodeficiency virus), suicide, violent behaviour, incarceration and early death. In addition, persistent substance abuse affects medication adherence, service engagement, health-care costs and housing stability, and substantially increases the burden on patients, their families and the health-care system. Although this often leads to clinicians feeling pessimistic towards this population, many individuals with FEP achieve remission and/or a reduction in the severity of substance abuse after entry to treatment, and a significant reduction in substance abuse is likely to be associated with improved clinical outcomes.

2.5.1 Management

It is essential that all patients with psychosis are assessed for co-occurring substance use, given the high rate of substance use within this population and the associated negative outcomes (Fig. 2.7). The assessment should include a detailed history of the type, amount, pattern and circumstances of substance use, negative consequences associated with use (including the impact on mental and physical health, and social and occupational functioning), the degree of physiological dependence, the interaction between psychosis and substance use, relevant risk issues (e.g. accidental or deliberate overdose, aggressive behaviour when intoxicated), reasons for use, previous attempts to control use and past treatment, and motivation/readiness to change substance use. Assessment is most accurate if the clinician establishes a collaborative therapeutic alliance, using an empathic non-judgemental approach. Biomedical investigations (e.g. γ-glutamyl transpeptidase [γGT], urine drug screen) and collateral information should also be sought, because patients may minimize their level of substance use. It is important to assess for any level of use, because people with schizophrenia are often more sensitive to the effects of psychoactive substances and experience greater adverse effects than would typically be expected.

Psychosis in the context of co-occurring substance use presents clinicians with a particularly difficult diagnostic challenge, especially as many psychoactive substances can induce psychotic symptoms during periods of intoxication or withdrawal. That said, psychosis can also occur with prolonged abuse, and

Recommendations for the management of substance use disorder in schizophrenia

Assessment

- Screen all patients for substance use and other psychiatric disorders (eg social phobia)
- Determine severity of use and associated risk-taking behaviours (eg injecting practices, 'unsafe sex')
- Exclude organic illness or physical complications of substance use
- Seek collateral history: families or close supports should be involved where possible

Treatment principles

- First engage patient, adopting a non-judgemental attitude
- Educate patient:
  - Give general advice about harmful effects of substance use
  - Advise about safe and responsible levels of substance use
  - Make links between substance use and patient's problems (eg cannabis use and worsening paranoia)
  - Inform patient about safer practices (eg using clean needles, not injecting alone, practising 'safe sex')
- Treat psychotic illness and monitor patient for potential side effects
- Help patient establish advantages and disadvantages of current use; motivate patient for change (see specific interventions)
- Evaluate need for concurrent substance use medications (eg methadone, acamprosate)
- Refer patient to relevant clinical and community services, as appropriate
- Devise relapse prevention strategies that address both psychosis and substance use
- Identify triggers for relapse (eg meeting other drug users, being paid, family conflict) and explore alternative coping strategies

General interventions

- Explore reasons for substance use, including relationship to psychiatric symptoms, antipsychotic treatment and feelings of social isolation
- Address patient's motivation and degree of commitment towards treatment of both the psychotic illness and the substance use
- Adopt concrete problem-solving approach with patient, where appropriate
- Set tasks that are simple and readily achievable (eg keeping a diary of substance use or psychotic symptoms; regularly taking medication; keeping appointments)
- Focus on specific skills to deal with high-risk situations, and consider use of role play (eg learning how to say 'no' to a dealer/drug-using friends)
- Suggest alternatives to substance use for coping with stressful situations (eg exercise, contacting a support person)
- Treat comorbid anxiety with behavioural techniques (eg breathing exercises, progressive muscular relaxation)
- Remain supportive and emphasize any gains made
- Encourage participation in alternative activities and contact with non-substance-using peer group (discuss available resources with local community health centre or mental health service)

Motivational enhancement techniques

- Useful therapeutic approach, based on a model conceptualizing stages through which behavioural change occurs. Emphasizes role of both ambivalence and relapse within process of change. Aims to match appropriate treatment options with patient's motivational level, based on their current stage within cycle

Figure 2.7 Recommendations for the management of substance use disorder in schizophrenia. (According to Lubman and Sundram 2003; Green 2006; Drake 2007.)

there is growing evidence that substance-induced psychotic episodes occur more frequently among individuals with substance use disorders. Although substance-induced psychotic symptoms are typically transitory in nature, generally lasting less than a week in most cases, there is a small but growing literature to suggest that, in a minority of chronic users, psychotic symptoms can last substantially longer than a month (especially among those with underlying schizoid or schizotypal traits). Nevertheless, the priority of initial assessment should be to identify treatment-relevant syndromes (such as the triad of psychosis, substance abuse and depression), and to start appropriate treatment. Indeed, those with substance-induced psychosis should not be excluded from treatment, especially as there is evidence to suggest that they are a particularly high-risk group for later transition. In this regard, the interaction between substance abuse and psychotic symptoms should be monitored longitudinally to ensure accuracy of the initial diagnosis.

It is important to acknowledge that many clinicians feel overwhelmed or not sufficiently skilled to manage patients with co-occurring disorders. Many are often pessimistic regarding outcomes and believe that substantial time and effort are required for little return. It is therefore not uncommon for clinicians to want limited involvement with such patients, and to try to refer them elsewhere. However, the reality is that few clinicians have had specialized training in managing co-occurring disorders, and practitioners need to acknowledge that substance abuse is a common concomitant of a psychotic illness. It should be borne in mind that appropriate interventions have been shown to be beneficial, and clinicians need to remain optimistic with realistic expectations over the long term.

Comprehensive treatment planning involves discussing the assessment with the patient (and key support/carer if the patient consents), providing education about the link between psychosis and substance abuse outcomes, identifying clear treatment goals, and discussing potential pharmacological and psychosocial interventions. The approach should be integrated, such that both the psychosis and the substance abuse are addressed simultaneously in a comprehensive treatment package. Effective pharmacological treatment of the psychotic illness with antipsychotic agents is critical, because improved medication adherence increases the effectiveness of adjunctive psychosocial interventions. In this regard, patients should be offered simplified medication regimens, as well as clear information about potential interactions between their prescribed medication and abused substances. Those who are consistently non-adherent or continually chaotic may benefit from switching to a longer-acting depot antipsychotic, although limited research has been conducted to

examine the effectiveness of this approach. Benzodiazepines should be used with caution because of their interaction with alcohol and other depressants, as well as their potential for abuse. Limited pharmacological trials for substance abuse have been conducted among patients with schizophrenia, but most addiction treatments appear to be safe and effective in combination with antipsychotics. Nicotine replacement therapies and bupropion have both been successfully and safely used in patients with schizophrenia.

Assertive outreach with intensive case management has been found to improve engagement and retention, as well as treatment outcomes, in those with co-occurring disorders; however, few such programmes exist. Nevertheless, ensuring that the patient's immediate needs are addressed, as well as offering practical assistance with everyday tasks, enhances engagement and increases motivation for treatment. Life-long abstinence may be a particularly difficult goal to achieve for this population, and it is more useful to adopt a harm-reduction framework focused on reducing the harm associated with the substance abuse and its consequences. In general, psychosocial interventions for substance abuse need to be modified for people with schizophrenia (eg adopting a concrete problem-solving approach, the use of role play), given associated negative symptoms, cognitive difficulties and poor self-efficacy. Motivational interviewing remains an important component of treatment, in terms of identifying the pros and cons of continuing or ceasing substance use, and accepting treatment, addressing ambivalence, building self-efficacy, identifying and implementing relevant strategies for change, encouraging new skills and rehearsing relapse prevention strategies (for both the psychosis and the substance abuse). It is important that 'lapses' are not viewed as failures, but should rather be discussed early in treatment as being something that is to be expected and viewed as an opportunity to refine the patient's set of coping strategies.

Lack of vocational opportunities, homelessness and contact with drug-abusing peers are obvious drivers of continued substance abuse, and these should be addressed early in treatment. Vocational and educational goals are also important motivators for change, and relevant support agencies should be included in treatment planning to ensure that relevant opportunities are considered. Links to alternative social networks and support groups are also essential. Finally, families play a particularly important role in supporting and monitoring treatment, as well as building self-efficacy and self-esteem, and should be involved early in treatment planning, with the patient's consent. Carers may need additional support themselves, because family conflict is common when patients have co-occurring disorders.

2.6 Childhood trauma in schizophrenia

Ingo Schäfer and Philippe Conus

Trauma and its consequences have long been a neglected issue in patients with schizophrenia and other psychotic disorders. However, over the past decade, interest in this topic has markedly increased. Patients suffering from psychosis are more likely to have been exposed to trauma than the general population. The existing evidence consistently shows a high prevalence of early trauma, especially childhood sexual abuse (CSA) and childhood physical abuse (CPA), in the lives of people with psychosis. In a recent critical review of 20 carefully selected studies of patients with psychotic disorders, 42% of the female patients reported CSA and 35% CPA. In male patients, these figures were 28% and 38% respectively. At least one form of abuse (CSA or CPA) was found in 50% of the patients, irrespective of gender. Among patients with bipolar disorder, the global rate of childhood trauma is 45–68%, 15–21% reporting exposure to sexual trauma and 21–28% to physical trauma.

Population-based studies suggest that childhood trauma is a causal factor for psychosis. In almost all of the existing studies, a history of trauma was related to psychotic symptoms during either adolescence or adulthood, eg in a prospective study of 4045 individuals aged 18–64 drawn from the Netherlands Mental Health Survey and Incidence study (NEMESIS), participants who had experienced emotional, physical or sexual abuse before the age of 16 were more likely to develop positive psychotic symptoms according to several different definitions during a 3-year follow-up period. These effects held after adjusting for a wide range of potential confounding variables (eg psychotic symptoms with need for care – adjusted odds ratio 7.3). Research into the consequences of early trauma suggests that both psychological and neurobiological factors may contribute to the development of schizophrenia and other adverse outcomes. At the psychological level, the focus has been on cognitive factors and their interplay with emotions. Neurobiological theories include alterations of the hypothalamic–pituitary–adrenal (HPA) axis and an altered function of the dopaminergic system. Although some of these mechanisms have been linked to a range of different mental health problems, others, eg information-processing abnormalities, might represent distinct processes specifically associated with schizophrenia and other psychotic disorders.

Psychotic patients with a history of childhood trauma have a more severe clinical profile compared with those without these experiences across a variety of measures. They have an earlier onset of the illness, a higher number of hospitalizations and a more severe clinical course. Patients with childhood trauma are more likely to have been re-victimized later in life, have high

rates of current post-traumatic stress disorder (PTSD), more current or lifetime substance abuse and suffer from more lifetime episodes of major depression. Victims of abuse also have higher levels of current depression and anxiety, and report more dissociative symptoms than patients without these experiences. In a study among schizophrenic patients in vocational training, victims of childhood abuse had a poorer level of participation, were less able to sustain intimacy and were more prone to emotional instability. Finally, abused patients have frequently been found to report more suicidal ideation and suicide attempts.

Although similar findings with regard to the consequences of early trauma have been reported for all psychiatric diagnosis, differences have also been reported concerning the type and content of psychotic symptoms. In patients diagnosed with schizophrenia, those who suffered CSA or CPA have repeatedly been reported to have more 'positive symptoms' (eg hallucinations, ideas of reference and thought insertion) and fewer 'negative symptoms' than those without a history of abuse. Although findings about the interrelationship of childhood trauma and delusions, thought disorder and 'negative symptoms' remain inconsistent, the link between childhood trauma and hallucinations has repeatedly been replicated and seems to exist across diagnostic boundaries and also in the general population. Finally, associations can be found between childhood trauma and the actual content of psychotic symptoms, eg a history of childhood abuse has been linked to a tendency to hear more malevolent voices in patients with schizophrenia and the themes of hallucinations (such as threat, guilt and humiliation).

Given the strikingly high number of patients with a history of trauma and the obvious clinical problems related to this issue, recommendations have been published to design trauma-sensitive services for people with severe mental illness. They call for a more systematic assessment of trauma history, better staff training and modification of standard services to recognize particular safety, control and boundary issues facing these clients. Some useful observations can be summarized as shown in the box.

Discussing previous trauma with patients who have schizophrenia

1. It is important to ask schizophrenia patients about a possible exposure to trauma

a. Without asking, only 10–30% of trauma histories are identified.

b. Although trauma is very rarely part of clinical assessment (because of other priorities for assessment, fear of destabilizing patients, doubt about veracity of reported trauma, fear of blaming families), 85% of patients who

have lived such events are relieved when they are offered an opportunity to talk about it.

2. When trauma is discussed with a patient

a. It is often a progressive process: it is not necessary to gather all details at once and patents need time to gradually expose what they went through.
b. Clinicians need to be available and to positively reinforce the efforts that patients make to talk about such issues.
c. It is also important to evaluate the risk for victimization, recurrence of trauma and suicide.

Trauma-specific treatments aim to directly address the effects of abuse. Although no sound evidence is available for differential pharmacological approaches, several psychotherapy treatments have proved effective in psychotic patients who experienced childhood trauma. Patients with early and complex trauma may benefit from integrated treatment programmes with an emphasis on psychoeducation, stabilization and the development of safe coping skills. Other approaches focus on PTSD. Several case studies and open trials reported that exposure-based treatments of PTSD can be used safely and effectively in patients with schizophrenia. More recently, a pilot study of a group-based cognitive–behavioural intervention for PTSD, with an emphasis on cognitive restructuring rather than exposure therapy, has yielded promising results in patients with severe mental illness. Independent of the strategy chosen, trauma treatments for patients with schizophrenia should take place in a context of comprehensive services, such as case management, medication management and integrated dual diagnosis treatment when substance abuse problems are present. Clearly, more research is needed to further develop and evaluate treatment approaches appropriate for this vulnerable population and to integrate them into routine practice.

2.7 New antipsychotics and new antipsychotic formulations

Tim Lambert

2.7.1 Quetiapine XR

Introduction

Quetiapine extended release (QXR) is a new formulation of quetiapine, previously available in an immediate-release form (QIR). Compared with QIR, QXR allows for once-a-day prescribing, initiation of therapy at higher doses, reaching a therapeutic target earlier and, through simpler delivery, improved convenience and, potentially, better adherence.

Pharmacology

QXR has a different pharmacokinetic profile to QIR. The most immediate difference is that it can be given once daily, achieving similar bioavailability to QIR given twice daily (assuming equivalent doses). Other differences include dose-proportional kinetics up to 800 mg/day, plasma peak at 6.0 as opposed to 1.5 hours, and a shallower plasma level profile (peak-to-trough excursion is less), with a half-life of 7 hours. Positron emission tomography (PET) indicates that once-daily dosing of QXR results in peak-and-trough dopamine D_2-receptor occupancy similar to twice-daily dosing of QIR, taking their respective pharmacokinetics into account. In terms of clinical pharmacodynamics, QXR behaves as might be expected from the profile and actions of QIR.

Clinical effectiveness

Clinical effectiveness can be viewed as a function of the costs (tolerability) and benefits (efficacy) and the resulting adherence with treatment. All three components should be reviewed when considering the potential for a treatment intervention in the clinical (real-world) setting.

Efficacy

In terms of efficacy, when doses are matched, QXR and QIR appear to be equally efficacious in stabilized patients. In acute settings, after 6 weeks of treatment with 400–800 mg/day, QXR shows a dose–response curve that has the near maximal effective dose at approximately 600 mg/day. In the latter study, all dose levels differed from placebo on the positive, general psychopathology and aggression–hostility factor subscales of the Positive and Negative Syndrome Scale (PANSS), whereas negative symptoms and depression factor scores were improved only with 600 and 800 mg/day. Similarly the higher doses were associated with significant reductions in Clinical Global Impressions – Severity of Illness Scale (CGI-S) scores, as was QIR 400 mg/day.

In a 12-week switching study it was found that 63% of patients improved on a median dose of QXR 575 mg/day. This study examined two subpopulations of switchers: those switched for intolerability (weight and extrapyramidal symptoms [EPSs] mainly) and those switched for lack of efficacy. The outcomes were, on the whole, similar between these two groups.

Tolerability

In terms of tolerability, QXR does not appear to contribute to dose-related side effects. The most common side effects are somnolence related in 6.3–17.8% and dizziness related in 5.3–14.0%. Although greater than placebo, these rates were

comparable to QIR 400 mg/day and, in both preparations, withdrawal due to these adverse events appears low.

As expected the rate of EPSs is very low in QXR-treated patients, with less than 10% showing any EPS-related adverse events. After a switch to QXR, between 74% and 95% of patients showed no change or a reduction in EPS over 12- and 6-week periods, respectively. Akathisia rates are generally very low and most patients who switched to QXR showed no increase in prevalence or severity.

Similarly, in all switching studies to date, prolactin levels fell significantly, supporting the prolactin-sparing quality of the QXR formulation.

With respect to metabolic syndrome risk factors, QXR has a weight gain potential similar to QIR, with 1.1–0.8 kg weight gain seen in the first 6 weeks of treatment, along with mild elevations in low-density lipoprotein (LDL)-cholesterol and triglycerides, a small reduction in high-density lipoprotein (HDL)-cholesterol and essentially unchanged glucose levels.

Adherence

As yet there are no studies contrasting the relative rates of adherence for QXR and QIR. Given the once-daily dosing, and the benign side-effect profile, higher rates of adherence might be expected in QXR. Over a 12-week study 95% of patients met adherence criteria (defined as taking >70% of medication, based on pill counts), which suggests a profile that is acceptable to patients receiving the new formulation. At the same time this higher than anticipated adherence needs to be replicated in further studies.

Switching

The proposed switching protocol for QXR is 300 mg on day 1, 1600 mg on day 2 and 400–800 mg in flexible dosing from day 4. All doses are given once daily in the evening and therapeutic doses may be achieved from the second day, ie at an appreciably faster initiation rate than with QIR. For patients receiving QIR and in whom QXR may be a preferred option, direct transition from twice- to once-daily prescribing with no cross-titration appears well tolerated. However, when switching from other antipsychotics to quetiapine, the general precautions relating to down-titration of the previous antipsychotic should be adhered to.

Clinical use

In the acute setting, the ability to achieve the target dose after 2–4 days may be of benefit, where it is necessary to achieve target doses in the shortest period.

Tolerability in this period is favourable and rates of discontinuation due to side effects are less than 2%. The short-term studies outlined above support the suggestion that switching for both inefficacy and/or tolerability reasons may lead to clinical improvement, especially where the switch is from a first-generation antipsychotic.

This may or may not be helpful in relapse prevention compared with QIR, because there is relatively short persistence at the dopamine receptors and missing a day or two may result in very low brain D_2-receptor occupancy and plasma levels in the presence of significant partial adherence. However, there is evidence to suggest that QXR is effective in relapse prevention, perhaps due to the simpler dosing regimen and good tolerability profile that lead to acceptance by patients.

2.7.2 Paliperidone ER

Paliperidone extended release (PER) is 9-hydroxyrisperidone (the primary active metabolite of risperidone) which uses the OROS system to deliver the medication over a longer period with fewer plasma level fluctuations.

Compared with risperidone (which generates risperidone and 9-hydroxy-risperidone as the active moiety), PER allows for once-daily prescribing, initiation of therapy at the target dose and, theoretically, fewer side effects due to this use of the new-to-psychiatry delivery system.

Pharmacology

Pharmacokinetically, paliperidone has a profile shaped by its delivery using the OROS technology. Based on an osmotically active trilayer core, the drug is slowly pumped out of the preparation with a slow rise in plasma levels. This leads to minimal plasma fluctuations over a 24-hour period and allows for once-daily dosing. This confers a number of advantages over oral tablets. First, the patient may be started at the target dose instead of needing gradual up-titration to avoid orthostatic hypotension and EPSs. Second, without high peaks and troughs a number of adverse effects are reduced. PER should be initiated at 6 mg, taken in the morning, and can be adjusted to 3–12 mg/day depending on further response.

PET indicates that, to achieve 70–80% D_2-receptor occupancy at steady state, a dose of 6–9 mg is required. The clinical pharmacodynamics are similar to those of risperidone, with potent $5HT_{2A}$- and D_2-receptor antagonism, weaker H_1-, α_1- and α_2-receptor adrenergic blockade, and no antimuscarinic properties. There is some evidence that the efficacy and tolerability of PER cannot simply be extrapolated from those seen with risperidone. Paliperidone

has much less variability in plasma concentration than the active moiety of risperidone, because the former is significantly less dependent on hepatic cytochrome P450 2D6 (CYP2D6) for its metabolism. This, in turn, is likely to reduce the possibility of drug–drug interactions, such as may be seen with risperidone.

Clinical effectiveness

Efficacy

The efficacy of PER has been demonstrated in placebo-controlled trials and appears to be equal to olanzapine 10 mg/day in doses of 3 mg/day. A dose–response relationship has been shown in short-term studies: all doses between 3 mg/day and 15 mg/day have increasing effect. In a 40-week maintenance study of relapse prevention, PER performed significantly better than placebo on rates of relapse and time to relapse. To date, there have been no head-to-head trials of risperidone and PER, and other maintenance trials are as yet unpublished.

Tolerability

PER is an SDA drug and as such would be expected to have dose-dependent EPSs. At plasma levels above about 45 ng/ml (about 9 mg/day) EPSs are more likely. Similarly, higher doses lead to hyperprolactinaemia, which may be somewhat more pronounced than in patients treated with risperidone. However, there is a low rate of reported side effects (<2%) in those on 3–12 mg/day, consistent with 'silent' hyperprolactinaemia. As with risperidone, real-world rates of sexual dysfunction may be higher in certain patient groups and direct enquiry should always be made. Postural hypotension occurs at a rate of between 2% and 5%. In short-term trials of 6 weeks, there is a favourable metabolic profile, with weight gain being of the order of 1.2 kg and without appreciable change in lipids, glucose or insulin. Discontinuations driven by side effects were 2–5% in these studies. Thus, PER has a very favourable metabolic profile in the short term. Longer-term studies examining metabolic risk factors are required.

Adherence

To date there is little evidence to support any comment on whether adherence rates have improved with PER compared with risperidone or other oral antipsychotics. The high completion rate in short-term studies and the equivalent persistence compared with olanzapine suggest better adherence, although this has yet to be formally tested.

Switching

To date no formal switching studies have been carried out. However, the key issues are as follows: PER may be started at the target dose, suggested to be 6 mg each morning. In terms of the previous antipsychotic, if that had any intrinsic anticholinergic activity, a very gradual reduction is needed or an anticholinergic such as benztropine should be added and slowly tapered down – to avoid cholinergic rebound in the switch process, PER having no intrinsic anticholinergic properties itself.

Clinical use

Until there are direct head-to-head studies, debate will ensue for some time over the advantages of PER compared with risperidone. Putative advantages may include the following:

- an adherence benefit from once-daily dosing
- avoidance of up-titration delays on commencement
- use in treating patients who are hepatically challenged; useful for those who are poor metabolizers of CYP2D6
- use where drug interactions may be deleterious (eg risperidone plus fluoxetine)
- avoidance of anticholinergic side effects
- use where lower EPs are required.

Finally, the use of PER will provide clinical experience with the molecule and allow for a better understanding of the role of the long-acting injection formulation of paliperidone.

2.7.3 Second-generation antipsychotic long-acting injections

Risperidone in its long-acting injection (LIA) form (RLAI) represents the first of the second-generation long-acting antipsychotics (SGA 'depots'). As shown in Fig. 2.8, long-acting injectable antipsychotics belong to one of three groups: the first-generation depot antipsychotics, representing the past; RLAI and olanzapine pamoate long-acting injection (OLAI) as the present state of the art; and the future as represented by at least one possible LAI medication: paliperidone palmitate (which has yet to be finally approved). A number of other second-generation antipsychotics (SGAs) may also appear as LAIs in the future.

Risperidone long-acting injection

Since its release in 2003, RLAI has shown itself to be a valuable component of the modern pharmacotherapy of schizophrenia. It has proved to be cost-effective in schizophrenia by reducing readmission rates. Switching studies have

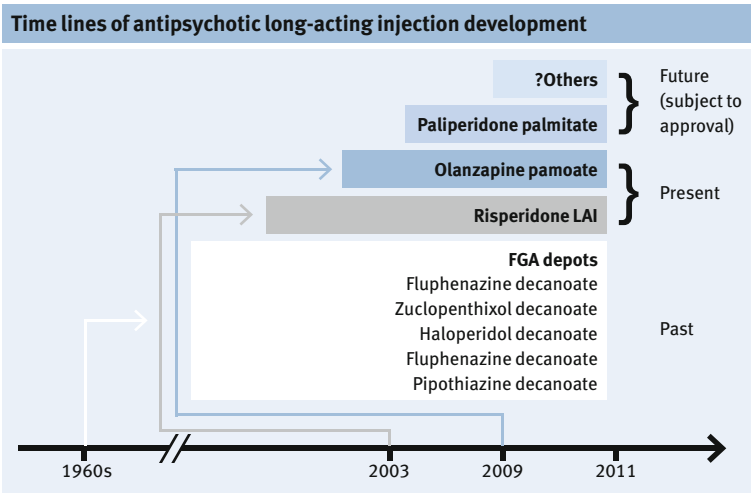


Figure 2.8 Time lines of antipsychotic long-acting injection development. FGA, first-generation antipsychotic; LAI, long-acting injection.

shown that switching is equally successful from oral and depot first-generation antipsychotics (FGAs), and it is gaining acceptance in managing misadherence in early psychosis.

A number of trends are worth noting. Early use was marked by two phenomena: selecting inappropriate patients (including those with long-standing refractory illness) and switching patients to suboptimal doses of RLAI. There is a tendency when any new medication is released to try it with the patients who have shown little or no response to most medicines, including clozapine. Using RLAI in this group is usually unsuccessful. To help select appropriate patients, guidelines for optimal patient selection have been developed.

The patient groups identified include those with: cyclical remission–relapse cycles (the 'square-wave' patient); revolving door syndrome; poor efficacy despite (apparent) good adherence; enduring poor tolerability despite adequate symptom control; recent treatment with FGA LAIs; and clinical histories in which resistance to treatment due to failure of adherence needs to be differentiated from treatment-resistant illness.

Switching to and maintenance of RLAI were somewhat difficult for some patients in the early years of its use. This may have come about because equivalence data were imprecise and many patients switched from relatively high to lower doses of antipsychotic. The suggestion that most patients should start on RLAI doses of 25 mg 2-weekly may not be optimal for many, eg using preliminary

estimates of equivalence, patients switched to RLAI with a lower equivalence were more likely to relapse and demonstrate an increase in psychopathology. For patients maintained in the Estar study over a 24-month period, mean doses increased from 26 mg to 43 mg 2-weekly, reflecting a pragmatic understanding of suitable equivalence.

In considering a range of pharmacokinetic and PET studies (Figs 2.9 and 2.10) there seems justification to conclude that the risperidone oral to LAI equivalence pairs are as follows: 2 = 25 mg, 3 = 37.5 mg and 4 = 50 mg 2-weekly. These equivalences should be considered an approximate guide because dose adjustments required in individuals when switching from oral to LAI forms (and vice versa) are hard to predict due to wide patient variations between patients. One flaw of the equivalence table approach is that it assumes equal and full adherence on both sides of the switch equation. In reality, LAI adherence is more likely to be higher than oral adherence and apparent lower

Risperidone oral and LAI dose equivalence by positron emission tomography

Oral dose (mg daily)	D_2-receptor occupancy[a] (%)	LAI dose (mg fortnightly)	D_2-receptor occupancy[b] (%)	D_2-receptor occupancy[c] (%)
2	59–71 (66)	25	25–48	53–55 (54)
4	67–78 (73)	50	59–83	63–68 (65.4)
6	74–83 (79)	75	62–72	71–79 (75)

Figure 2.9 Risperidone oral and LAI dose equivalence by positron emission tomography. Values in parentheses are means. LAI, long-acting injection. (From: [a]Kapur et al 1995, [b]Gefvert et al 2005 and [c]Remington et al 2006.)

Dose equivalence of oral and LAI risperidone on the basis of pharmacokinetics

	Oral dose (mg daily)/RLAI dose (mg 2-weekly)		
Pharmacokinetic parameter	**2/25 i.m.**	**4/50 i.m.**	**6/75 i.m.**
$AUC_{14\ days}$			
Oral dosing (ng h/mL)	5996	12 027	18 056
Depot intramuscular dosing (ng h/mL)	5303	11 571	16 886
Intramuscular/oral ratio (%)	88	96	94
90% confidence interval	81–97	89–104	85–102
C_{av} (average concentration)			
Oral dosing (ng/mL)	17.8	35.8	53.7
Depot dosing (ng/mL)	15.8	34.4	50.3

Figure 2.10 Dose equivalence of oral and LAI risperidone on the basis of pharmacokinetics (Eerdekens et al 2004). AUC, area under the curve; i.m., intramuscularly; RLAI, risperidone long-acting injection.

equivalences may reflect prior partial adherence with nominated risperidone oral doses. Therapeutic drug monitoring may be a useful clinical tool in such situations.

Clinical experience with RLAI informs us that it is well tolerated. In particular EPSs are reasonably low, consistent with the striatal D_2-receptor occupancy of <80% in most patients with doses of ≤50 mg. The mean peak steady-state concentrations of the active moiety of RLAI are 25–32% lower than with oral risperidone, and their fluctuations 32–42% lower, which might also explain the low rate of motor side effects. RLAI does, however, show marked elevation of prolactin and one of the most frequent complaints is of sexual dysfunction. Retinal occlusion by RLAI microspheres has been reported, suggesting that care should be taken to avoid inadvertent intravenous injections. Otherwise, side effects are similar in type and frequency to those found with oral risperidone, and cost–benefit decisions should be undertaken within that general framework along with the features described above.

On a pragmatic note, a formulation suitable for deltoid injection will soon be available which may make injections less threatening for some patients who dislike gluteal injections.

In summary, RLAI has proved the effectiveness of SGA LAIs and has set the stage for the further growth of the SGA LAI class.

Olanzapine pamoate long-acting injection

Olanzapine long-acting injection (OLAI) is a salt of pamoic acid and olanzapine, suspended in an aqueous vehicle for deep gluteal intramuscular injection. It represents the first of the SGA LAIs to be formulated in a non-oil, non-microsphere preparation. Unlike previous LAIs, it provides adequate and sustained plasma levels of olanzapine within 3 days of injection (Fig. 2.11).

According to Lauriello et al. (2008) the oral equivalences for OLAI after 2 months are:

- OLAI 150 mg 2-weekly or 300 mg 4-weekly is approximately equivalent to 10 mg/day of oral olanzapine
- OLAI 210 mg 2-weekly or 405 mg 4-weekly is approximately equivalent to 15 mg/day of oral olanzapine
- OLAI 300 mg 2-weekly is approximately equivalent to 20 mg/day of oral olanzapine

These pharmacokinetic equivalence estimates are consistent with a PET study that found that 300 mg 4-weekly of OLAI resulted in a mean striatal occupancy of approximately 60% after 6 months of treatment. The equivalent oral dose of

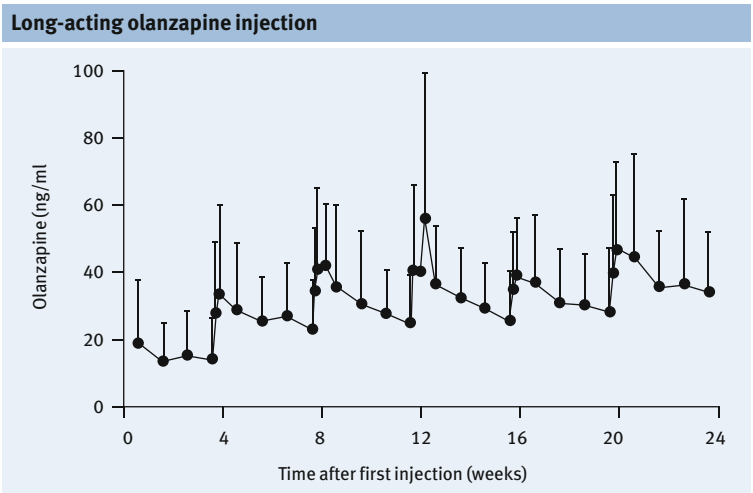


Figure 2.11 Long-acting olanzapine injection. Long-acting olanzapine injection: plasma concentrations after repeated-dosing (405 mg at intervals of 4 weeks). Data from Assessment Report for Zypadhera, Doc.Ref.: EMEA/608654/2008. London: European Medicines Agency, 2008.

olanzapine (7.5–10.0 mg) has been shown in previous studies also to occupy about 60% of receptors at steady state.

In the only clinical study published to date, OLAI was investigated in the management of acute relapse of schizophrenia comparing three OLAI regimens with a placebo arm. The patient population was of chronic patients with marked illness severity (PANSS total scores of approximately 100). The switch from previous medication was of the abrupt type. OLAI is unique for an LAI (first or second generation) in that it releases olanzapine at a clinically useful level from the first injection; there is neither the 1-month delay between injection and peak release seen with RLAI, nor the 2- to 4-month period to steady state seen with FGA depots. Therefore it is not surprising that, in the acute study, symptomatic improvement was significant by day 4 of treatment. Significant reductions in all PANSS measures were observed by week 8. Interestingly, those who switched from previous depots had a less robust response than those who were depot naive, although the response was still significant. Other demographic and treatment covariates had no significant influence on the outcomes.

In terms of adverse events, only those receiving OLAI 300 mg 2-weekly (the highest dose) experienced significantly different side effects from the placebo-treated patients. These patients had higher rates of sedation and increased appetite. Metabolic risks were very much in keeping with those seen with oral

olanzapine. Compared with placebo (12.4%), 23.6–35.4% of OLAI patients gained more than 7% of body weight. In addition, there were significant increases in total cholesterol and triglycerides, but there were no significant changes in fasting glucose. Thus, the study revealed the action of OLAI to be very similar to that of oral olanzapine, with the same cost–benefit considerations for the prescriber to weigh up.

Of clinical importance is occurrence of 'post-injection syndrome'. This occurs in 1.4% of all patients (which corresponds to 0.07% of all injection events). The aetiology is, as yet, unclear. Inadvertent intravascular injection has been considered as a possible cause, although other possibilities exist. The syndrome is related to an excessively high olanzapine plasma level. Among patients for whom olanzapine plasma levels were known for previous injections, those who experienced post-injection syndrome had correspondingly much higher levels, consistent with the known clinical pattern of an oral olanzapine overdose. Most patients developed following symptoms:

- Sedation (ranging from mild sedation to coma)
  and/or
- Delirium (including confusion, disorientation, agitation, anxiety and other cognitive dysfunctions)
- Other symptoms including extrapyramidal motor symptoms, speech disorder, ataxia, aggression, hypertension and seizures.

Post-injection syndrome typically starts with mild symptoms, which increase in severity over time: 80% of cases occur within the first hour after injection, 20% within hours 1 to 3, and only one case has been reported at > 3 hours after injection.

With respect to the clinical course of post-injection syndrome, all patients fully recovered. The time to full recovery was 1.5–72 hours; in approximately 70% of patients OLAI was continued.

In consideration of the potential for post-injection syndrome, the following safety guidelines should always be applied:

- Before injection: patients should be made aware that they are not to leave the clinic alone and that a period of observation in the clinic is required.
- After injection: patients must remain in the clinic for at least 3 hours after injection and need to be monitored at least hourly by a trained physician
- Before leaving the clinic: it must be ascertained that the patient is awake, well orientated, and has no signs of post-injection syndrome. Patients must be advised to be alert for signs of post-injection syndrome during the first 24 hours after injection and that they are not allowed to drive a car or to handle machines during that period

- It is recommended that patients carry with them an information card that clearly outlines the processes involved in receiving the injection, the period immediately following the injection, and what to do in the event of manifestations of post-injection syndrome.

Clinically, OLAI represents a powerful alternative to FGA LAIs because (1) it offers immediate onset of action, (2) it allows flexible 2- or 4-week dosing, and (3) it has all the clinical attributes of oral olanzapine (both good and bad).

Paliperidone palmitate

To date there have been no publications concerning the pivotal trials of paliperidone palmitate. A number of phase III trials are under way, including a head to head with RLAI. Reconstituted in water and involving Elan nanocrystal technology, 1-month injections will be available with the likelihood of both gluteal and deltoid delivery options being available. It is likely that paliperidone palmitate will require injections at days 1 and 8 as a loading strategy, with subsequent injections monthly.

Given that the pharmacological profile of paliperidone extended release is quite different from that of olanzapine, the availability of a choice of two SGA LAIs that can be given monthly should help expand the possibilities for helping the 40% of patients who may be non-adherent at any one time.

Chapter 3

Organization of care and treatment

3.1 General principles of care and service requirements

3.1.1 Good clinical practice

Good clinical practice requires a close, cooperative, multidisciplinary network for patients and relatives. The effects of schizophrenia on a patient's life can create such difficulties and impairments that multidisciplinary care providers have to work together. For professionals, three main requirements across all phases of care are important:

1. Shared knowledge of good clinical practice
2. Transition of this knowledge into daily clinical practice
3. The same positive attitude towards possible success of treatment.

The guidelines of the National Institute for Health and Clinical Excellence (NICE), and other guidelines for schizophrenia (eg the American [APA], Canadian [CPA] and Australian guidelines for schizophrenia [RANZCP]), have summarized recommendations for good clinical practice, attitude, and care in first- and multiple-episode schizophrenia. The following principles should be considered:

- An optimistic attitude towards the patient, with respect to outcome
- Providing effective treatment at the earliest possible opportunity
- Full assessment of the needs for health and social care
- Working in partnership with service users and carers
- Supportive and understanding relationships between service users and carers
- Providing good information and mutual support
- Cooperation regarding the choice of treatment
- Presence of a global treatment context.

3.1.2 Early detection and intervention in prodromal patients

The rationale for early detection and specialized treatment of prodromal patients who are possibly on the way to develop schizophrenia includes the following:

- Prevention in the prodromal phase, with the hope of decreasing the incidence of the illness
- Early detection, with the hope of reducing the duration of the untreated prodromal phase
- Reduction of treatment delay in the active prodromal phase
- Better therapeutic alliance, especially for those patients who have been engaged before transition to psychosis
- In the prodromal phase, many patients already have potential psychosocial problems, eg positive symptoms starting, negative and cognitive symptoms that are probably already set to be long lasting, depression, substance abuse disorders, problems in school or education. The logical recommendation is that many prodromal patients need a complex integrated care similar to that for patients with a first-episode psychosis (FEP).

3.1.3 Early detection and early intervention in first-episode psychosis patients

Several potential benefits of early detection and early intervention in FEP have been discussed (see pp. 3–4), and probably the most important ones are:

- Reduction of the duration of the active psychotic phase
- Reduction of delayed treatment in the active psychotic phase
- Both can improve the course of the illness with:
  - possibly an increased speed of recovery and a more complete recovery
  - lower use of hospitalization
  - reduced burden for relatives and other caregivers
  - decreased risk of damaging socioeconomic consequences
  - reduced risk behaviour of secondary comorbid problems, including substance abuse, suicide and/or aggressive behaviour
  - reduced risk of relapse
  - preservation of functional level, including the chance for a better functional outcome
  - better short- and long-term prognosis.

3.1.4 Service requirements

Successful needs-adapted integrative care of patients with schizophrenia, regardless of whether in the prodromal, first-episode or chronic phase, has specific service requirements, the most important of which are:

- Transfer of inpatient resources into outpatient services, which results in a better quality of care in long-term treatment
- Development of specialized services for prodromal and FEP patients
- Treatment of young people and young adults in a single service, with continuity of care
- Cooperation of child and youth and adult psychiatrists as a single treatment team
- Cooperation of various health professionals in one treatment network
- Treatment of each patient and family by the same team of clinicians throughout the complete treatment period.
- Implementation of a specialized assertive community treatment (ACT) team, with the tasks of initial and ongoing service engagement, adherence assurance, longitudinal diagnostic assessment and crisis intervention
- Continuous education of service employees with regard to psychological and pharmacological interventions to enhance quality of care
- Continuous community awareness and health professional education programmes to improve access and reduce treatment delay.

A number of services that integrate these service requirements have been developed. Representative specialized FEP programmes can be found in Australia (ORYGEN Youth Health and Research Centre including the Early Psychosis Prevention and Intervention Centre [EPPIC]) and Canada (Prevention and Early Intervention Program for Psychosis [PEPP]). Other services have included specialized prodromal and first-episode programmes in a broader service structure (eg Psychosis Early Detection and Intervention Centre [PEDIC] in the Psychosis Centre at the University Medical Centre, Hamburg, Germany) (Fig. 3.1).

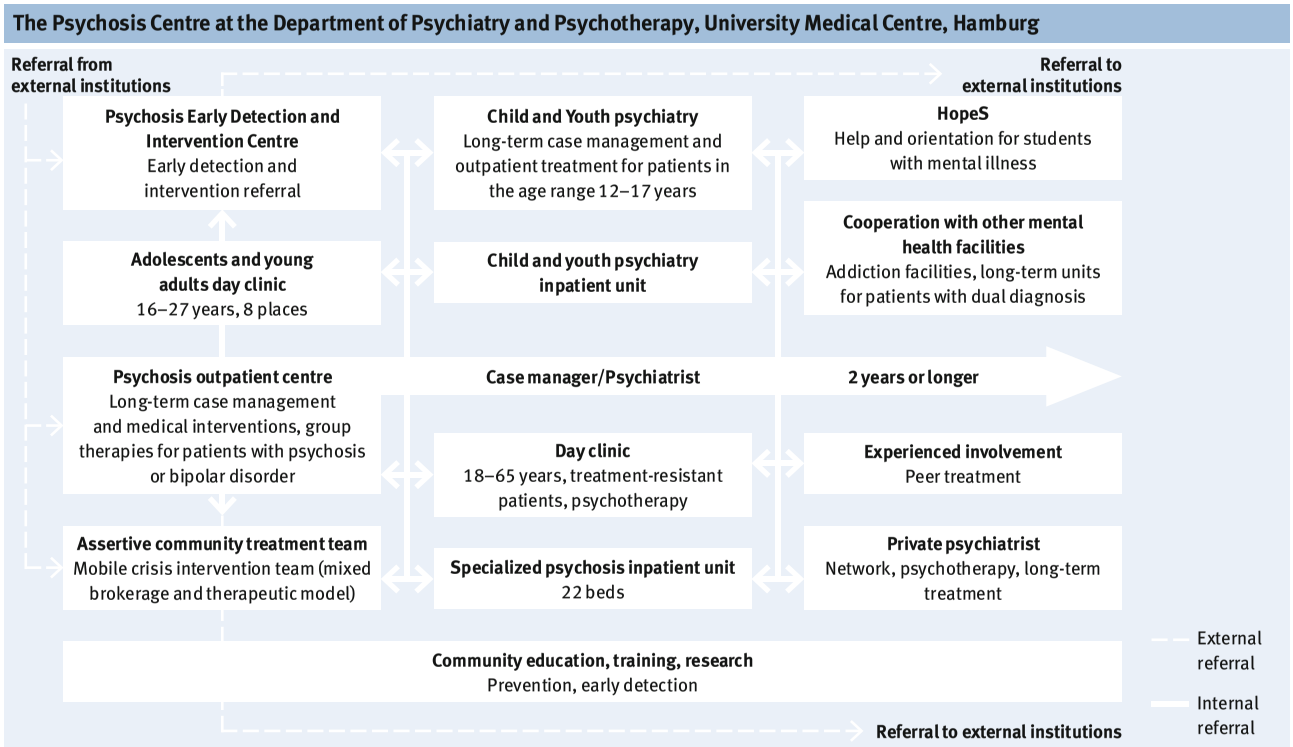
3.2 Phase-specific treatments for schizophrenia

Treatments for schizophrenia are separated according to different phases of illness, ie:

- the prodromal phase
- the acute phase (including first- or recurrent multiple-episode)
- the long-term phase (including a chronic or fully or partially recovered course of illness).

Across these phases of illness the following treatment principles should be applied:

- A strong working alliance with patient and relatives should be developed.


The Psychosis Centre at the Department of Psychiatry and Psychotherapy, University Medical Centre, Hamburg
Referral from external institutions
Referral to external institutions
Psychosis Early Detection and Intervention Centre
Early detection and intervention referral
Child and Youth psychiatry
Long-term case management and outpatient treatment for patients in the age range 12–17 years
HopeS
Help and orientation for students with mental illness
Adolescents and young adults day clinic
16–27 years, 8 places
Child and youth psychiatry inpatient unit
Cooperation with other mental health facilities
Addiction facilities, long-term units for patients with dual diagnosis
Psychosis outpatient centre
Long-term case management and medical interventions, group therapies for patients with psychosis or bipolar disorder
Case manager/Psychiatrist
2 years or longer
Day clinic
18–65 years, treatment-resistant patients, psychotherapy
Experienced involvement
Peer treatment
Assertive community treatment team
Mobile crisis intervention team (mixed brokerage and therapeutic model)
Specialized psychosis inpatient unit
22 beds
Private psychiatrist
Network, psychotherapy, long-term treatment
Community education, training, research
Prevention, early detection
Referral to external institutions
External referral
Internal referral

- The patient's initial discomfort should be minimized.
- Treatment should target a broad range of symptoms, comorbidity and problems.
- Professional treatment should be continuous and interruptions should be avoided.
- Interventions should be age and stage appropriate.
- Pace and timing of reintegration should be considered carefully.
- Family involvement should be regarded as being important.
- In the acute phase, behavioural emergencies should be separated from the usual acute treatment.

3.2.1 Treatment in the prodromal phase

Patients identified as being 'ultra-high-risk' prodromal stage are assumed to meet criteria for one or more of the prodromal syndromes (Fig. 3.2). Nevertheless, prodromal patients often have a multiplicity of other psychosocial symptoms/problems, such as negative symptoms (eg social withdrawal), cognitive dysfunctions, comorbid psychiatric disorders (85% fulfil criteria for at least one and 55% for at least two comorbid psychiatric disorders, especially substance abuse disorder [eg cannabis], personality disorder [eg schizotypal or avoidant personality disorder], affective or anxiety disorder [eg social phobia]) and various social problems (eg problems in school or education, or within family or partnership). For this reason, in many respects prodromal patients can be viewed as FEP patients without continuous positive symptoms. Concordantly, the quality of life of prodromal patients is comparable with that of FEP patients and in some domains even worse (eg affective wellbeing).

The multiplicity and complexity of the psychosocial problems of many 'ultra-high-risk' prodromal patients make multidimensional integrated care mandatory. This includes:

- strategies of engagement
- supportive psychosocial therapy
- psychosocial case management

Figure 3.1 (*opposite*) The Psychosis Centre at the Department of Psychiatry and Psychotherapy, University Medical Centre, Hamburg. Integrated care is provided for patients with schizophrenia spectrum disorders and bipolar disorders and their relatives. Each patient is treated by a team of case manager, psychiatrist and, in cases of need, an assertive community treatment team. Patients can use all facilities of the psychosis centre and, through integrated care, treatment by private psychiatrists. Health insurance finances integrated care over 2 years through a yearly paid package. For further information, see Psychosis Early Detection and Intervention Centre at www.uke.uni-hamburg.de/keiniken/psychiatrie/index_40441.phg.

Characteristics (criteria) of ultra-high risk syndromes of schizophrenic psychoses

Attenuated positive symptom syndrome

- Within past year, attenuated (subclinical positive) but not frankly psychotic symptoms have occurred
- Symptoms have occurred at least once a week in the past month

Brief intermittent psychotic syndrome

- Brief, time-limited, frankly psychotic experiences have occurred within the past 3 months
- Experiences do not meet DSM-IV criteria for psychotic disorders
- Symptoms occur for at least several (but not more than 60) min/day, up to 4 days a week
- Symptoms are not seriously disorganizing or dangerous

Genetic risk and recent deterioration syndrome

- Individual has either schizotypal personality disorder or first-degree relative with psychosis
- In past year, function reduced by 30 points or more on GAF scale for a month or more

Figure 3.2 Characteristics (criteria) of ultra-high risk syndromes of schizophrenic psychoses. DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, 4th edn*; GAF, global assessment of functioning.

- cognitive–behavioural treatments
- treatments of comorbid disorders, particularly substance use
- family involvement, usually in the form of multifamily group psychoeducation
- pharmacotherapy with both antipsychotic and non-antipsychotic compounds.

The psychosocial interventions mentioned above are described in detail in section 3.4 (see page 108). Aspects of psychosocial interventions specific to prodromal patients are summarized in Fig. 3.3.

There are several major risk factors for the transition to psychosis, including a genetic risk for schizophrenia with recent deterioration in functioning, early onset of prodromal symptoms, impaired cognitive performance, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, a history of substance abuse and the severity of schizotypal personality traits. In the individual patient, the positive predictive power of these risk factors for the progress to psychosis is especially high if several of these factors coexist.

Recommendations for psychosocial interventions in the management of prodromal schizophrenia

Engagement

- Offering practical help
- Working initially with patient's primary concerns and source of distress
- Flexibility with time and location of therapy (office based, school, patient's home)
- Provision of information and education about symptoms
- Working with family members as well, if appropriate
- Collaborative goal-setting

Supportive interpersonal therapy (SIT)

Aim: to improve ongoing functioning and social integration. Divided into five phases over 23 weeks:

- Phase 1 (3 sessions) establishes a therapeutic alliance using supportive interactive techniques, eg empathy, unconditional positive regard and patient-initiated process
- Phase 2 (2 sessions) determines and articulates which social and functional areas in the patient's daily life are the most problematic. A list of potential goals is given to patients who have difficulty formulating specific targets
- Phase 3 (2 sessions) prioritizes social and functional problems and develops a mutually agreed treatment plan
- Phase 4 (13 sessions) mobilizes treatment plan with goal being better integration of patient into his or her social world. Includes modelling appropriate social skills, role-playing problematic social situations, identifying and monitoring patient's positive attributes over the course of each week, reality testing experiences of stigmatization, and assigning tasks that bring patients into contact with other people
- Phase 5 (3 sessions) reviews goals attained and skills learned; develops a post-SIT treatment plan, and elicits feelings and issues regarding termination

Case and stress management

- Supportive therapy that deals with more immediate stressors and concrete administrative issues (eg finding housing, handling money, applying for work/school)
- Stress management emerges from stress-vulnerability model of schizophrenia and aims to reduce both occurrence of stress and patient's dysfunctional responses to it

Cognitive–behavioural therapy (CBT)

CBT attempts to provide missing or avoided 'normalization' with a variety of strategies:

- Developing relationship with patient
- Education about symptoms, their biopsychosocial germination, their frequency in the population and their manageability
- Avoiding terms schizophrenia and psychosis
- Verbally challenging and reality testing delusional thoughts and hallucinations while generating and testing alternative explanations
- Teaching coping strategies eg stress management, distracting attention & strategic withdrawal
- Normalizing psychotic-like experiences by suggesting that symptoms experienced are relatively common and manageable
- Reality testing perceptual aberrations and suspiciousness by devising experiments to test beliefs
- Self-monitoring symptoms to enhance connection between external events & emotional states
- Modelling insight, judgement and metacognitive functions
- Reducing distress and fear of catastrophe attending psychotic-like experiences

Other non-specific interventions

- Family-based treatment (eg family intervention, multifamily psychoeducation)
- Cognitive–motivational addiction therapy

Figure 3.3 Recommendations for psychosocial interventions in the management of prodromal schizophrenia. (According to McGlashan et al 2007.)

Apart from specific psychosocial interventions there is an ongoing discussion about the pharmacological treatment of prodromal patients. The current knowledge and clinical practice is as shown in the box.

Current clinical practice in the prodromal phase of schizophrenia

- To date, no clear recommendations or guidelines have been formulated for the pharmacotherapy of prodromal patients.
- The decision to start antipsychotic medication, as well as other pharmacological interventions, should be made jointly with the patient and his or her relatives in a shared decision-making process. For children and young people, parents must give informed signed consent.
- Patients with an 'ultra-high-risk' prodrome can be successfully treated with low-dose antipsychotics. A common dose recommendation for prodromal patients is up to the lower threshold of dose range of patients with a first-episode psychosis (eg risperidone 0.25–2 mg/day, quetiapine 25–300 mg/day).
- It remains unclear whether patients with a high transition risk (with several of the risk factors mentioned earlier) should be generally treated with antipsychotics.
- Additional (comorbid) symptoms, syndromes and diagnoses should be treated according to published guidelines, eg major depression or anxiety disorder with antidepressants, recurrent mood episodes with mood stabilizer or anxiety disorder with intermittent benzodiazepine treatment.
- Treatment recommendations for no or incomplete response and ongoing prodromal symptoms remain undefined. One current clinical approach is to increase the dosage first and then to switch medication. According to early antipsychotic response studies in schizophrenia, for a complete non-responder a switch without a previous dose increase is another promising option.
- The optimal duration of antipsychotic medication, especially in the case of recovery from the prodromal state, also remains undefined.

3.2.2 Treatment in the acute phase

Treatment in the acute phase has to be separated into acute treatment with and treatment without behavioural emergency. This differentiation is needed

because treatment guidelines for psychiatric emergencies differ markedly from guidelines for 'usual' acute treatment in schizophrenia.

Goals of non-pharmacological management of the acute phase

In the acute phase, the overall and non-pharmacological goals of management are engagement and development of a therapeutic alliance with the patient and her or his family, treatment of possible behavioural emergencies, accomplishment of a comprehensive psychobiological assessment, treatment of psychotic symptoms and possible comorbid symptoms/disorders, formulation of an integrated short- and long-term treatment plan, and connection of the patient with appropriate aftercare.

Engagement and development of a therapeutic alliance

Both the quality of the relationship with clinicians during the initial contact and the subsequent development of a trusting therapeutic alliance appear to be important determinants of a positive patient attitude towards treatment, adherence to medication and overall treatment engagement. However, the initial engagement process can be damaged by a variety of factors, eg negative attitudes towards psychiatry, the current mental state of the patient including behavioural disturbances, fears, suspiciousness, unawareness of the illness, cognitive problems in processing information, and concerns of the family and carers. Unfortunately, by the time of first presentation most patients fulfil at least one of these complicating factors. Consequently, the first contact with the service is often critical, and engagement, initial assessment and (early) treatment need to occur as a parallel process. Therefore, planning of the initial contact is important. All sources of information should be gathered before arranging the first assessment. This information will assist in choosing the most appropriate setting, ie the one with the highest chance of engagement, safety and successful initiation of treatment. Well-trained and experienced staff, an individually adapted interview situation and an appropriate interview technique are important requirements for successful first contact and assessment.

Treatment of behavioural disturbances

In the acute phase, an important treatment goal is to prevent and control acutely disturbed behaviours such as agitation, hostility, violence/aggression, pathological excitement or suicidal ideation in a way that does not traumatize the patient and his or her family. A detailed overview is given later in section 4.2 in Chapter 4 (see page 123).

Comprehensive psychobiological assessment

A comprehensive psychiatric investigation always comprises a number of psychosocial and neuromedical assessments. A neuropsychological assessment is recommended in prodromal and FEP patients as well as in patients with certain cognitive deficits that are clinically apparent. The identity of the psychotic disorder as well as possible comorbid psychiatric disorders should be decided on the basis of this information.

A detailed overview is given in section 4.2, Chapter 4 (see page 123).

Treatment of psychotic symptoms and possible comorbid symptoms and disorders

Treatment of psychotic symptoms and possible comorbid symptoms and disorders is the most important aspect of treatment in the acute phase. These interventions can be based in hospital or they can be carried out at home if safety is accurately addressed. A detailed overview is given later in this section.

Formulation of an integrated short- and long-term treatment plan

Another goal of acute treatment is the formulation of an individual phase- and stage-specific integrated treatment plan, which should be actively discussed with patients, relatives and treatment providers in a shared decision-making process. The success of the previous plan of care, the present level of symptomatic remission, residual symptoms and functioning, social problems (eg living situation) and risk factors for the success of the intended treatment plan (eg risk of medication non-adherence or service disengagement) are the main factors on which an appropriate plan of care is based. Once the patient begins to recover, the goals of treatment – and thereby the therapeutic strategies – shift towards a more intense psychotherapeutic approach, with the goals of complete remission of symptoms, improvement in social functioning and achievement of an adequate quality of life (see section 3.2.3, page 76). The vulnerability–stress–coping model provides a framework for integrating the different therapeutic strategies and adapting interventions to the patient's functioning level (see section 4.1, Chapter 4, page 117).

Connecting the patient with appropriate aftercare

Connection with appropriate aftercare is an important challenge for patients with schizophrenia. It is complicated by the tendency of some patients to become directly service disengaged after inpatient treatment. Most appropriate is a link with an ACT team that has already become involved in the patient's care during inpatient treatment.

Pharmacotherapy of acute schizophrenia

Principles of treatment to support successful pharmacotherapy in acute schizophrenia

- **Integrated care is required for optimal antipsychotic response.** Studies on incomplete remission and treatment resistance have shown that insufficient psychosocial intervention is a risk factor for poor response to antipsychotics and poor outcome.
- **Reduction of treatment delay improves response to antipsychotics.** Prolonged duration of untreated psychosis (DUP), especially in combination with other response risk factors, seems to predict decreased response and poor outcome.
- **Treatment of comorbid psychiatric disorders may promote response.** Untreated and persistent comorbid psychiatric disorders are related to an increased risk of incomplete or no response. This was shown repeatedly for persistent substance abuse and is now also evident for comorbid disorders such as major depression, anxiety disorder or personality disorder. In other words, untreated comorbidity lowers the chance of remission and recovery in schizophrenia. Second-generation antipsychotics (SGAs) are increasingly used as add-on therapy for various non-psychotic disorders, which is an argument for their first-line use.
- **Patients and relatives should participate in treatment planning.** Patients' participation in treatment planning is being increasingly advocated in mental health. The shared decision-making model is proposed as a promising method of engaging patients and their families in medical decisions, especially with respect to the choice of antipsychotic and other medications.
- **FEP patients have specific pharmacotherapeutic characteristics.** FEP patients are more responsive to treatment and more sensitive to antipsychotic side effects than patients with multiple episodes (especially side effects related to dopamine blockade). Most respond to a lower antipsychotic dose than is recommended for multiple-episode patients (see section 3.1, page 53 on dosage of antipsychotics).
- **Reasons for relapse should be considered before switching antipsychotics.** As partial or complete non-adherence with medication is the most common reason for relapse, reasons for relapse should be considered before switching antipsychotic medications. If non-adherence has caused the relapse, reasons for this (effectiveness and tolerability) should be explored. A switch of medication is appropriate if poor tolerability has caused medication non-adherence.

- **Medication side effects should be avoided or treated early to promote response and future adherence.** All antipsychotics can cause side effects, and side effects can cause major subjective distress. As several antipsychotic side effects, such as extrapyramidal motor symptoms, are dose dependent and often caused by rapid titration, a low starting dose and a slow titration procedure are recommended. Early detection and treatment of side effects and early treatment adaptation are also important (see section 3.3, page 81). The goal is always a 'minimal effective dose'.
- **Short-term response predicts future response.** Antipsychotic response within the first 2–4 weeks (defined, for example, as a decrease of ≥25% in the total score on the Brief Psychiatric Rating Scale, or an increase of ≥20% in the Subjective Wellbeing under Neuroleptic Treatment scale (SWN-K) total score; see scales on page 135-136) predicts future responds. In cases of complete non-response within the first 2–4 weeks, early switching of antipsychotic medications should be considered.
- **After two unsuccessful antipsychotic trials, clozapine should be considered.** If response-confounding factors are ruled out (see section on Pharmacological treatment of TRS), and the patient has been treated with two different antipsychotics over a sufficient time with a sufficient dosage without success, a course of medication for treatment-resistant schizophrenia (TRS) should be considered. Clozapine is the most appropriate antipsychotic option in TRS.

Choice of medication

The choice of medication will be determined by the drugs available in the formulary (Fig. 3.4), stage of illness (acute, stable), history of response and compliance, efficacy and tolerability of the available medications, effectiveness in different comorbid psychiatric disorders or suicidal behaviour, and cost-effectiveness. Consideration of all these elements is required to make the right choice for a given patient, along with the considerations in the box.

Choosing medication in acute schizophrenia

- **First- and second-generation antipsychotics are not homogeneous groups of medications.** Antipsychotics within these groups are approved for different indications, have varying pharmacokinetic profiles, are available in different formulations and have side-effect profiles of different prevalence and intensity. On the basis of this, an antipsychotic should be chosen that the patient prefers, which has demonstrated effectiveness for the specific symptoms or syndromes and is effective in the treatment of possible comorbid psychiatric conditions (eg substance abuse disorder or major depression).

- **Currently, most guidelines recommend SGAs as first choice of treatment in patients with acute schizophrenia.** SGAs are especially preferred in patients who:
  - are antipsychotic naïve because of their high sensitivity for the occurrence of EPSs
  - have high EPS sensitivity and early stage or already existing tardive dyskinesia (TD)
  - have primary negative symptoms, possibly in combination with an antidepressant
  - have cognitive dysfunction (SGAs reduce the difference from healthy people, but often do not normalize cognitive deficits)
  - have comorbid psychiatric conditions, especially given that SGAs have shown effectiveness as add-on therapy in several psychiatric disorders, which are frequent in schizophrenia
  - have already shown a poor response or unacceptable side effects under FGAs.
- **Patients who can be treated with FGAs are those who:**
  - are currently responding well to an FGA and have no EPSs, akathisia or tardive dyskinesia
  - have a history of responding better to FGAs than to SGAs.

  In such cases, the lowest dose of a high potency antipsychotic drug is usually the best choice. Thus, haloperidol 2–10 mg/day or its equivalent will be effective and reasonably well tolerated in most patients. The lowest dose is usually not effective in more chronic patients but may suffice in some FEP patients. High doses are likely to cause severe EPSs. The main disadvantage of the FGAs besides EPSs and the risk of tardive dyskinesia, is their lack of effect on cognition and negative symptoms.
- **Choices within the SGAs and FGAs can be additionally made on a variety of dimensions,** the most important being: formulation; cost; need for titration; effect on weight gain, lipids and risk for diabetes; EPS liability; prolactin elevations; mechanism of action; and full side-effect profile (Fig. 3.4).
- **In patients with confirmed treatment-resistant schizophrenia (TRS), clozapine is the medication that has repeatedly shown the best effectiveness.** However, as 40–70% of patients on clozapine are not free of symptoms, subsequent augmentation therapy or antipsychotic combination therapy could be necessary (see section on Treatment-resistant schizophrenia, page 68-76).
- **In the acute phase, many patients require additional treatment with benzodiazepines,** such as for agitation (eg diazepam), anxiety (eg lorazepam) or

Approved labelling, available formulations and dosage strengths of often used first- and second-generation antipsychotics

Antipsychotic	Approved indications	Tablet/capsules (mg)	Liquid	Short-acting intramuscular	Orally disintegrating (mg)	Long-acting injectable (mg)
Second-generation antipsychotic						
Amisulpride	S	50, 200, 400		Yes		
Aripiprazole	S, ABE, MTBD	2, 5, 10, 15, 20, 30	Yes	Yes	10, 15, 20, 30	
Clozapine	S	25, 100			25, 100	
Olanzapine	S, ABE, ABD, MTBD	2.5, 5, 7.5, 10, 15, 20		Yes	5, 10, 15, 20	210, 300, 405
Paliperidone	S	3, 6, 9 (ER)				
Quetiapine IR	S, ABE, ABD	25, 50, 100, 200, 300, 400				
Quetiapine XR	S, ABE, ABD	50, 200, 300, 400 (ER)				
Risperidone	S, ABE	0.25, 0.5, 1, 2, 4	Yes		0.5, 1, 2, 3, 4	25, 37.5, 50
Ziprasidone	S, ABE	20, 40, 60, 80 (capsules)	Yes	Yes		
First-generation antipsychotic						
Chlorpromazine	SZ, ABE	10, 25, 50, 100, 200	Yes	Yes	20, 75, 150	
Haloperidol	S	0.5, 1, 2, 5, 10, 20	Yes	Yes		50, 100
Perphenazine	S	2, 4, 9, 16	Yes	Yes		100

Figure 3.4 Approved labelling, available formulations and dosage strengths of often used first- and second-generation antipsychotics. ABD, acute bipolar depression; ABE, acute bipolar/manic episode; ER, extended release; MTBD, maintenance treatment of bipolar disorder. (Adapted from Weiden 2007.)

sleep disturbance (eg oxazepam). Treatment with benzodiazepines should be used with caution in patients with comorbid substance abuse disorder.

- **For the treatment of behavioural emergencies, there are several short-acting injectable antipsychotic formulations** (Fig. 3.4). They have to be applied according to guidelines for psychiatric emergencies in schizophrenia (see section on Treatment of behavioural emergencies, page 61-68).
- **With the approval of the first second-generation long-acting injectable antipsychotic, prescribing practice for depot antipsychotics has changed.** Risperidone long-acting injectable (RLAI) is the first second-generation depot antipsychotic. It is enclosed in 'microspheres': the microspheres are injected into the body, and slowly dissolve, releasing a constant amount of the risperidone medication. Depot antipsychotics have several advantages compared with oral antipsychotics, and some disadvantages (see Fig. 3.5), as does RLAI compared with conventional depot antipsychotics (see Fig. 3.5).

Advantages and disadvantages of different formulations of antipsychotics

	Advantages	Disadvantages
Depot antipsychotics compared with oral antipsychotics	• Less frequent administration • Certainty of medication delivery, especially by overcoming covert non-adherence • Reduced fluctuations in serum concentration (avoidance of first-pass metabolism), resulting in reduction in metabolites with a decreased risk of drug interactions and reduced dosage with fewer side effects • Reduced risk of accidental or deliberate overdose • Enriched interaction between patient and treatment team, with concomitant increase in opportunities for psychosocial support	• Delayed disappearance of distressing side effects after discontinuation of medication • Occasionally local tissue reactions at injection site
Risperidone long-acting injection compared with depot formulation first-generation antipsychotics	• Avoidance of 'early peak phenomenon' with its increased risk of extrapyramidal symptoms • Avoidance of accumulation in the body with its delayed washout period if medication is discontinued	• Interaction with fluoxetine and paroxetine • Delayed onset of antipsychotic action because of gradual hydrolysis • Must be given every 2 weeks instead of monthly injections with haloperidol decanoate

Figure 3.5 Advantages and disadvantages of different formulations of antipsychotics.

Recommended dosages of oral FGAs and SGAs for acute treatment of schizophrenia					
Antipsychotic	**Usual starting dosage (mg/day)**	**Dose interval[a]**	**Target dose first episode (mg/day)**	**Target dose multiple episode (mg/day)**	**Maximal dosage (mg/day)**
Second-generation antipsychotic					
Amisulpride	200	(1)–2	100–300	400–800	1200
Aripiprazole	(10)–15	1	5–15	15–30	30
Clozapine[b]	25	2–(4)	100–250	200–450	900
Olanzapine	5–10	1	5–15	5–20	20[c]
Paliperidone	6	1	3–6	3–9	12
Quetiapine IR or ER	50–300	IR: 2, XR: 1	300–600	400–750	750[c]
Risperidone	2	1–2	1–4	3–6(10)	16
Ziprasidone	40–80	2	40–80	80–160	160[c]
Zotepine	25–50	2-(4)	50–150	75–150	450
First-generation antipsychotic					
Chlorpromazine	50–150	2–4	300–500	300–1000	1000
Fluphenazine	0.4–10	2–3	2,4–10	10–20	20–(40)
Haloperidol	1–10	(1)–2	1–4	3–15	100
Perphenazine	4–24	1–3	6–36	12–42	56

[a]Recommended distribution of the daily total dose: one time point = 1, two time points = 2, etc; if applicable, higher than recommended doses have to be distributed on several time points.
[b]Clozapine is usually not indicated in first-episode schizophrenia.
[c]Highest approved dose. In some SGAs there are positive experiences of higher than approved doses in special populations (off-label use).

Figure 3.6 Recommended dosages of oral FGAs and SGAs for acute treatment of schizophrenia. Selected FGAs and SGAs are listed. ER, extended release (quetiapine ER is also known as quetiapine prolonged release); IR, immediate release; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

Dosage of antipsychotics

Despite years of clinical and research experience, definitive dose–response curves do not exist for antipsychotic drugs. Figure 3.6 summarizes dosage recommendations for various first- and second-generation antipsychotics.

Determining the dosage for antipsychotics

- **The minimal effective dose (best effectiveness/side-effect ratio) should be chosen.** Lower doses are generally recommended in (1) FEP patients, who tend to be more responsive to treatment and more sensitive to side effects; (2) elderly people, who may metabolize antipsychotic drugs at substantially lower rates and are also more sensitive to side effects; and (3) women, who often require lower overall antipsychotic dosages and are sensitive to prolactin-related side effects.
- **The optimal dose range for FGAs is between 300 and 800 mg chlorpromazine equivalents per day** (6–16 mg haloperidol equivalents per day). There are no significant advantages to using dosages of haloperidol >10–20 mg/day for acute treatment; indeed, dosages of 20 mg may be associated with a substantial number of adverse neurological effects if prophylactic anti-parkinsonian medication is not also given.
- **The dose recommendations for SGAs are consistent with the respective summary of product information (SPI), with some exceptions.** Compared with the respective SPIs there are some differences in clinical practice:
  - Studies on the starting dose of quetiapine immediate release (IR – 200–300 mg/day) and ziprasidone (80 mg/day) have shown successful initiation of treatment with higher than the approved initial dose.
  - Studies of quetiapine IR have found that a titration scheme other than the licensed one was comparably well tolerated (200 to 400 to 600 to 800 mg from day 1 to day 4). Whether it is more effective than the recommended one is still unclear.
  - Several case reports suggest that a number of SGAs possibly have some positive effects in doses above the licensed range. However, robust controlled data, eg on quetiapine, suggest that the standard dose range is appropriate for clinical use in most cases.

Therapeutic drug monitoring

For some antipsychotics it is known that therapeutic drug monitoring (TDM) increases the likelihood of response and reduces the risk of antipsychotic side effects. For these medications TDM should be part of standard care. Within

Therapeutic drug monitoring (TDM) for different antipsychotics

Antipsychotic	Recommended plasma levels (ng/mL)[a]	Recommendations for the use of TDM[b]
Second-generation antipsychotic		
Amisulpride	100–400	3
Aripiprazole	150–250	4
Clozapine	350–600	1
Olanzapine	20–80	1
Paliperidone	?	?
Quetiapine IR	70–170	3
Quetiapine XR	?	?
Risperidone	20–60	2
Ziprasidone	50–120	4
Zotepine	12–120	3
First-generation antipsychotic		
Chlorpromazine	30–300	2
Fluphenazine	0.5–2	1
Flupenthixol	>2	2
Haloperidol	5–17	1
Perazine	100–230	2
Perphenazine	0.6–2.4	2
Zuclopenthixol	4–50	3

[a] Recommended plasma levels are medication concentrations in serum or plasma within the steady state with the highest chance of antipsychotic response.

[b] The graduation is the estimation for the usefulness of TDM for dosage optimization:

1. Highly recommended: several studies support the usefulness of TDM
2. Recommended: at least one prospective study has shown a relationship between plasma concentration and antipsychotic response and there are reports about intoxications within concentrations above the normal range
3. Useful: retrospective studies und single case reports make it plausible that there is a relation between plasma concentration and antipsychotic response
4. Possibly useful: pharmacokinetic studies report about plasma concentrations within therapeutic effective dosages
5. Not recommended: from pharmacological studies TDM is not useful

Figure 3.7 Therapeutic drug monitoring (TDM) for different antipsychotics.

the FGA group this is known for haloperidol, perphenazine and fluphenazine, in the SGA group, for clozapine, olanzapine and risperidone (Fig. 3.7). TDM is important in patients treated with clozapine: studies of treatment-resistant schizophrenia (TRS) have shown a higher response rate for plasma levels >350 ng/mL (8–38% at <350 ng/mL vs 50–75% at >350 ng/mL).

There are also several other indications for TDM:

- When patients fail to respond to what is usually an adequate dose
- When it is difficult to discriminate drug side effects from symptoms such as agitation or negative impairments (eg a high blood level might be associated with increased adverse effects)
- When antipsychotic drugs are combined with other drugs that may affect their pharmacokinetics (drug–drug interactions), such as fluvoxamine, fluoxetine or carbamazepine.
- In very young children, elderly people and patients who are medically compromised in whom the pharmacokinetics of antipsychotics may be significantly altered (eg patients with renal and/or liver insufficiency/cardiovascular diseases)
- When non-compliance or poor compliance is suspected or when compliance is imposed by the legal system
- For monitoring of medications with compulsive TDM for safety reasons (eg lithium).

Antipsychotic treatment algorithm for acute schizophrenia

Algorithms for the treatment of schizophrenia are helpful tools for understanding the course and order of subsequent intervention steps, and in Fig. 3.8 one is presented for acute schizophrenia.

Starting with an SGA

In non-emergency acute schizophrenia, for most patients antipsychotic treatment should start with an SGA. At the time of writing seven different SGAs are available, along with paliperidone and quetiapine extended-release formulations (XR). Choice of medication depends on various factors, which have been described above and are shown in Fig. 3.7. In patients with psychotic relapse, the assessment of the respective reason(s) is the main requirement for an adequate choice of medication. In most, the reason for relapse is partial or full non-adherence with medication. Therefore, simply choosing a new antipsychotic is probably not the right approach because non-adherence is markedly influenced by other factors.

Starting with monotherapy

It should be emphasized that monotherapy should start with a single antipsychotic drug and choice of drug should be based on tolerability, efficacy, cost-effectiveness and cost. Patients should receive an adequate trial without casual addition of a second antipsychotic drug for the duration of that trial, which can then be terminated if

Algorithm for the acute treatment of acute schizophrenia

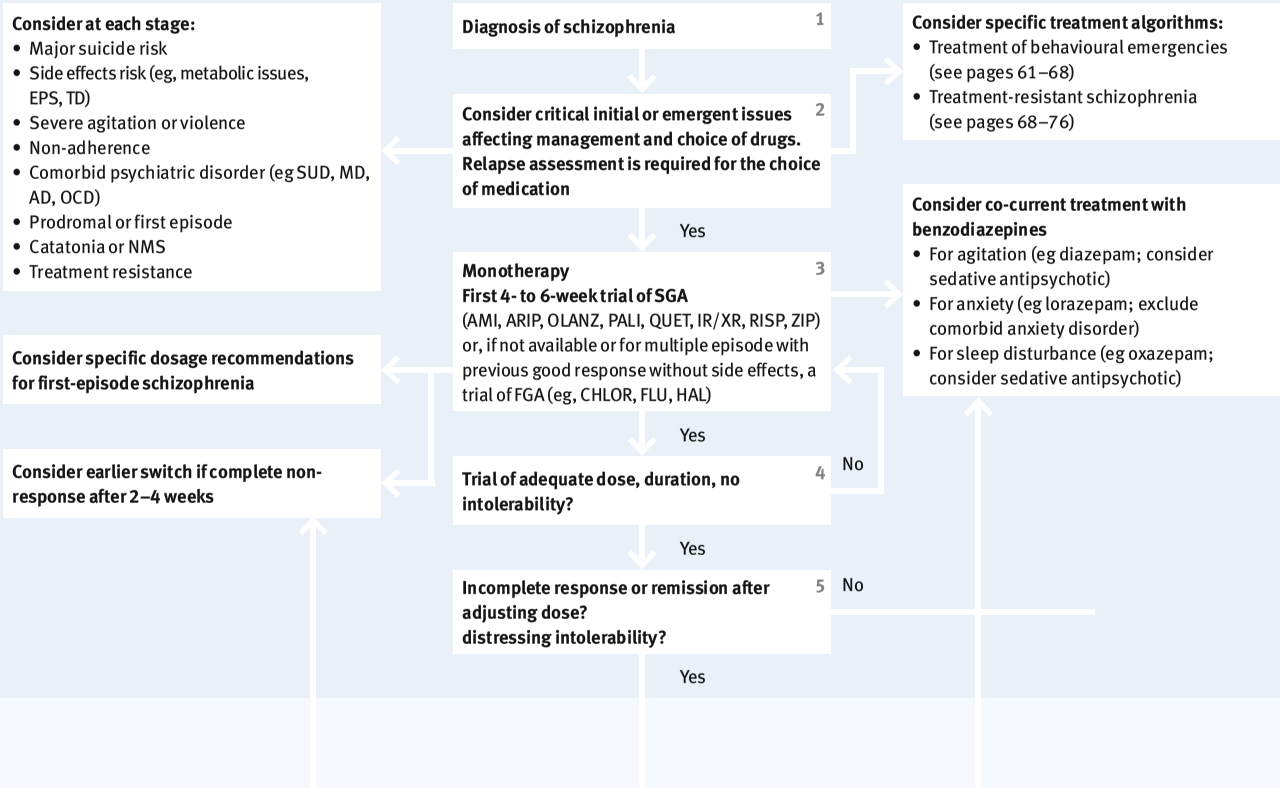


Figure 3.8 Algorithm for the acute treatment of acute schizophrenia. Adapted from the International Pharmacology Algorithm Project (2000).
FGA, first-generation antipsychotics: CHLOR, chlorpromazine; FLU, fluphenazine; HAL, haloperidol. SGA, second-generation antipsychotics: AMI, amisulpride; ARIP, aripiprazole; CLOZ, clozapine; OLANZ, olanzapine; PALI, paliperidone; QUET, quetiapine; RISP, risperidone; zip, ziprasidone.
AD, anxiety disorder: EPS, extrapyramidal motor side effects: XR, extended release: IR, immediate release: MD, major depression: NMS, neuroleptic malignant syndrome: OCD, obsessive–compulsive disorder: SUD, substance abuse disorder: TD, tardive dyskinesia: TRS, treatment-resistant schizophrenia.

there is lack of efficacy or tolerability. Furthermore, the evidence to support the concurrent use of a mood stabilizer or antidepressant during the initial stages of treatment is minimal, so clinicians should be cautious in starting treatment with both an antipsychotic and one or both of these other types of drugs.

Starting dose, titration scheme and target dose

These depend on several factors:

- The target dose for a specific antipsychotic depends on the optimal dose range separated into antipsychotic-naïve and antipsychotic-adjusted patients
- Antipsychotic-naïve patients should generally start on a lower dose, and their target dose is lower compared with antipsychotic-adjusted multiple-episode patients (a 24- to 48-hour antipsychotic-free interval should be considered if indicated)
- Higher starting doses, accelerated titration schemes and higher target doses are recommended in very acute patients
- Antipsychotics in XR formulations can be immediately started at an effective dose
- For the treatment of primary negative symptoms (deficit syndrome) a lower target dose is recommended
- The risk of side effects related to a specific antipsychotic and to individual risk factors should finally guide the starting dose, titration scheme and target dose.

Factors determining antipsychotic response

Response can be partial or full, or there can be complete non-response; it depends on several factors. Some of these factors are not related to a specific antipsychotic, including long DUP, persistent comorbid substance abuse and a low premorbid functioning level. Factors related to the antipsychotics themselves include an adequate dose and an adequate duration of treatment.

Currently, guidelines recommend waiting for 4–6 weeks before considering a patient with schizophrenia to be a non-responder and before switching antipsychotics. However, several study results have questioned this clinical practice. Early response studies have shown that:

- the major psychopathological improvement occurs within the first week
- no or only minimal improvement in the first 2 weeks predicts non-response after 4–6 weeks
- the symptomatic improvement within the first 4 weeks is significantly higher than the additional change during the next year. Overall, these results have questioned the commonly held 'delayed-onset' hypothesis of antipsychotic drugs. Nevertheless, a trial of a single antipsychotic should generally last 2–6 weeks, with at least 2–4 weeks on a dose within the therapeutic range. A

failed trial is one in which the medication dose and duration were adequate and no concomitant medication might be expected to interfere with efficacy, but in which clinical response in core outcome measures, particularly control of positive symptoms, was inadequate and had plateaued at an inadequate level. A trial terminated for lack of tolerability before it meets these criteria should not be considered an adequate trial.

Switching antipsychotics

The decision to switch an antipsychotic can be based on insufficient efficacy, unacceptable tolerability or other inadequate reasons (eg patient's wish). The switching guidelines following should be taken into account (Fig. 3.9).

Guidelines for switching antipsychotics

- Before considering switching, the dose of the current treatment should be optimized to give it an adequate trial. Some side effects decrease over time (eg sedation, hypotension) and it is worth waiting for adaptation. Comorbid symptoms/disorders should be treated adequately before a switch is made. It should be noted that a switch from clozapine to another antipsychotic is often unsuccessful; in such instances, assisting patients to cope with side effects is worthwhile.
- The decision to switch is mainly based on an efficacy/tolerability ratio, with realistic expectations.
- When deciding whether to switch, drug efficacy, receptor profile, tolerability and safety should be considered, as well as variables regarding the patient, illness and patient's environment.
- Psychoeducation should be provided and the patient and family involved in the decision-making process.
- Switching should be done in a crossover procedure; with few exceptions; abrupt switching is neither advisable nor necessary. Crossover has two main advantages: (1) lower relapse risk and (2) reduced likelihood of physical and mental withdrawal reactions.
- Switch should be slower in females and older patients.
- There are three different crossover procedures: (a) taper switch, (b) cross-taper switch and (c) plateau cross-taper switch.
- For patients with unacceptable side effects procedures (a) and (b) are recommended, for patients with insufficiently treated symptoms (c) is recommended. It should be noted that procedure (c) has a greater risk to keep patients on poly-antipsychotic treatment because of enhanced efficacy during the switch.

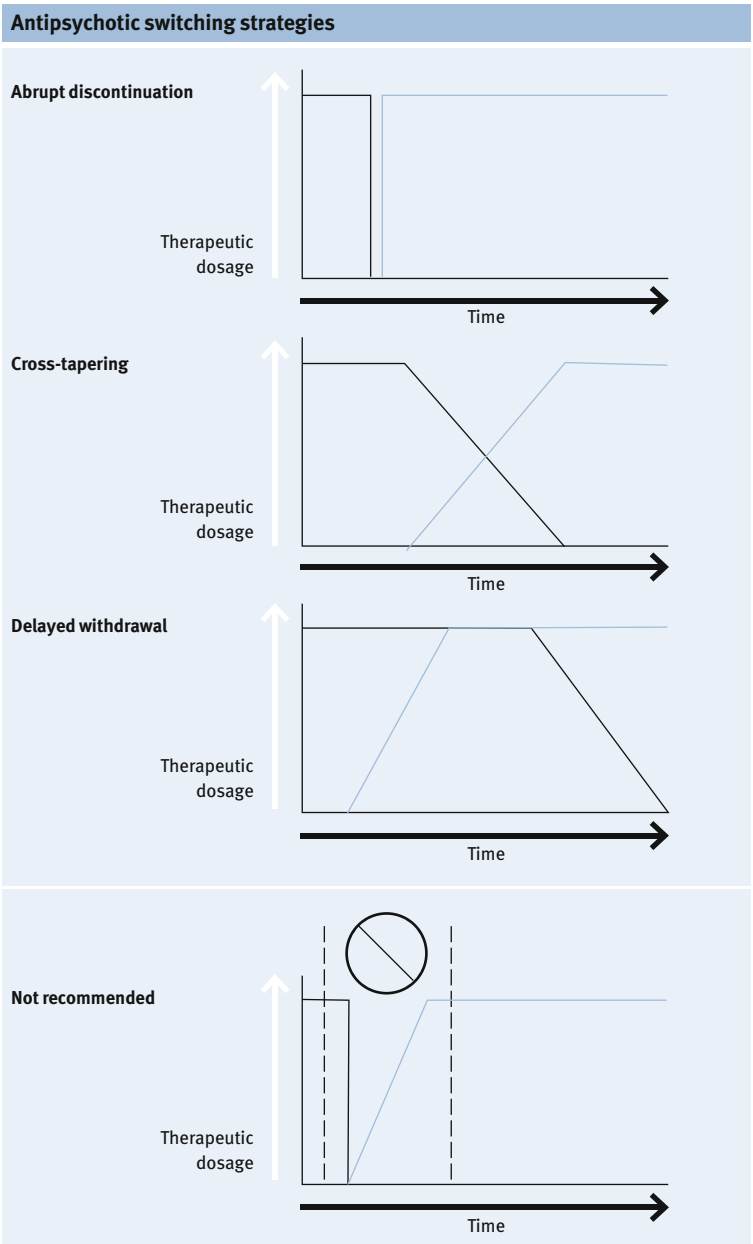


Figure 3.9 Antipsychotic switching strategies.

- If changes are not needed, other medications should not be changed during the switching period.
- Vigilance for emerging side effects or withdrawal symptoms, and appropriate treatment, are required (add respective medication and continue for at least 2 weeks after the side effects disappeared).
- Be available to deal with problems.

There are no clear data to indicate which antipsychotic should be tried when an adequate trial of another antipsychotic fails to control positive symptoms adequately. Before turning to clozapine, most guidelines recommend a second monotherapy trial with an SGA other than clozapine if patients have persistent psychotic symptoms. The choice of the second drug will depend upon the first drug and reasons that may have caused or contributed to the treatment failure. Some experts, in addition, recommend a switch from primary D_2-receptor blocker (eg risperidone, amisulpride) to antipsychotics with a 'dirty' drug profile (multi-receptor antipsychotics, eg quetiapine, olanzapine) and vice versa.

Deciding whether there is treatment resistance

Approximately 30% of patients might be expected to have an unsatisfactory response to two trials of SGAs or FGAs, if response is defined as persistence of moderate-to-severe delusions, hallucinations and disorganized thinking. Patients should also be considered treatment resistant if they have severe negative symptoms despite the control of positive symptoms, suicidal thoughts or aggressive behaviour on a chronic basis. Clinical evidence suggests that treatment with clozapine is indicated for the patient with schizophrenia who has failed two trials with other antipsychotic drugs, regardless of class. For further treatment recommendations see Pharmacological management of TRS (page 68-76).

Treatment of behavioural emergencies

During an acute psychotic episode of schizophrenia, some patients become behaviourally disturbed and may need emergency pharmacological (and psychological) interventions. In the USA 21% of all psychiatric emergencies are due to agitation in schizophrenia. On admission to hospital, 14% of all patients with schizophrenia show aggressive behaviour; 8–10% have to be physically restrained at least once in their life.

There is a variety of preventive strategies to decrease the incidence and severity of psychiatric emergencies in schizophrenia:

- Education and community awareness about schizophrenia
- Environment adaptation (intensive care area [ICA] on the acute ward)
- Implementation of action by an ACT team, with the goal of early detection of deterioration, relapse and psychiatric emergencies
- Aggression management training (AMT) and education for staff
- Early detection of psychiatric emergencies during inpatient treatment, ie assessment of risk factors (see below) and regular assessment of behavioural disturbances in patients at risk
- Use of interpreters for patients who have language difficulties
- Early treatment of low levels of agitation and sleep disturbances.

There are various risk factors for agitation in schizophrenia, which are listed in Figure 3.10. Diagnostic tests may be an important adjunct to the history and physical examination of the agitated schizophrenic patient. Treatable medical conditions should be ruled out. However, most commonly, agitation results from non-adherence with maintenance therapy and disease progression.

Reducing the incidence and severity of psychiatric emergencies

To do this it is necessary to ensure that the environment is prepared and that staff are well trained. The goal of emergency management is to assure safety for patients and staff alike, and to resolve the situation without harm and traumatic experiences.

Risk factors for agitation in schizophrenia

- Male gender
- Medication non-adherence
- Severe psychopathology, especially delusions and hallucinations
- Disorganized subtype of schizophrenia
- Comorbid personality disorder or traits (especially antisocial or borderline)
- Comorbid substance abuse disorder
- Current drug and/or alcohol intoxication
- Admission against will
- History of aggressive behaviour
- Language difficulties
- Low IQ
- Hardness of hearing

Figure 3.10 Risk factors for agitation in schizophrenia.

Non-pharmacological interventions in psychiatric emergencies

There are various possible non-pharmacological interventions, such as placing the patient in a quiet non-threatening environment (eg ICA), reduction of external noise and other stimuli, behavioural management (ie granting privileges for appropriate behaviour), close observation, calm conversation and active listening. The clinician should avoid unprepared confrontations; possibly the patient's key clinician should establish the patient's concerns and attempt to resolve conflict.

Pharmacological interventions in psychiatric emergencies

Oral antipsychotics as first-line therapy

Before resorting to the emergency use of acute intramuscular agents, the first-line pharmacotherapeutic intervention is to convince the patient to accept oral or liquid antipsychotic preparations (Fig. 3.11). The are two possibilities:

1. Use of antipsychotic monotherapy, eg an emergency high dose of an atypical antipsychotic at first (day 1) and an emergency maintenance dose (days 2–5), has been found to be effective.
2. Use of an antipsychotic and benzodiazepine combination, eg risperidone (liquid) plus lorazepam (orally dissolving tablet), has been found to be as effective as haloperidol (intramuscular) plus lorazepam (orally dissolving tablet).

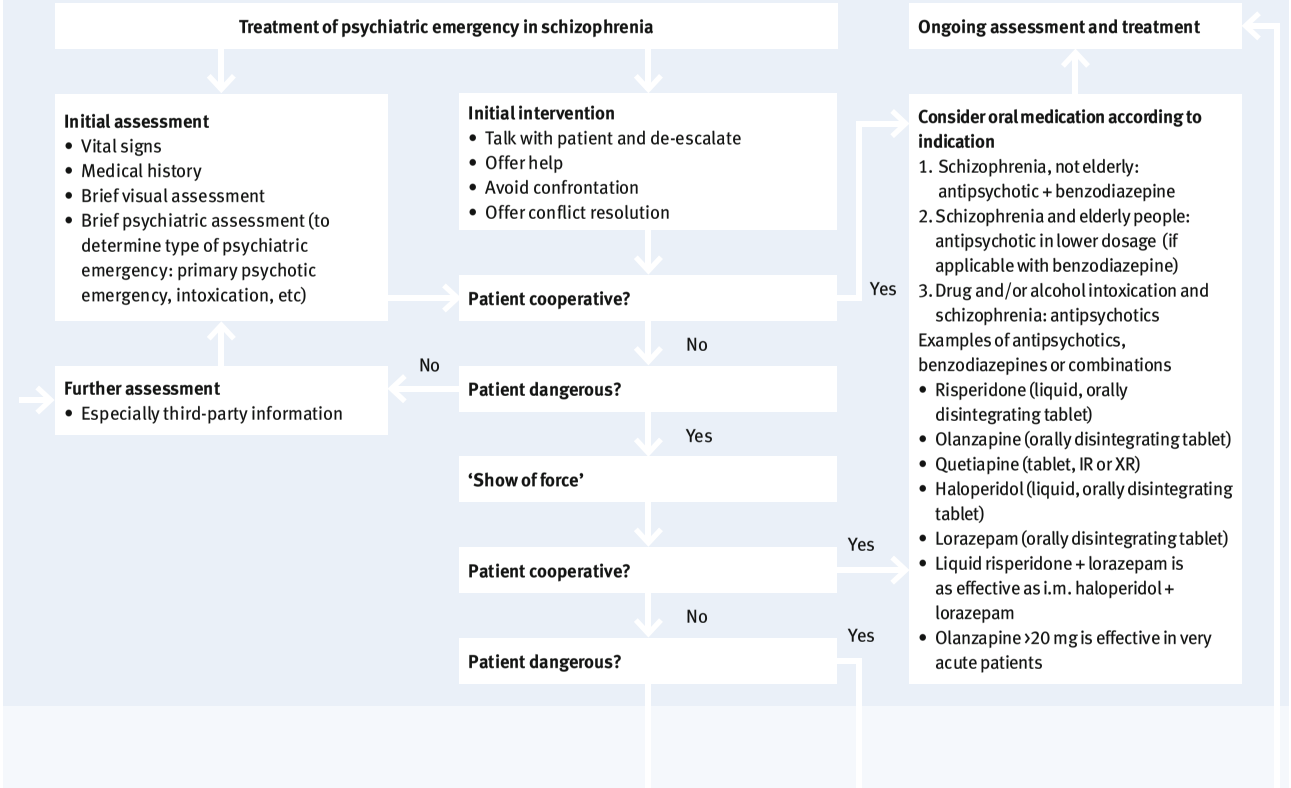
In many patients, this step is sufficient to resolve the crisis, although it should be noted that the use of adjunctive benzodiazepines is restricted or forbidden in older patients with schizophrenia or if drug or alcohol intoxication has caused the emergency.

If the patient refuses medication, the next step is 'show of force'. In this, a larger group of staff tries to convince the patient to accept oral medication by explaining that parenteral medication will be necessary if he or she will not accept oral medication.

Intramuscular antipsychotics as second-line pharmacotherapy

If the patient still refuses medication, or if a rapid response is needed due to violent behaviour or other behavioural disturbances, parenteral medication (intramuscular injection) will be necessary (Fig. 3.12). In this situation, the team members must all ensure that they clearly communicate the necessity of parenteral medication and calmly explain this to the patient. Here, it is necessary to understand that agitation usually results from psychotic anxiety and that measures taken against the will of the patient can exacerbate this anxiety and lead to traumatization. Therefore, such a decision should be taken only after all alternatives have been considered and a psychiatrist has been consulted.

Treatment algorithm for psychiatric emergencies in acute schizophrenia



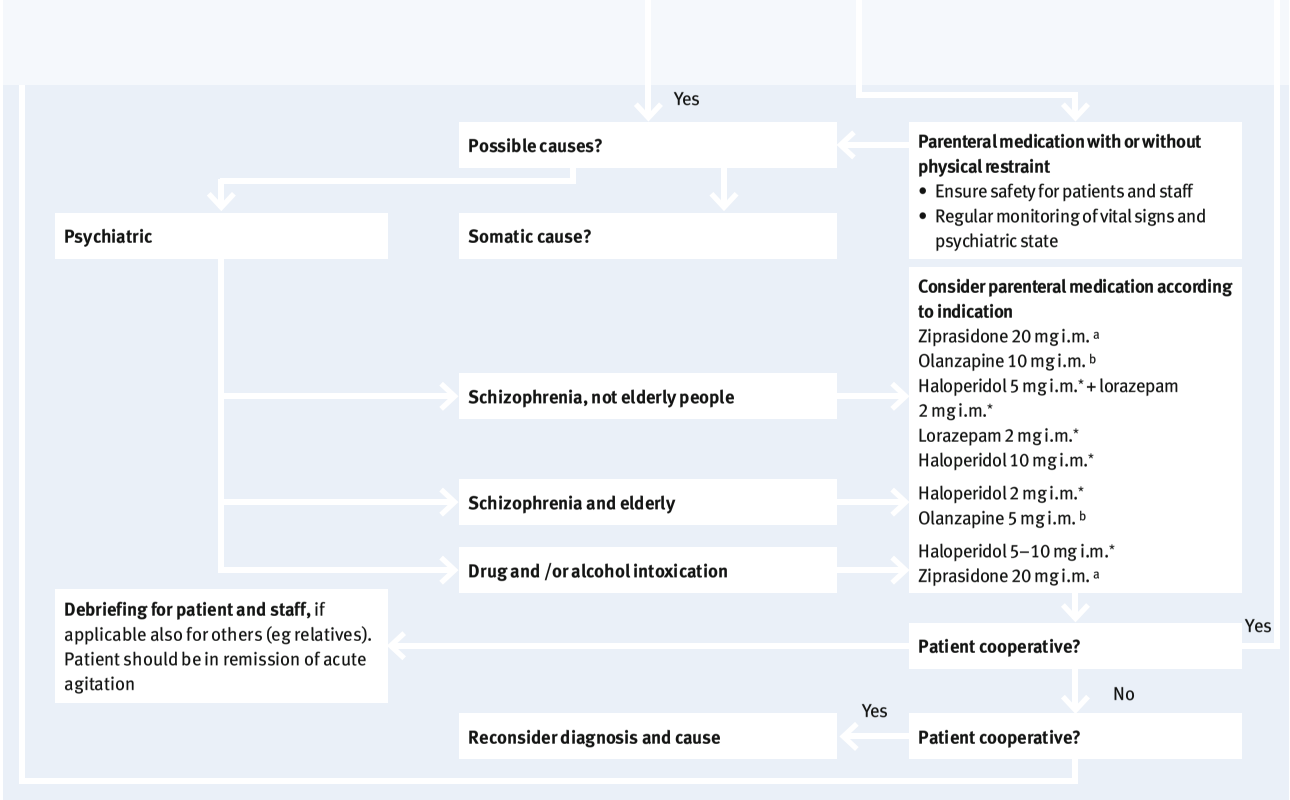


Figure 3.11 Treatment algorithm for psychiatric emergencies in acute schizophrenia. i.m., intramuscularly; IR, immediate release; i.v., intravenously; XR, extended release. (Adapted from Allen et al 2001, 2005.) [a] Not for use if QTc interval prolonged. [b] Not for use together with benzodiazepines. *Also as i.v. (intra venously) usable.

Recommended indications and doses of intramuscular medications for emergency treatment of schizophrenia

Medication	Approved indications	Dosage (mg)	PPL (h)	Advantages	Disadvantages
Lorazepam IM	• Psychiatric emergency • Status epilepticus • Pre-anaesthetic • Anxiety state	• 0.5–2.5 • Up 10 mg/day • IV not more than 2 mg in one application	10–20	• Treatment of concurrent alcohol withdrawal • IV application possible	• No antipsychotic effect • Respiratory depression
Haloperidol IM	• Schizophrenia • Psychotic disorders, especially paranoid • Mania and hypomania • Behavioural disturbances in mental retardation or organic brain damage • Adjunct therapy in psychomotor agitation, excitement, violent or dangerously impulsive behaviour • Nausea and vomiting	0.5–7.5	12–36	• Persistent antipsychotic effect • IV application possible	• EPS • Reduced epileptic threshold • No treatment of concurrent alcohol withdrawal
Ziprasidone IM	• Agitation • Psychotic disorders	10–20	2.2–3.4	• Persistent antipsychotic effect • No or low risk for EPS • Less experience compared with other drug IM options	• QTc prolongation • No treatment of concurrent alcohol withdrawal
Olanzapine IM	• Agitation • Psychotic disorders • Bipolar disorder	10	34–38	• Persistent antipsychotic effect • No or low risk for EPS • Less experience compared with other drug IM options	• No concurrent treatment with benzodiazepines possible • No treatment of concurrent alcohol withdrawal • Weight gain in long-tem treatment
Zuclopenthixol acuphase IM	• Agitation • Psychotic disorders • Bipolar disorder	50–150	36	• In most cases no repeated injections necessary	• EPS • Contraindication in case of alcohol and/or drug intoxication • Severe sedation • Delayed onset of action (6–8 h after injection)

Figure 3.12 Recommended indications and doses of intramuscular medications for emergency treatment of schizophrenia. EPS, extrapyramidal motor symptoms; IM, intramuscular; IV, intravenous; PPL, peak plasma level. [a]No use in case of prolonged QTc interval. [b]No use together with benzodiazepines.

Short-acting intramuscular haloperidol or its equivalent is the most widely used agent in the emergency situation. Doses of 5 mg are usually given and may be repeated at intervals as needed. The maximum total daily dose of short-acting intramuscular haloperidol should not exceed 20 mg/day. For patients receiving short-acting intramuscular haloperidol, it is recommended that anticholinergics be started at the time of the first injection and continued for at least 1 week before tapering and discontinuing. Alternative SGAs are intramuscular olanzapine and intramuscular ziprasidone. Intramuscular olanzapine is usually given in doses of 2.5–10 mg; the acute dose of intramuscular ziprasidone is 10–20 mg. Intramuscular ziprasidone and haloperidol have been shown to prolong QTc to the same extent. Serious cardiac adverse effects with ziprasidone appear to be quite rare in the absence of pre-existent cardiac conduction disorders or other predisposing risk factors; no cases of torsades de pointes have been reported with intramuscular and oral ziprasidone.

Treatment with intramuscular SGAs might be recommended in patients with known sensitivity to develop EPSs or other situations where it is imperative to avoid EPSs, eg FEP patients for whom possible dystonic reactions would be most distressing. Apart from short-acting SGAs, short-acting intramuscular benzodiazepines (lorazepam i.m.) may be quite helpful as an adjunctive treatment or an alternative to intramuscular antipsychotic drugs.

In prolonged emergencies, a well-established option to avoid repeated intramuscular injections is the use of short-acting depot medications (eg zuclopenthixol acetate). A disadvantage of this is the delayed onset of action (2–8 h), although patients may respond after 30–45 min. Zuclopenthixol acetate is effective for 24–36 h; repeated zuclopenthixol injections within 24 hours of a previous dose are mostly not required (see Figs 3.11 and 3.12). As a result of concerns about its prolongation of the QTc interval (see pages 105–107), intramuscular droperidol should not be a first-line option for the agitated psychotic patient. It is not appropriate to start long-acting depot preparations in this setting.

After parenteral tranquillization, vital parameters should be monitored, including temperature, pulse, blood pressure and respiratory rate, every 10 min for 1 hour, then half-hourly to hourly according to the half-life of the medication. Caution should be applied because of the risk of reduced respiratory rate, irregular or slow pulse, fall in blood pressure or unconsciousness. Patients receiving high-potency conventional antipsychotics in short-acting intramuscular forms should be monitored daily for signs of acute dystonia, akathisia or impending neuroleptic malignant syndrome. If available, ECG monitoring is also recommended. With the reduction of the acuteness of the situation,

growing awareness and traumatic reactions in patients, staff, family members or other caregivers make a 'debriefing process' necessary. All emergency steps including the debriefing process should be documented.

Pharmacological management of TRS

The management of patients with TRS includes its early detection and pharmacological and psychosocial treatment.

Early detection of TRS

Early detection of TRS represents a significant clinical challenge because it is complicated by several factors:

- The multidimensional approach of TRS
- The absence of distinct categories along the continuous spectrum from treatment response to complete non-response
- The lack of generally valid predictors for TRS.

Early identification is a major objective because pharmacological and psychological interventions for refractory patients differ from those for non-refractory patients. The possibility of TRS should be considered right from the start of treatment. This recommendation, especially evident for patients who fulfil the diagnostic criterion of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) of 6 months' duration of psychotic symptoms at initial presentation, is mainly based on the following research results:

- Several of the risk factors for TRS are already evident at initial presentation (Fig. 3.13), eg structural brain abnormalities, long duration of untreated psychosis or poor pre-morbid functioning, and some of them are not treatable by this stage. As such, patients with certain risk factors have to be monitored for TRS quite early in treatment
- Response in the first 3–6 months after start of initial antipsychotic treatment is highly predictive for subsequent TRS
- With each relapse, there is a great risk for secondary TRS.

Pharmacological treatment of treatment-resistant schizophrenia

Patients with TRS require specific pharmacological interventions, best applied according to a TRS treatment algorithm. Pharmacological treatment of TRS is a difficult task because resistance to treatment can occur in various phenomenological domains including symptoms, psychosocial functioning and/or quality of life, and pharmacological and psychosocial interventions for each of these domains can differ markedly (Fig. 3.14). However, in most cases treatment resistance affects many of these domains simultaneously.

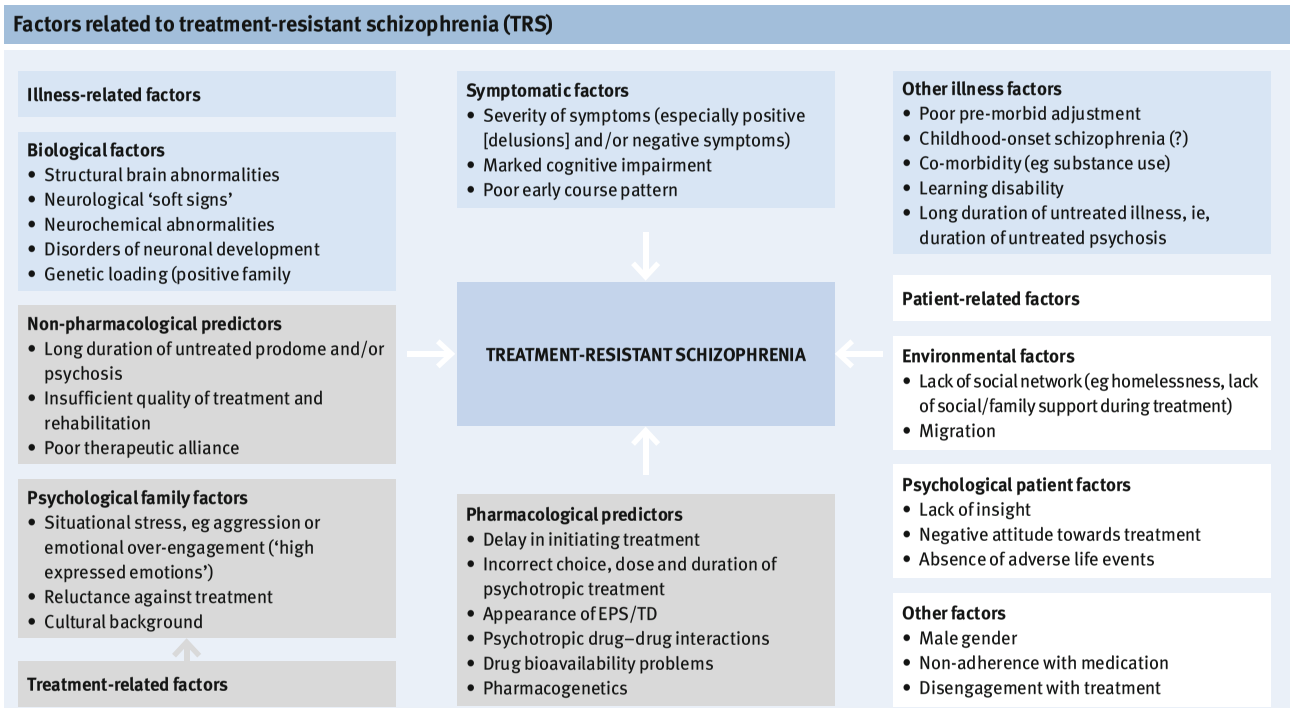
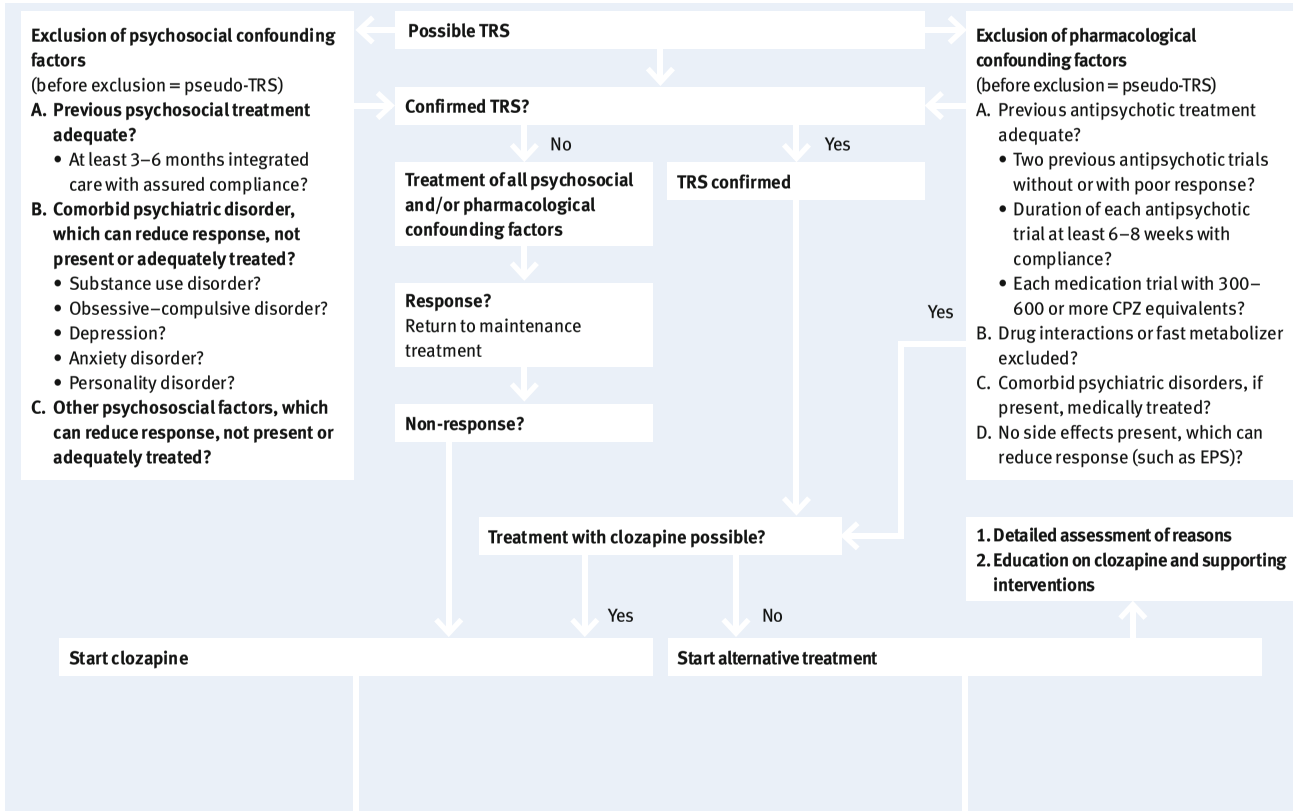


Figure 3.13 Factors related to treatment-resistant schizophrenia (TRS). EPS, extrapyramidal symptoms; TD, tardive dyskinesia.

Pharmacotherapeutic algorithm for treatment-resistant schizophrenia (TRS)



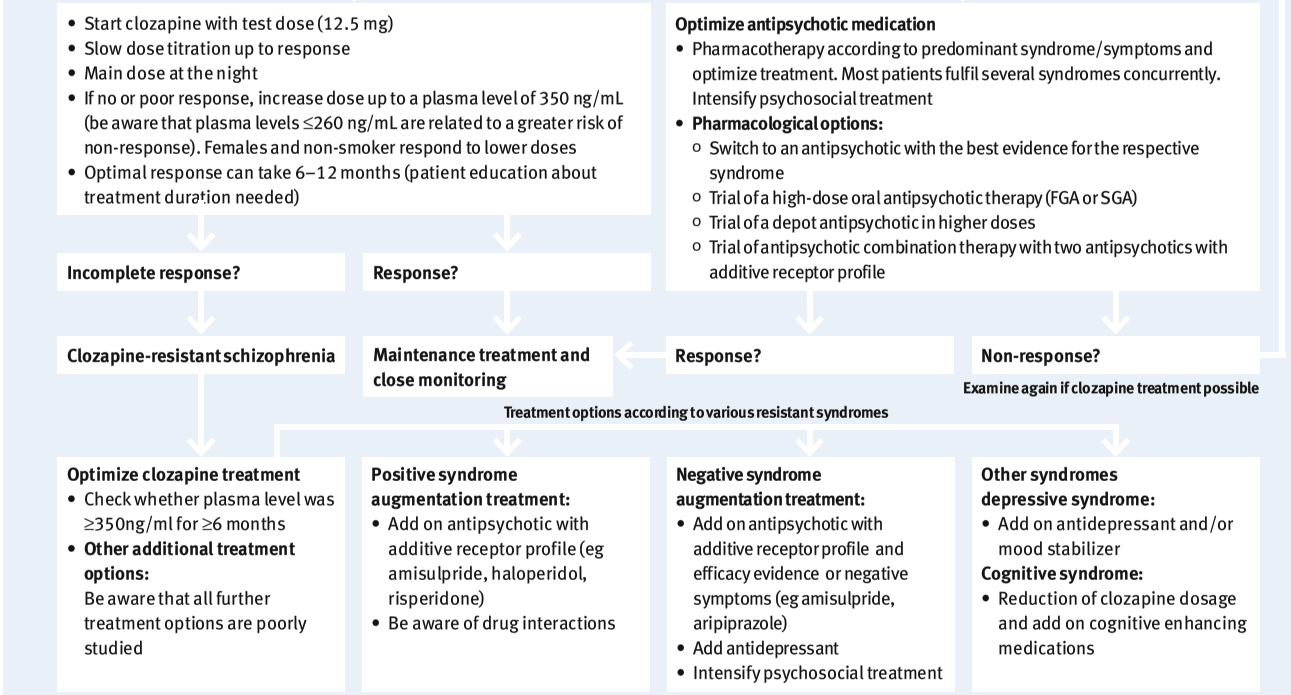


Figure 3.14 Pharmacotherapeutic algorithm for treatment-resistant schizophrenia (TRS). These are general guidelines that must be adapted to the individual needs of each patient. FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

Pharmacological management of TRS can be conducted in four stages, as follows.

Stage 1

At first, the phenomenological domain affected by treatment resistance must be identified (Fig. 3.14). However, it is rare that only one domain such as symptoms or functioning is affected, and in most cases there are typical domain combinations affected by TRS, eg:

- Chronic delusions and concurrent social and behavioural deviations such as recurrent aggression and hostility
- Chronic acoustic hallucinations with impaired social functioning
- Chronic negative symptoms with concurrent cognitive deficits and social withdrawal and vocational deficits.

In stage 1, the clinician must also ensure that the patient truly meets the criteria for TRS. There are a variety of confounding factors that have to explored and excluded before TRS is diagnosed (Fig. 3.14); these are clinical factors that simulate resistance even though the patient is not really resistant. Probably the most common and important are insufficient previous pharmacological interventions, repeated medication non-adherence, persistent substance abuse or an insufficient prior psychosocial treatment. At this stage it is therefore necessary to review risk factors for TRS, the type and success of previous interventions, and the respective course of illness.

The most common scenario is that the patient already had several TRS risk factors at initial presentation (most commonly long DUP, poor premorbid functioning, lack of insight), was already responding poorly to the first treatment, and was repeatedly non-adhering to medication with subsequent relapse and illness progression. Review of the course of illness and treatment history should, at the same time, guide the optimization of interventions. This includes the administration of antipsychotic medication at sufficient dosage and with sufficient compliance for at least 4–6 weeks or even longer, the successful treatment of possible comorbid psychiatric disorders, especially affective and substance abuse disorders, and concurrent management of medication side effects, especially those that can affect antipsychotic response (eg EPSs) or induce persistent symptoms (eg depression or negative symptoms related to untreated EPSs). In the case of medication non-adherence, intramuscular depot preparations, preferably SGAs, should be used. At this point, if the patient is still not responding to treatment, stage 2 can be entered.

Stage 2

After identification of the treatment-resistant domain or treatment-resistant domain combination, the exclusion of important confounding factors and the optimization of biopsychosocial interventions, the next step is a switch to clozapine (see Fig. 3.14). Clozapine is considered to be the most effective antipsychotic in TRS; this holds true with respect to both FGAs and SGAs. However, the benefits of the drug must be weighed against its serious adverse effects, including potential risks of neutropenia and agranulocytosis, weight gain, obesity and diabetes, epileptic seizures and cardiomyopathy.

A clozapine dose of approximately 350–500 mg/day is considered to be sufficient for many patients with optimal plasma levels between 350 and 420 ng/mL. The dose must be slowly raised to minimize hypotension and sedation; before determining that it has not been more effective than previous treatments, it should be increased up to as much as 900 mg/day if the patient can tolerate it. No other antipsychotic drug should be given concomitantly, except during the titration period if indicated to control symptoms.

There are conflicting findings with respect to the necessary duration of treatment before response can be evaluated properly. In several studies, treatment-resistant patients showed strongest improvement within the first 8–12 weeks (50% of patients), whereas other studies report longer periods of 6–12 months. There is consensus that clinicians should consider a minimum trial duration of 6 months, but they should be aware that many as 40–70% of those treated with clozapine do not respond adequately even to an optimal treatment regimen.

The decision about when clozapine should be discontinued or combined with another antipsychotic is also difficult, mainly due to a lack of alternatives, negative experiences after patients were switched from clozapine back to another antipsychotic, and the fact that clozapine has additional potential effects of special importance (eg reduction of aggressive behaviour, reduced suicidality, and positive influence on tardive dyskinesia and comorbid substance abuse disorder).

What if the patient refuses clozapine, or was unable to tolerate it during a past trial? First, it should be determined whether the patient's refusal is based on incompetence to consent to the trial. It may be that the patient is unable to appreciate the potential benefits, due to denial or lack of insight into the severity of the disease. Appropriate action to obtain guardianship may be indicated. If there has been a previous trial of clozapine, full details of what happened should be obtained: perhaps the side effects that led to premature termination of the trial were not

contraindications to a re-trial of clozapine. Once other treatments have been tried and the patient remains treatment resistant, it may be worth re-trying clozapine with more cautious dosage escalation, avoidance of potential drug interactions and aggressive management of the side effects. Seizures, sedation and hypotension are side effects that might be dealt with more successfully on a second course.

If clozapine is definitely not an option, and monotherapy trials have been fully adequate, there are a number of antipsychotic combination strategies available. All have a very limited evidence base for usefulness. The pharmacotherapy at this stage depends on the affected TRS domains. For resistant positive symptoms, a primary D_2-receptor blocker (eg risperidone, paliperidone or haloperidol) could be combined with a 'dirty' drug profile antipsychotic (multi-receptor antipsychotics such as olanzapine or quetiapine); adjunctive therapy with a mood stabilizer could be also an option. For resistant negative symptoms, adjunctive therapy with antidepressants is an option. Finally, the success of previous interventions should be reviewed and the most successful previous pharmacological intervention reinstated.

Stage 3

With respect to positive symptoms, 40–70% of those treated with clozapine monotherapy do not respond adequately despite optimal administration. This condition has been designated clozapine-resistant schizophrenia (CRS). CRS affects approximately 10% of all patients with schizophrenia, with subsequent proportional increase with each relapse. Before establishing the diagnosis of CRS it is necessary to confirm that:

- the patient has been taking clozapine adequately for at least 6 months
- clozapine blood levels are in the therapeutic range (≥350 ng/mL)
- the clozapine plasma level was >350 ng/mL during the complete 6-month treatment period
- uncontrolled comorbid drug abuse is absent.

If factors compromising clozapine response are ruled out, a next possible treatment step is clozapine augmentation (see Fig. 3.14). However, the current body of evidence consists largely of data from smaller open trials and case series/reports, although data from a limited number of controlled studies are now available. In general, augmentation trials should be guided by existing evidence and a treatment plan incorporating a clear understanding of target symptoms. A means of evaluating outcome effectively needs to be in place, and the trial should be circumscribed to prevent needless polypharmacy. As a first principle, an endpoint needs to be established and the trial discontinued unless results confirm added benefits.

There are various augmentation strategies (see Fig. 3.14), including numerous medications and electroconvulsive therapy (ECT). With respect to antipsychotics, risperidone, amisulpride, olanzapine, quetiapine and aripiprazole have been found to have positive effects, and also aripiprazole and amisulpride, especially in the case of resistant negative symptoms. Mood stabilizers, including lithium, valproate and lamotrigine, may be helpful in some patients. The most robust evidence for improving positive symptoms in partial responders to clozapine suggests that a course of ECT is most effective.

Stage 4

Maintenance treatment with clozapine requires some specific clinical procedures:

- Patients must be monitored with respect to the occurrence of agranulocytosis
- Other side effects should be monitored closely
- Dose reduction or discontinuation of clozapine should be done with caution.

Agranulocytosis presents with symptoms such as fever, stomatitis and neutropenia, with normal erythrocyte and thrombocyte count in peripheral blood. There is a higher risk of agranulocytosis for patients with previous bone marrow disorder or co-medication with risk of bone marrow injury. Women aged >40 years who have been treated with high dosages of antipsychotics are also at high risk. Of all agranulocytosis cases 85% occurred within the first 18 weeks of treatment. Therefore, weekly leukocyte counts for the first 18 weeks and 4-weekly counts subsequently are current treatment requirements. If the leukocyte count decreases or influenza-like symptoms, such as fever, sore throat, cold shivers or mouth sores, appear, an immediate total leukocyte and differential count should be carried out on an emergency basis. If it shows a leukopenia $<3500/mm^3$ or neutrophil granulocytes $<1500/mm^3$, clozapine must be discontinued. After discontinuation the haematological picture generally normalizes within 2–4 weeks. Prognosis in agranulocytosis is better when it is detected and treated early on with haematopoietic growth factor; nowadays the mortality is significantly lower than in the past.

Clozapine has some potential side effects such as weight gain, obesity, metabolic syndrome, type 2 diabetes, epileptic seizures and cardiomyopathy. Education about weight, diet and exercise is recommended from the start of clozapine treatment. Reducing or reversing the weight gain requires attention to diet and exercise as the first line of treatment. Dosage reduction may be needed to control the weight gain associated with clozapine in some but not all patients.

There have been no systematic studies of reduction of the dose of clozapine at some time after the optimal dose has been established. For that reason, if dosage reduction is attempted, it should be done very gradually. Of great importance in using clozapine is the possibility of withdrawal psychosis if withdrawal is abrupt. This may be severe and unresponsive to medications other than clozapine. Therefore, whenever possible, clozapine should be tapered as another antipsychotic drug is introduced. One month of overlap is likely to minimize the risk of withdrawal psychosis. If clozapine is stopped for more than 48 hours, it must be re-started with a dose of 12.5–25 mg and then, if there are no respiratory/cardiovascular symptoms, the dose may be quickly raised back to its previous level. If necessary, in order to obtain some degree of relief of very severe psychosis after withdrawal, the initial dose may be higher.

3.2.3 Treatment in the maintenance phase including relapse prevention

While patients typically recover from a first episode of schizophrenia, the long-term course for many patients is still characterized by chronic illness, disability and relapse. However, a moderately large subgroup of patients experience periods of recovery, including both adequate psychosocial functioning and the absence of major symptoms, lasting several years or longer.

The long-term, or maintenance, phase should be separated into a stabilization phase and a relapse prevention (recovery) or 'stable' phase. This differentiation is helpful in understanding the greater vulnerability of patients in the stabilization after the acute phase and the fact that many patients need a considerable period of time for complete recovery. The following points with respect to the maintenance phase, including relapse prevention, are important: the two phases are the stabilization phase (approximately 3–6 months after the acute phase) and the 'stable' phase. The stable phase is usually associated with maintenance treatment, for patients who meet criteria for being stable as well as those who continue to have persistent symptoms. General recommendations for treatment in the maintenance phase are listed in Fig. 3.15.

Relapse is common in schizophrenia. During the first 5 years after initial treatment more than 80% relapse, most of them more than once. Risk factors for relapse mainly comprise medication non-adherence (see section 2.4, Chapter 2, page 11), service disengagement (see section 2.4, Chapter 2), persistent substance use (see section 2.5, Chapter 2, page 15), incomplete remission within the first treatment (see section 3.2.2, page 44), cognitive deficits with reduced stress tolerance and reduced medication adherence (see section 2.2, Chapter 2, page 4) and inappropriate psychosocial treatment (see section 3.4, page 108).

Recommendations for maintenance treatment of schizophrenia

General principles

- Assertive community treatment (ACT) can support service engagement and medication adherence. It could further reduce the risk of full relapse by early relapse detection and early relapse intervention. Compared with intensive case management (ICM), ACT is better in preventing relapse
- Maintenance treatment should comprise interventions to prevent relapse and to promote recovery, most importantly psychoeducation, family interventions, compliance therapy, cognitive–motivational addiction therapy, cognitive–behavioural therapy interventions, social skills training and social support
- Maintenance treatment should be organized within one specialized centre and provided by two clinicians (ie case manager and physician) supported by an ACT team
- Maintenance care should further focus on:
  - regular assessment of mental state including information given by relevant others
  - regular review of pharmacotherapy, including efficacy, tolerability, early detection and treatment of somatic illnesses, and risk of non-adherence
  - regular social support if needed
  - regular assessment of suicidal behaviour, risk of suicide attempt and completed suicide
  - regular assessment (and treatment) of comorbid psychiatric disorders

Use of antipsychotics

- Maintenance dose range is 300–600 chlorpromazine (CPZ) equivalents (oral or depot) per day (‹300 mg CPZ equivalents/day increases risk of relapse)
- Reassessment of dosage level or need for maintenance antipsychotic therapy should be ongoing
- Continuous dosage regimens should be used: targeted, intermittent dosage maintenance strategies should not be used routinely instead of continuous dosage regimens because of increased risk of symptom worsening or relapse (see text). Exceptions are patients who refuse maintenance or for whom some other contraindication to maintenance therapy exists, such as side-effect sensitivity
- Depot antipsychotics should be strongly considered for patients who have difficulty complying with oral medication or prefer the depot regimen; depot therapy may be used as a first-option maintenance strategy
- Duration of pharmacotherapy depends on several factors (see text)

Figure 3.15 Recommendations for maintenance treatment of schizophrenia.

Maintenance treatment with antipsychotics

The efficacy of antipsychotics in preventing relapse is uncontested, and a number of studies support this:

- A study of 3500 patients found that relapse rates of patients treated with placebo were 75% compared with 15% in patients treated continuously with antipsychotics
- On a monthly basis, the relapse rate with placebo was 10%, compared with 2–3% seen with antipsychotic treatment
- The difference between placebo and antipsychotic medication is approximately 50–60%, with most studies referring to a time period of 1–2 years.
- Studies have also shown good relapse prevention in the long term: in one study patients who had remained relapse free for 2–3 years had then discontinued antipsychotic treatment. Thereafter, the 1-year relapse rate was 65%, with most relapses occurring between 3 and 7 months after discontinuation
- A similar relapse rate in patients who had been relapse free for 3–5 years before discontinuing antipsychotic treatment (62% relapse rate after discontinuation).

Thus, accumulated evidence suggests that the vast majority of patients with schizophrenia will experience a relapse after discontinuation of antipsychotics, even after more than 5 years of successful maintenance treatment. Recommendations for the use of antipsychotics in the maintenance phase are listed in Fig. 3.15.

Maintenance therapy strategies

There are three different long-term maintenance therapy strategies:

1. Continuous antipsychotic treatment with oral or depot antipsychotics in usual dosage
2. Continuous antipsychotic treatment with oral or depot antipsychotics in low dosage
3. The targeted or intermittent treatment strategy.

With respect to (1) and (2), the decision about the optimal drug dosage during the maintenance phase can be particularly difficult, especially because the drug cannot be titrated against clinical response in the stable phase. If the dosage is too low, this may not be apparent until the patient relapses. In addition, the low-dosage strategy has not been studied with SGAs. Thus, comparable to the recommendation within the acute phase, the antipsychotic dosage in the maintenance phase should be 'minimally effective'.

In strategy (3), patients who are stable have their antipsychotics gradually decreased until medications are completely discontinued. At the earliest signs of symptomatic recurrence, antipsychotics are reinstituted. Accumulated evidence suggests that intermittent treatment results in relapse rates that are twice as high as those with continuous treatment. This difference is caused mainly by difficulty in detecting early warning signs, difficulty of predicting relapse through early warning signs, and the abruptness and speed of relapse in some patients. Exceptions are patients who refuse maintenance or for whom there is some other contraindication to maintenance therapy, such as side-effect sensitivity.

Depot antipsychotics in the maintenance phase .

Antipsychotics can be administered in long-acting injectable forms. There are several injectable FGAs, but only two SGAs, risperidone and olanzapine, are available in depot formulation (Fig. 3.16). For a comparison of depot and oral formulations, as well as depot formulations of FGAs and SGAs, see figure 3.5 (page 51).

3.2.4 Duration of prevention of antipsychotic relapse

Several factors must be taken into account when considering how long the patient should be treated with medication. In general, there is a growing body of evidence to suggest the value of continuing medication for a sustained and possibly indefinite period. There are several findings that support this:

- It is still not known for how long the patient must remain stable before discontinuation of antipsychotics is safe with respect to relapse. Relapse rates after discontinuation are high in the first 2–5 years (70–90%). Following discontinuation after a 5-year stable phase the relapse rate is still >60%.
- Each relapse can have several consequences for the long-term outcome and prognosis:
  - decreased antipsychotic response with the need for higher antipsychotic dosages and the risk of increased side effects
  - a prolonged duration to reach symptomatic remission
  - increased risk of residual symptoms with each subsequent relapse.

Taking these findings into account, general guidelines applicable to all patients are not available and would possibly be contradictory. As noted earlier, the decision about how long a patient should take an antipsychotic should be made together with the patient and relatives, taking into account not only current knowledge about relapse prevention but also the personal context of the patient (eg psychiatric history, comorbidity and knowledge about early warning signs).

Recommended doses of depot first- and second-generation antipsychotics in maintenance treatment of schizophrenia

Antipsychotic	Strength supplied	Dose multiplication factor[a]	DI[b]	Dosage in the long-term treatment (mg/pre DI)	Highest possible dosage (mg/pre DI)
Second-generation antipsychotics					
Risperidone microspheres	25 mg, 37.5 mg and 50mg	?	• Every 2 weeks • Onset of action after 3 weeks • Peak plasma level: 4–6 weeks	25–50	50
Olanzapine pamoate	150, 210, 300 mg/2 weeks 405 mg/4 weeks	?	• Every 2–4 weeks	150–405 mg every 2–4 weeks	300 mg/2 weeks
First-generation antipsychotics					
Flupenthixol decanoate	(2%)–10 mg (0.5 mL) (2%)–20 mg (1 mL) (10%)–100 mg (1 mL)	3–5	• Every 2–3 weeks • Initial recommended dose: 20 mg • Peak plasma level: 4–7 days	20–60	100
Fluphenazine decanoate	12.5 mg (0.5 mL) 25 mg (1 mL) 50 mg (0.5 mL) 100 mg (1 mL)	2.5–6	• Every 4 weeks • Initial recommended dose: 2.5–12.5 mg • First peak plasma level: 8–12 hours • Second peak plasma level: 8–12 days	• 6.25–25 every 2–3 weeks • 25–50 every 4 weeks	100
Haloperidol decanoate	50 mg (1 mL) 150 mg (3 mL)	10–15	• Every 4 weeks • Peak plasma level: 3–9 days	• Symptom suppression: 100–200 • Prophylaxis: 25–150	300
Zuclopenthixol acetate	50 mg (1 mL) 100 mg (2 mL)	–	• Every 1–3 days • Peak plasma level: 36 hours	50–150	200
Zuclopenthixol decanoate	200 mg (1 mL)	5–10	• Every 2–4 weeks • Peak plasma level: 4–7 days	100–350	400

[a]Dosage of depot antipsychotic in relation to oral dosage = previous oral dosage x multiplication factor.
[b]DI, dosage interval.

Figure 3.16 Recommended doses of depot first- and second-generation antipsychotics in maintenance treatment of schizophrenia.

From a risk–benefit perspective, actual and possible future side effects should also be taken into account.

Several expert consensus guidelines recommend that patients with first-episode schizophrenia should be maintained on an antipsychotic for 12–24 months after remission of psychotic symptoms. This recommendation is also applicable for children and adolescents with schizophrenia. Nevertheless, studies suggest that there is a relapse risk of 70–90% within the first 5 years of first-episode schizophrenia, and that those patients who discontinue antipsychotic medication have the highest risk. In reverse, it can be argued that approximately 20% of the patients would remain well without maintenance antipsychotic treatment. However, identifying patients who do not need ongoing antipsychotic treatment in the long term is difficult. Although some patient and illness characteristics appear to indicate a lower risk of future relapse, criteria of definitive prognostic relevance are still lacking; no predictor alone or in combination with others allows a dependable prognosis. As a general rule, patients with two or more relapses may be treated with standard dosages for prolonged periods of up to 5 years or longer.

3.2.5 Discontinuing antipsychotic treatment

Patients discontinuing antipsychotics abruptly have a 50% higher risk of relapse within the next 6 months than patients who discontinue medication by slow reduction over 6–9 months. The dosage should not be decreased by more than 20% within a period of 4–8 weeks. During this phase of reduction and discontinuation, psychotherapeutic measures should be intensified. After discontinuation, all patients need ongoing treatment, including close monitoring and easy access to services, in case a relapse appears possible.

3.3 Management of significant side effects and physical illness

3.3.1 General considerations

Compared with the general population, people with schizophrenia have a lifespan that is up to 20% shorter; in the USA, for example, it is approximately 15–20 years shorter. This is caused mainly by a higher prevalence of life-shortening physical diseases such as cardiovascular disease (CVD), smoking, obesity, dyslipidaemia, hypertension, metabolic syndrome, type 2 diabetes, HIV infections and hepatitis, and by the insufficient organization of health services to prevent, detect and treat these physical diseases early on and at later stages. The increased frequency of physical diseases in schizophrenia might be the result of factors related to the illness itself (eg nicotine, reduced physical activity, drug and/or alcohol use,

functioning level, symptoms and stigma, which aggravate access to care, or poor nutrition) and its treatment (eg antipsychotic or polypharmacological treatment with possible side effects such as weight gain, obesity or metabolic syndrome). There are several possible approaches to deal with this problem:

- Awareness and education programmes on physical diseases in schizophrenia for students, psychiatrists, primary care physicians, patients and relatives
- Implementation of an integrated network of psychiatrists and primary care physicians
- Improved access to medical care for people with schizophrenia
- Consequent clinical implementation of already existing treatment guidelines.

Optimal management of (antipsychotic) side effects is one requirement to prevent the development of life-shortening physical illnesses. Here, the clinician has to separate tolerability and safety issues. Tolerability issues can be defined in relation to non-lethal, time-limited or manageable adverse events (eg mild parkinsonism, nausea or sedation), whereas safety issues can be defined as life-threatening, treatment-related adverse events that can occur on an acute or chronic basis (eg neuroleptic malignant syndrome or metabolic syndrome). Some side effects can start as a tolerability issue (eg weight gain) and could be a safety issue later on (weight gain can lead to obesity, which can lead to metabolic syndrome, etc).

All antipsychotics have the potential to produce adverse effects of different prevalence and severity. Each adverse event can be subjectively quite distressing and therefore has the potential to diminish patients' wellbeing (for side effects of all SGAs and some FGAs, see Fig. 3.17).

3.3.2 Extrapyramidal motor side effects

Acute EPS (parkinsonism, akathisia, acute dyskinesia or dystonia) should be considered separately from those side effects that occur only after months or years of antipsychotic treatment (TD; Fig. 3.18). Current knowledge about EPS can be summarized as follows:

- 50–70% of patients taking FGAs experience a clinically significant degree of acute EPS, which is sometimes only subjectively detectable but is often combined with great distress. Antipsychotic-induced parkinsonism affects 10–80% and akathisia 20–50% of patients taking FGAs.
- Antipsychotic-naïve patients have a higher sensitivity to EPS, with a prevalence of 70–80%.
- SGAs generally have a lower propensity to induce EPS. With some SGAs the prevalence of EPS is comparable to placebo across the complete dose range; in others the risk of EPS is dose dependent.

Selected side effects of commonly used antipsychotics									
Type of side effect[a]	Haloperidol	Amisulpride	Aripiprazole	Clozapine	Olanzapine	Quetiapine IR/XR	Paliperidone	Risperidone	Ziprasidone
Akathisia/Parkinsonism	+++	0–+	+	0	0–+	0–+	0–++	0–++	0–+
Tardive dyskinesia	+++	(+)	?	0	(+)	?	(+)	(+)	?
Seizures	+	0	(+)	++	0	0	0	0	0
QT prolongation	+	(+)	0 (?)	(+)	(+)	(+)	(+)	(+)	+
Glucose abnormalities	(+)	(+)	0	+++	+++	++	++	++	0
Dyslipidaemia	(+)	(+)	0	+++	+++	++	++	++	0
Constipation	+	++	0	+++	++	+	++	++	0
Hypotension	++	0	+	(+)	(+)	++	++	++	+
Agranulocytosis	0	0	0	+	0	0	0	0	0
Weight gain[b]	+	+	+	+++	+++	++	++	++	0–+
Prolactin elevation	+++	+++	0	0	(+)	(+)	++	++	(+)
Galactorrhoea	++	++	0	0	0	0	++	++	0
Dys-/Amenorrhoea	++	++	0	0	0	(+)	++	++	0
Sedation	+++	0–+	0	+++	+ –++	++	+	+	0–(+)
Malignant neuroleptic syndrome	(+)	?	(+)	(+)	(+)	(+)	(+)	(+)	?

[a]0, no risk; (+), occasionally, may be no difference to placebo; +, mild (‹1%); ++, sometimes (‹ 10%); +++, frequently (› 10%); ?, not stated possibly due to lack of data.

[b]Weight gain during 6–10 weeks: +, low (0–1.5 kg); ++, medium (1.5–3 kg); +++, high (›3 kg).

Figure 3.17 Selected side effects of commonly used antipsychotics. Frequency and severity of side effects refers to information obtained by drug companies, FDA, additional literature and various guidelines (eg APA [American Psychiatric Association], CPA [Canadian Psychiatric Association]). ER, extended release; IR, immediate release. FDA, US Food and Drug Administration.

Acute extrapyramidal motor side effects

Side effects	Acute dyskinesia or dystonia	Parkinsonism	Akathisia
Prevalence[a]	• Dyskinesia: 5% • Dystonia: up to 25% • Depending on type of antipsychotic and dose • 50% in the first 2 days, 90% in first 4–5 days	• 15–35% • 50–75% within first 4 weeks • 90% within first 3 month	• 20–25% • 50% within first 4 weeks • 90% within first 2–3 months
Cause	Increased dopamine synthesis[b]	Dopaminergic hypoactivity or cholinergic hyperactivity	Blockade of mesocortical dopaminergic receptors[b]
Risk factors	• Children/adolescents • Antipsychotic naïve • High-potency antipsychotic • High initial dosage • Rapid dosage increase • Reduction of initially high dosage • Re-exposition with antipsychotic, which previously induced EPS • Previous EPS	• Children/adolescents • Antipsychotic naïve • Female/male = 2:1 • Elderly patients • High-potency antipsychotic • High initial dosage • Rapid dosage increase • Reduction of initially high dosage • Re-exposition with antipsychotic, which previously induced EPS • Previous EPS	• Children/adolescents • Antipsychotic naïve • High-potency antipsychotic • High initial dosage • Rapid dosage increase • Re-exposition with antipsychotic, which previously induced EPS • Previous EPS
Clinical presentation	• Abnormal movements of head and neck (eg retrocollis or torticollis) • Cramped masseter muscles (locked jaw, mouth pulled open, grimacing, trismus) • Difficulties swallowing (dysphagia), speaking or breathing (cramped hyopharyngeal muscle, dysphonia) • Slurred or unclear speech, due to dysarthria and macroglossia • Extended or dysfunctional tongue • Ocular cramp or cramped closure of eyelid (oculogyric crisis) • Opisthotonos	• Hypokinesia/akinesia: lack of movement, animia (= mask face), monotone voice, hypersalivation, reduced associated movement of arms • Rigidity: increased muscle tone, usually symmetrical, affects arms and legs, cogwheel phenomenon • Tremor: slow rhythm tremor, with frequency of 3–6 beats/s, affecting extremities, head, mouth and tongue, rabbit syndrome • Cognitive and emotional impairments	• Subjective: feeling of unrest, unable to relax, anxiety, nervousness, irritation • Objective: unable to sit still, festinating gait, stamping, recurring movements of arms and legs, pacing to alleviate unrest

Figure 3.18 Acute extrapyramidal motor side effects (*continued opposite*). EPS, extrapyramidal symptoms. [a]With respect to all patients receiving antipsychotic treatment. [b]Not yet securely established.

Acute extrapyramidal motor side effects (*continued*)

Side effects	Acute dyskinesia or dystonia	Parkinsonism	Akathisia
Clinical consequences	• Perceived as agonizing • Influences future compliance • Speech difficulties • Swallowing difficulties • Risk of suffocation	• Reduced capability to move and think impairs rehabilitation • Stigmatization • Differential evaluation to negative or depressive symptoms not easy • Associated with poor response	• Perceived as agonizing • Influences future compliance • Differential evaluation to psychotic agitation not easy
Prevention and treatment	• Use of second-generation antipsychotics • Initiate treatment with low dosage • Slow dosage increase • No rapid reduction • Lowest effective dosage • intravenous application of benzatropine (inject slowly, symptoms disappear within 10–30 min) • Oral treatment: adults 1–3 sustained-release tablet daily, children (3–15 years) 1–2 mg benzatropine one to three times daily • Antipsychotic dose adjustment • Switch of antipsychotic	• Use of second-generation antipsychotics • Initiate treatment with low dosage • Slow dosage increase • No rapid reduction • Lowest effective dosage • Use of anticholinergics	• Use of second-generation antipsychotics • Initiate treatment with low dosage • Slow dosage increase • No rapid reduction • Lowest effective dosage • Use of propranolol 30–80 mg/day • Use of benzodiazepines

Figure 3.18 Acute extrapyramidal motor side effects (*continued*).

- Compared with haloperidol, all SGAs require less concomitant administration of anticholinergic drugs.
- Acute EPSs can have several consequences:
  - reduced response to antipsychotic medication
  - impaired subjective wellbeing and quality of life
  - cognitive dysfunctions, associated either, directly, through motor disturbances or, indirectly, through additional anticholinergic drugs
  - higher risk of developing TD
  - higher risk of medication non-adherence
  - social consequences, especially stigmatization
  - high risk of misdiagnosis (eg parkinsonism as depression, akathisia as psychotic agitation).

Parkinsonian EPS is most commonly treated with the administration of anticholinergic drugs (eg biperiden or benzatropine). β Blockers, such as propranolol, and benzodiazepines are used to treat akathisia.

3.3.3 Tardive dyskinesia

Tardive dyskinesia is a neurological syndrome caused by the use of antipsychotic drugs. Repetitive, involuntary, purposeless movements, eg grimacing, tongue protrusion, lip smacking, puckering and pursing, or rapid eye blinking characterizes TD. Movements of the arms, legs and trunk may also occur. Involuntary movements of the fingers may appear as though the patient is playing an invisible guitar or piano. Diagnosis of antipsychotic-induced TD requires a patient to meet certain criteria, which need the exclusion of the most important differential diagnosis (Fig. 3.19). There are populations at especial risk for TD, and these are listed in Fig. 3.20.

The rate of TD increases with age, as does the rate of spontaneous dyskinesias. Current evidence supports a lower TD risk with SGAs (annualized incidence 1–2%) than with FGAs (annualized incidence 4–8%). Risk for TD is related to age: 0.35% in children taking SGAs, 2.98% in adults taking SGAs compared with 7.7% with FGAs, 5.2% in elderly patients taking SGAs

Tardive dyskinesia (TD): diagnostic criteria and differential diagnosis
Diagnostic criteria acccording to Schooler and Kane (1982).
At least 3 months of cumulative antipsychotic exposure
At least moderate abnormal involuntary movements in one or more body area or mild movements in two or more body areas
The absence of differential diagnoses that produce involuntary hyperkinetic dyskinesias
Most important differential diagnosis
Withdrawal TD after discontinuation of antipsychotics (in many cases TD already existed and was suppressed by antipsychotic treatment)
Other movement disorders (eg Parkinson's disease, Pisa or rabbit syndrome, Gilles de la Tourette's syndrome)
Spontaneous hyperkinesias, often among older women
Hyperkinesias related to other disorders (eg Wilson's disease or Huntington's disease)
Hyperkinesias related to other medications (eg L-dopa, tricyclic antidepressants, lithium, antihistamines, anticonvulsants, phenytoin, metoclopramide, buspirone, flunarizine, selective serotonin reuptake inhibitors, anticholinergic drugs)
Other differential diagnoses (eg grimaces, stereotypes and mannerisms as part of schizophrenic psychosis, psychomotor symptoms for agitated depression)

Figure 3.19 Tardive dyskinesia (TD): diagnostic criteria and differential diagnosis.

Populations at risk of tardive dyskinesia (TD)	
Population	Potential reason
Older patients	Rate of TD increases with age (50% in a group of elderly schizophrenic patients)
Elderly women	Decreased oestrogen levels and increased phenylalanine levels
Patients who have used DRAs for >3 months	Increased exposure to DRAs
Patients with diabetes, independent of use of DRAs (though risk does increase with use of DRAs)	Increased exposure to DRAs
Patients with previous drug-induced parkinsonism	Not related to the use of anticholinergic drugs
People with phenylketonuria	Increased phenylalanine levels

Figure 3.20 Populations at risk of tardive dyskinesia (TD). DPAs, dopamine-receptor antagonists.

compared with 5.2% taking FGAs. In a middle-aged population of 40- to 45-year-old patients with schizophrenia, the prevalence of TD with SGAs was 13.1% for antipsychotic-free patients, 15.6% and 32.4% for patients treated with FGAs.

There is no standard treatment for TD; treatment is difficult, lengthy and generally oriented to its severity (Fig. 3.21). In many cases the medication will be adjusted to use the lowest possible dose, or discontinued if at all possible. However, for many patients with a severe underlying condition this may not be a feasible option. Replacing the antipsychotic drug with other medications (SGAs) may help some patients, especially those who were treated with FGAs. Treatment with clozapine is another promising option. Other drugs such as vitamin E or B_6, benzodiazepines, adrenergic antagonists and dopamine agonists may also be beneficial (Fig. 3.21).

Symptoms of TD may remain even after the medication is stopped. Data on the long-term course of TD suggest that approximately 40% of patients show a worsening of symptoms over time. The remaining 50–60% show less severe symptoms with no progression or remission. However, with careful management, some symptoms may improve or disappear with time.

Prevention of TD includes early recognition and the prescription of SGAs in the lowest possible dose. In all cases, for antipsychotic medication to be prescribed the benefits of taking it should be judged to outweigh the risks of developing TD.

Recommendations for treatment of tardive dyskinesia

Mild-to-moderate TD, no symptom suppression required

- Re-evaluate necessity for antipsychotic treatment (relapse/TD ratio). Be aware that complete and permanent reversibility of TD is rare. The clinical feasibility of antipsychotic withdrawal is severely limited by the high risk of psychotic relapse in psychotic patients
- Adjust dose to lowest possible dose if antipsychotic has to be maintained; otherwise consider switch to SGA (eg quetiapine or olanzapine)[a]
- If symptoms persist after switch to SGAs, consider concurrent treatment with tiapride over 6–12 weeks (600 mg/day)
- If symptoms persist, consider symptom suppression treatment with SGAs (see below)
- If symptoms persist, consider switch to clozapine and follow guidelines for severe TD

Severe TD, symptom suppression required

- Adjust dose to lowest possible dose if antipsychotic has to be maintained. Be aware that severe TD is often concurrent with severe (chronic) courses of schizophrenia and that risk of relapse with dose reduction is high
- Consider switch to SGAs (eg quetiapine or olanzapine), increasing the dose gradually until symptoms of TD are suppressed, ie disappear
- If symptoms persist after TD suppression with SGAs, consider concurrent treatment with tiapride over 6–12 weeks (600 mg/day)
- If symptoms persist, switch to clozapine. Wait 6–12 months before symptoms of TD are judged to be chronic
- The following drugs could be added to SGA or clozapine. Their effects are relatively uncertain and some of these drugs only protect against deterioration of TD rather than improve symptoms of TD
  - vitamin E (1200–1600 IU/day) over a period of 3 months[b]
  - vitamin B_6 (400 mg/day)
  - calcium channel blocker (eg nifedipine 40–80 mg/day)
  - α_2-agonist (eg clonidine)
  - benzodiazepine
  - amine-depleting drugs (eg reserpine, tetrabenazine): block reuptake of dopamine, noradrenaline and serotonin, thereby depleting central availability of these neurotransmitters. Significant side effects limit the use of these drugs

[a]Worsening of TD can occur if high potency (FGAs are switched to SGAs).
[b]Newer reviews indicate that vitamin E protects against deterioration of TD, but there is no evidence that vitamin E improves symptoms of TD.

Figure 3.21 Recommendations for treatment of tardive dyskinesia. FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; TD, tardive dyskinesia.

3.3.4 Neuroleptic malignant syndrome

The rare occurrence of neuroleptic malignant syndrome (NMS), in certain countries also known as malignant neuroleptic syndrome (MNS), is characterized by hyperthermia and severe muscle rigidity after intake of antipsychotics. These primary symptoms are accompanied by at least five of the following symptoms (relevant for diagnosis): a severe hyperhidrosis, dysphagia, tremor, incontinence, reduced consciousness (from confusion to stupor up to coma), mutism, tachycardia, increased or fluctuating blood pressure, leukocytosis

Symptoms and diagnostic criteria of neuroleptic malignant syndrome (NMS)

Syndrome	Possible symptoms
Extrapyramidal motor side effects	• Hypokinesia/akinesia, muscle rigidity (typically evident) • Tremor • Hyporeflexia • Opisthotonus, trismus • Oculogyric crisis
Vegetative symptoms	• Hyperthermia (>38°C) • Tachycardia, increased blood pressure • Incontinence
Psychic symptoms	• Stupor • Confusion • Mutism • Impaired consciousness • Catatonia
Conspicuous lab findings	• Creatine kinase and liver enzyme elevation • Myoglobinuria (in case of rhabdomyolysis) • Leukocytosis • Metabolic acidosis

Diagnostic criteria

- Antipsychotic treatment in the last 4 weeks
- Hyperthermia (>38°C)
- Muscle rigidity
- Existence of at least five of the following symptoms:
  - change of the mental state (psychic symptoms)
  - tachycardia
  - hypotension or hypertension
  - incontinence
  - diaphoresis or sialorrhoea
  - increase of creatine kinase or myoglobinuria
  - metabolic acidosis
  - leukocytosis
- Exclusion of other reasons

Figure 3.22 Symptoms and diagnostic criteria of neuroleptic malignant syndrome (NMS).

(between 10 000 and 20 000, present among 50% of patients) and laboratory findings indicating muscle injury (such as increased creatine phosphokinase [CPK] >300 U/L, present in only 50% of the cases) (Figure 3.22). Muscle cramps, fasciculation or opisthotonos can very occasionally also be seen. Pathological laboratory findings are defined as an increased blood sedimentation rate as well as an increase in AST (aspartate transaminase) and ALT (alanine transaminase) due to the increased rigidity.

Furthermore, a tachypnoea with metabolic acidosis can be found, sometimes even with respiratory insufficiency. Urine of NMS patients can be dark due to myoglobinuria. The syndrome can be accompanied by agitation or acute dystonic reactions. For the diagnosis it is important to ascertain that symptoms are not due to the consumption of other medications (eg phencyclidine), a neurological or other medical disorder (eg viral encephalitis), or even another psychiatric disorder such as disorders with catatonic symptoms, especially schizophrenia.

Studies on the frequency of NMS report a prevalence of 0.02–2.4%. Also second-generation antipsychotics have been reported to cause NMS (eg clozapine, risperidone, olanzapine, zotepine or quetiapine).

NMS usually develops in the early phase of antipsychotic treatment (most cases develop within the first 4 weeks, with two-thirds appearing in the first week, yet cases may develop even after months of treatment). It occurs mostly under treatment with high-potency FGA, most often in young male patients. Other risk factors include previous NMS, rapid dosage increase, concurrent dehydration, parenteral antipsychotic treatment, an anxious–depressive agitation, previous cerebral injuries and combination treatment with medications, which can induce NMS itself (eg lithium, carbamazepine, tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs] or selective noradrenaline reuptake inhibitors [SNRIs]).

Differential diagnoses include the serotonin syndrome, malignant hyperthermia, allergic medication reactions, heatstroke, hypokinetic crisis in Parkinson's disease, infections of the central nervous system, toxic encephalopathia or febrile catatonia.

The most important causal intervention is to stop the antipsychotic treatment immediately. All other interventions focus on the somatic symptoms of NMS and aim to reduce life-threatening complications. After discontinuation of antipsychotic treatment, NMS gradually goes into remission within 2 weeks for oral medication and 4 weeks for depot medication; the average duration of NMS is 5 days. In 4–20% of cases NMS has proved fatal, which is mainly due to secondary complications such as renal failure (myoglobinaemia with the risk of developing a crush syndrome), respiratory insufficiency, and cardiac and circulatory failure. Treatment on an intensive care unit is usually necessary and highly recommended.

In most cases, antipsychotic treatment has to be re-started after NMS is in remission. A previous NMS is, however, the most powerful predictor for a subsequent NMS. As such, the next antipsychotic has to be started at a low dose and should be increased slowly, co-medications that can induce NMS should not be given, and patients have to be monitored closely within the first 4 weeks of treatment (eg hyperthermia, rigidity and creatine kinase).

Classification of weight in adults and waist circumference

Category	BMI (kg/m²)	Risk for metabolic and cardiovascular diseases
Underweight	<18.5	Low
Normal weight	18.5–24.9	Average
Overweight	≥25.0	
Preobesity	25–29.9	Marginally increased
Obesity degree I	30–34.9	Increased
Obesity degree II	35–39.9	High
Obesity degree III	≥40	Very high

Classification of the waist circumference with the related risk for metabolic and cardiovascular diseases	Waist circumference (cm)	
	Male	Female
Increased	≥94	≥80
Considerably increased	≥102	≥88

Figure 3.23 Classification of weight in adults and waist circumference Classification of weight in adults according to the body mass index (BMI) and classification of the waist circumference with the related risk for metabolic and cardiovascular diseases.

Classification of weight according to the body mass index (BMI)

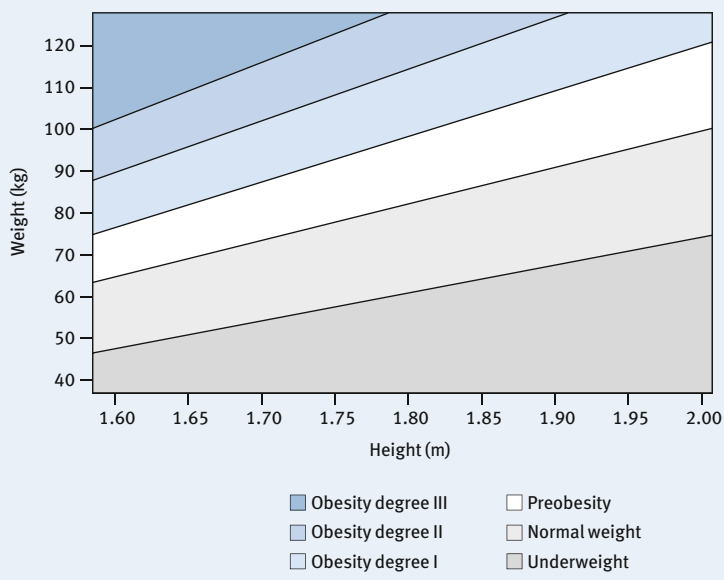


Figure 3.24 Classification of weight according of the body mass index (BMI).

Causes of weight gain in patients with schizophrenia

General causes

- Familiar disposition, genetic causes
- Lifestyle (reduced exercise, malnutrition)
- Chronic stress
- Eating disorder (eg binge-eating disorder, bulimia)
- Endocrine disorders (eg hypothyroidism, Cushing's syndrome)
- Medications (eg some antidepressants, some antipsychotics, some medications against hypertension)
- Other causes (eg pregnancy, cessation of nicotine use)

Specific causes in patients with schizophrenia

- Antipsychotics that cause weight gain (for mechanism of antipsychotic-induced weight gain, see Fig. 3.26)
- Combinations of medications that can cause weight gain
- Symptoms and consequences of schizophrenia, which can cause inactivity and decrease the ability to live healthily, eg negative symptoms, depression, reduced functional level, reduced financial resources

Figure 3.25 Causes of weight gain in patients with schizophrenia. Causes of weight gain in general and specifically for patients with schizophrenia as well as mechanism of antipsychotic-induced weight gain.

3.3.5 Weight gain and obesity

People with schizophrenia are more likely to be overweight or obese than the general population. It has been estimated that weight gain and increased appetite affect 45–55% of patients at levels that exceed ideal body weight by 20% or more. Extreme weight gain of 10–20 kg occurs in approximately 10–20% of cases (see Fig. 3.23 for a classification of obesity and classification of waist circumferences and Fig. 3.24 for easy assessment of BMI). Besides the degree of obesity, the fat distribution pattern is important for the risk of metabolic syndrome and cardiovascular disease (Fig. 3.23).

Weight gain is a multi-factorial occurrence related to various general factors and to factors related to the illness itself as well as its treatment (Figs 3.25 and 3.26). Many antipsychotics and other psychotropic medications can cause weight gain, although prevalence and extent of weight gain vary from drug to drug (Fig. 3.27). Predictors of weight gain are poorly understood. Besides the previously described causes, the following predictors are known in schizophrenia: increased appetite directly after start of drug treatment (binge-eating behaviour), good clinical response, low baseline BMI (<23), younger age and concurrent treatment with other medications that induce weight gain. The time course of the weight gain is also poorly researched, but the highest weight gain is in the first 6–9 months of antipsychotic treatment, mainly in the first 12 weeks.

With respect to SGAs, clozapine and olanzapine have a fairly high potential for causing weight gain, especially if combined with other psychotropic drugs that have high weight gain potential. To a lesser extent, zotepine, risperidone, paliperidone, quetiapine (IR and XR) and amisulpride have some potential to cause weight gain, whereas ziprasidone and aripiprazole hardly affect body weight (Fig. 3.27). Contrary to earlier beliefs, several FGAs also have a potential to induce weight. The risk of weight gain related to treatment with low-potency FGA or chlorpromazine is lower compared with clozapine and olanzapine; whereas the risk with haloperidol, perphenazine and fluphenazine, at least in the short term, is comparable to ziprasidone, ie low. However, some long-term studies have found considerable weight gain with haloperidol and other FGAs.

Various physical diseases are related to obesity (increased relative risk according to increased BMI): metabolic syndrome, diabetes type 2, hypertension, dyslipidaemia or CVD (Fig. 3.28). However, the consequences are not only seen at the somatic level; adherence, subjective wellbeing, self-esteem, social functioning, stigmatization and quality of life are also affected by being overweight or obese. Therefore clinicians should alert patients and their caregivers to the health risk associated with excess weight and encourage patients to self-monitor their weight and other risk factors (Fig. 3.29). The management of weight gain, once it has occurred, involves a multidisciplinary approach (Fig. 3.29). Switching to antipsychotics with less potency of weight gain can lead to a decreased weight. The reduction of weight is possibly greatest if an antipsychotic with no risk of weight gain is combined with a specific weight loss intervention and physical training. Recommendations for treatment of weight gain are given in Fig. 3.29.

3.3.6 Metabolic syndrome and cardiovascular disorders

The metabolic syndrome is defined by the presence of three or more cardiometabolic risk factors associated with insulin resistance, including abdominal obesity, dyslipidaemia, elevated blood pressure and glucose intolerance (for criteria for the metabolic syndrome and fasting lipids/dyslipidaemia, see Fig. 3.30). A special aspect of the metabolic syndrome is insulin resistance, which is a pre-state of type 2 diabetes. Type 2 diabetes occurs after a longer period of metabolic syndrome if the pancreas is unable to compensate for the reduced insulin effect by increased insulin distribution. There is often a delay between the occurrence of the metabolic syndrome and the onset of type 2 diabetes, which opens the possibility of early detection. The early diagnosis of disturbed glucose tolerance is possible only through an oral glucose tolerance test. Testing fasting glucose or HbA1c (glycated haemoglobin) is indicated only to monitor already existing type 2 diabetes.

Mechanism of antipsychotic-induced weight gain

Effects on the basic metabolic rate

- Antipsychotics, such as clozapine, can reduce basal metabolic rate and thereby energy expenditure. For other antipsychotics with increased weight gain risk, this direct association has not been found (eg olanzapine)

Effects on receptors

- Antagonism of serotonin 2c (5HT2$_c$) and histamine H_1-receptors can induce increased appetite and thereby weight gain. Further, H_1-receptor blockade can reduce appetite-reducing effects of leptin
- Clozapine and olanzapine show a strong affinity to both receptors and are associated with a high risk of weight gain
- Risperidone shows a lower affinity and is associated with a lower risk of weight gain
- Ziprasidone shows a high affinity to $5HT_{1a}$- and $5HT_{2c}$-receptors. Its weight-neutral profile is explained by synaptic inhibition of serotonin and noradrenaline reuptake
- Aripiprazole shows a partial D_2-receptor and $5HT_{1a}$-receptor agonism and $5HT_{2a}$-receptor antagonism. Its weight-neutral profile is explained by lack of $5HT_{2c}$-receptor antagonism
- Other less well researched receptors may also be involved (eg α_2-adrenergic and SREBP-1)

Pharmacogenetic findings

- Patients with low BMI show greatest weight gain. Early and fast weight gain is a well-known predictor for the degree of long-term weight gain. Both findings support pharmacogenetic influences
- $5HT_{2c}$-receptor promoter region polymorphism ($5HT_{2c}$-receptor promotor-759c/t) shows strong association with weight gain and increased risk for metabolic syndrome. The underlying hypothesis postulates an interaction with the circulating leptin level

Leptin

- Leptin is coded by the 'obese' gene and is produced in fat cells. Its receptors are located in two different brain regions: nucleus arcuatus and nucleus paraventricularis of the hypothalamus. With reduction of fat depots in the body, the level of circulating leptin is reduced, which results in increased appetite. However, newer studies have demonstrated that obese people have increased levels of leptin, which shows that obesity can cause leptin resistance; the effect of leptin on the brain regions is reduced
- Several studies have shown that antipsychotics can influence leptin secretion, circulating leptin level and leptin resistance. However, they did not control for the level of obesity. Studies that controlled for obesity have found a positive correlation for the degree of obesity, gender and leptin secretion. The association between antipsychotic treatment and leptin is not fully understood yet

Ghreline

- Ghreline (growth hormone-release-inducing hormone) is an appetite-increasing hormone, produced in the gastric mucosa which stimulates the secretion of neuropeptide Y. Neuropeptide Y itself increases food intake and possibly decreases anxiety and depression. The influence of antipsychotics on ghreline secretion is currently unclear. Some studies found no antipsychotic-increased secretion of ghreline; others, on olanzapine, found an increased secretion

Weight gain through indirect effects on glucose and lipids

- Hyperglycaemia and hyperlipidaemia are seen as consequences of weight gain and obesity. There are, however, studies that have found hyperglycaemia and hyperlipidaemia independent of the degree of obesity, eg for olanzapine or clozapine. Through increased insulin resistance, some antipsychotics are associated with a higher risk of type 2 diabetes. Dyslipidaemia itself causes insulin resistance, which leads to an increase of adipose tissue. Correspondingly, there is a complex association of antipsychotics, hyperglycaemia, hyperlipidaemia and weight gain

Figure 3.26 Mechanism of antipsychotic-induced weight gain. (Newcomer and Haupt 2006)

Degree of weight gain with different antipsychotics and other psychotropic medications within the first 3 months of treatment

Weight gain	High	Average	Low
Antidepressants	AmitrIptyline Doxepine Maprotiline Mirtazapine Trimipramine	Clomipramine Imipramine Nortriptyline	Citalopram Fluoxetine Fluvoxamine Sertraline
Antipsychotics	Clozapine Olanzapine	Chlorpromazine Paliperidone Quetiapine IR or XR Risperidone Zotepine Zuclopenthixol	Amisulpride Aripiprazole Fluanxol Fluphenazine Haloperidol/ Ziprasidone
Mood stabilizer	Lithium Valproate	Carbamazepine	Gabapentine Lamotrigine Topiramate

Figure 3.27 Degree of weight gain with different antipsychotics and other psychotropic medications within the first 3 months of treatment.

Weight gain and obesity in schizophrenia: consequences and complications

- Carbohydrate metabolism dysfunctions (eg insulin resistance, type 2 diabetes mellitus)
- Dyslipidaemia
- Hyperuricaemia/gout
- Haemostasis dysfunctions
- Chronic inflammation
- Hypertension, left ventricular hypertrophy
- Cardiovascular diseases (eg coronary heart disease, stroke, cardiac insufficiency)
- Increased cancer risk (in female: eg endometrium, cervix, ovarian, breast, kidney, colon; in male: eg prostate, colon, gallbladder, pancreas, liver, kidney, oesophagus)
- Hormonal dysfunctions
- Pulmonary dysfunctions (eg dyspnoea, hypoventilation, sleep apnoea syndrome)
- Gastrointestinal diseases (eg fat liver, fat liver hepatitis, reflux disease)

Degenerative diseases of the musculoskeletal system

- Increased operation and anaesthesia risk
- General disturbances (eg increased sweating, exposure dyspnoea)
- Decreased activity
- Reduced quality of life
- Increased accident hazard
- Increased complication during pregnancy and birth
- Psychosocial consequences such as depression, anxiety, stigmatization, self-worth problems, social isolation
- Reduced medication compliance

Figure 3.28 Weight gain and obesity in schizophrenia: consequences and complications.

Patients with schizophrenia in general, and especially those on continuous antipsychotic medication, have a higher risk of metabolic syndrome:

- 17% in first episode (duration of illness <1.5 years)
- 28.5% in short-term illness (1.5–10 years)
- 42.4% in subchronically ill patients (10–20 years)
- 49.4% in chronically ill patients (>20 years).

In the age range 35–45 years the risk of metabolic syndrome in schizophrenia is threefold higher than in the general population, and in the range 45–55 years twofold higher (Fig. 3.31). As shown in the CATIE study, females (51.6%) have a higher risk compared with males (36.0%). Patients with the following risk factors have the highest risk for metabolic syndrome: higher age, women during the menopause, lower income, unhealthy nutrition and physical inactivity (Fig. 3.31).

Metabolic syndrome is associated with an increased risk of developing a CVD, including coronary heart disease (CHD), cerebrovascular disease and type 2 diabetes mellitus. Furthermore, there are also other CVD risk factors that are more frequent in people with schizophrenia compared with the general population, eg smoking (68% vs 35%), diabetes (13% vs 3%), hypertension (27% vs 17%) and lower HDL-cholesterol (43.7 mg/dL vs 49.3 mg/dL).

The risk of weight gain, obesity, type 2 diabetes and dyslipidaemia differs considerably between different antipsychotics (Fig. 3.32). Clozapine and olanzapine have a potential for causing type 2 diabetes and dyslipidaemia, especially if combined with other psychotropic medications that have high weight gain potential. Whether zotepine, risperidone, paliperidone, quetiapine (IR and XR) and amisulpride have some potential for type 2 diabetes has not currently been fully researched. Ziprasidone and aripiprazole hardly affect body weight and are not related to type 2 diabetes and dyslipidaemia (Fig. 3.32).

Recommendations for the prevention and management of metabolic syndrome in schizophrenia are given in Figs 3.33 and 3.34.

3.3.7 Endocrine and sexual side effects

Sexuality and sexual disorders play an important role in the treatment of schizophrenia patients, even though this topic often receives little attention in clinical practice. Effective assessment of sexual function disorders depends greatly on the attitude of the treating physician. However, only 6–8% of doctors reported always interviewing their patients on sexuality. This contradicts the relevance from the patients' view. In a study of patients treated with antipsychotics, they were asked to evaluate the relative importance of 19 psychotic symptoms and 20 adverse effects. Sexual dysfunction was rated the most unpleasant side effect and equally as impairing as paranoid delusions. Impotence was rated as more unpleasant than any of the psychotic symptoms.

Weight gain and obesity in schizophrenia: prevention and treatment

Recommendations for prevention

The need for prevention is related to the following research results:

- With increased duration and severity of obesity treatment gets more complex with less chance of weight reduction
- The somatic and psychosocial after effects of obesity are mostly irreversible
- The prevalence of obesity in the industrial nations is meanwhile so high that the economic health resources are not sufficient anymore
- The psychosocial consequences of schizophrenia reduce the ability to participate in weight loss treatments adequately
- Weight gain and obesity reduce the medication compliance and are thereby an important prognostic factor

Recommendations for treatment

- Basic programmes for weight gain management comprise interventions with respect to nutrition, exercise and behavioural therapy. Weight loss programmes should comprise two steps: first, weight reduction and, second, stabilization of weight
- The nutrition therapy comprises several steps. Patients can enter at each step. The complete social environment should be involved. The patient should be informed about each step:
  - step 1: reduction of fat intake (possible weight loss: 3.2–4.3 kg in 6 months)
  - step 2: energy-reduced food (possible weight loss: 5.1 kg in 12 months)
  - step 3: meal replacement with formula products (possible weight loss: 6.5 kg in 3 months)
  - step 4: formula diet (possible weight loss: 0.5–2 kg in 12 weeks)
- Exercise leads to increased energy consumption. Weight loss is possible with an energy consumption of 2500 kcal/week
- Behavioural interventions can support motivation for exercise and nutrition therapy. The most important elements are:
  - self-monitoring of eating and drinking behaviour and of exercise, eg with protocols or nutrition diaries
  - practice of flexible and controlled eating behaviour
  - learning to cope with eating stimuli to reduce eating impulses
  - use of enhancement techniques (eg praise) to support the new eating behaviour and to reduce relapses
  - social support
  - management of relapse and prophylaxis

Approved medications for weight loss:

1. Sibutramine: a selective serotonin and noradrenaline reuptake inhibitor that leads in the general population to weight loss of 2.8–4.4 kg in 3–12 months. Sibutramine can induce panic attacks, psychosis or mania, and should be thereby used with caution. Dosage: 5–20 mg/day
2. Orlistat: a lipase inhibitor that leads in the general population to weight loss of 2.8 kg. In people with disturbed glucose tolerance, orlistat can reduce the conversion to type 2 diabetes. Dosage: 120 mg three times daily with food; intake of other medication 1 h before or after intake of orlistat

- **Off-label medications for weight loss:**

1. Amantadine: originally designed for the treatment of influenza A virus. As a result of its side effects, such as depression, hallucinations or epileptic seizures, it is currently rarely used in this indication. For weight loss in schizophrenia there are two randomized controlled trials that did not show a deterioration of the mental state. Dosage: 300 mg/day (studied with olanzapine)
2. Topiramate: blocks glutamate binding at the AMPA receptor and enhances the inhibitive effects of GABA receptors. It is used in epilepsy, migraine and cluster headache. For weight loss in schizophrenia there are two randomized controlled trials, which did not show a deterioration of the mental state. Dosage: 25–200 mg/day
3. Metformin: reduces the glucose production in the liver. Contraindications are type 1 diabetes, liver and kidney insufficiency, alcohol dependency, cardiac insufficiency. Dosage: 3 × 500 mg/day

- **Surgery: indicated only if other interventions have failed:**
  - for patients with obesity degree III (BMI ≥40)
  - obesity degree II (BMI ⁑35) with severe comorbidities (eg type 2 diabetes)

Figure 3.29 Weight gain and obesity in schizophrenia: prevention and treatment. AMPPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BMI, body mass index; GABA, γ-aminobutyric acid.

Criteria for metabolic syndrome and fasting lipids/dyslipidemia

Metabolic syndrome					
Definition: three or more risk factors required for definition					
Risk factors			**Defining level**		
Abdominal obesity (cm) (inches) Men Women			Waist circumference ›102 (›40) ›88 (›35)		
Fasting plasma triglycerides (mg/dL)			≥150 or drug treatment		
HDL cholesterol (mg/dL) Men Women			 ‹40 ‹50		
Fasting lipid levels and values for dyslipidaemia (mg/dL)					
	Optimal/ desirable	Near optimal	Borderline high	High/ undesirable	Very high
Total cholesterol	‹200		200–239	›240	›240
LDL	‹100	100–129	130–159	160–189	160–189
HDL	›60		‹40		
Triglycerides	‹150		150–199	200–499	200–499

Figure 3.30 Criteria for metabolic syndrome and fasting lipids/dyslipidaemia. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Risk factors for cardiometabolic disorders in schizophrenia, its prevalence and relative risk compared with the general population

Risk factor	Prevalence of risk factor (%)	Relative risk
Obesity	45–55	1.5–2 ×
Smoking	50–80	2–3 ×
Type 2 diabetes	10–14	2 ×
Hypertension	≥18	
Dyslipidaemia		Up to 5 ×

Figure 3.31 Risk factors for cardiometabolic disorders in schizophrenia, its prevalence and relative risk compared with the general population.

With respect to the prevalence of sexual dysfunctions, studies reported a wide range of 30–80% with differences related to gender, the type of antipsychotic treatment, the type pharmacological combination therapy, etc. Female patients most often experience menstrual disorders (about 80%), of which dysmenorrhoea is the most frequent. For male patients ejaculation and erectile dysfunctions (30–60%), as well as difficulty in reaching orgasm (up to 60%), are the main sexual disorders (Fig. 3.35).

Risk of metabolic abnormalties with different second-generation antipsychotics

Drug	Weight gain	Risk for diabetes	Worsening of lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Paliperidone	++	D	D
Risperidone	++	D	D
Quetiapine IR and XR	++	D	D
Aripiprazole	±	–	–
Ziprasidone	±	–	–

*Newer drugs with limited long-term data.

Figure 3.32 Risk of metabolic abnormalities with different second-generation antipsychotics: +, increased effect; –, no effect; D, discrepant results; ± newer drugs with limited long-term data.

Monitoring protocol for patients on antipsychotic treatment

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	x					x	
Weight (BMI)	x	x	x	x	x		
Waist circumference	x					x	
Blood pressure	x			x		x	
Fasting plasma glucose	x			x		x	
Fasting lipid profile	x			x		x	x

Figure 3.33 Monitoring protocol for patients on antipsychotic treatment. BMI, body mass index.

There are two main causes of sexual dysfunctions in schizophrenia: the illness itself and the pharmacological treatment. With respect to pharmacological treatment, prolactin (PRL) elevation is considered of central importance in the aetiology of sexual dysfunction. The lactotroph hormone PRL is produced in the anterior lobe of the pituitary gland and induced physiologically by the sucking reflex. The secretion of PRL leads to a suppression of the release of gonadotrophin. The control of PRL synthesis and secretion is part of a complex neurochemical and hormonal metabolism. The blockade of tuberoinfundibulum dopamine receptors of the hypothalamus can lead to cessation of the physiological suppression of PRL and therefore to increase in

Recommendations for prevention and management of metabolic syndrome in schizophrenia

General recommendations

- Take responsibility for the patient with respect to psychiatric and somatic care
- Implement systematic education programmes on physical diseases in schizophrenia – for students, psychiatrists, primary care physicians, patients and relatives
- Improve parity and health-care access and provision
- Forge collaborative teamwork of psychiatrists with primary care physicians, especially in long-term outpatient treatment
- Consequent implementation of long-term treatment facilities for patients with schizophrenia, including somatic monitoring (integrated care)

Specific recommendations

- Consequent clinical application of already published monitoring protocols and treatment guidelines (see Fig. 3.33)
- Preventive approach in antipsychotic treatment (see Fig. 3.34)
- Monitoring of early warning signs for the respective physical disease, eg weight loss, polyuria or polydipsia for diabetes
- Regular diabetes screening (every 3 years) is indicated in patients ≥45 years or in patients with certain risk factors: (1) obesity (BMI ≥27), (2) diabetes in first-degree relatives, (3) hypertension, (4) dyslipidaemia (low HDL and/or low LDL values), (5) already existing metabolic syndrome, (6) women with a history of gestational diabetes, (7) positive family history for diabetes or (8) patients with albuminuria
- Early detection of type 2 diabetes according to pathological values: (1) fasting glucose level: ≥126 mg/dL, (2) plasma glucose level: ≥200 mg/dL, HbA1c: ›6.1%. Fasting glucose level of 100–126 mg/dL is classed as pre-diabetes
- In case of existing type 2 diabetes, refer patient to a diabetes specialist and facilitate that the patient is getting regular (precaution) assessments
- Regular dyslipidaemia screening is indicated in patients with certain risk factors: (1) obesity (BMI ≥27), regular imbalance between energy (food) intake and energy expenditure (mainly resting metabolism and physical activity), (3) diabetes mellitus, (4) renal insufficiency, (5) hypothyroidism or (6) treatment with certain medications (eg diuretics, β blockers)
- In case of existing CVD risk factors, discuss risk–benefit ratio and possibly switch to an antipsychotic with no or low potential of weight gain, eg aripiprazole or ziprasidone, or an antipsychotic on which the patient was successfully treated without weight gain

Figure 3.34 Recommendations for prevention and management of metabolic syndrome in schizophrenia. BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

PRL levels. Besides this dopamine-mediated increase of secretion, PRL can also be directly released through a variety of physiological and pathological mechanisms (Fig. 3.36).

Normal plasma levels for both women and men are in the range 5–25 ng/mL with a high degree of interindividual variability. A grey area is between 25 and 200 ng/mL, values >40 ng/mL are related to PRL-induced complications (Fig. 3.36), and values >200 ng/mL are clearly pathological and justify an assessment of whether the patient has a tumour of the pituitary gland.

Clinical short- and long-term consequences and complications related to increased prolactin

Affected persons	Short- and long-term consequences and complications
Females	• Hypogonadism (clinical manifestation of an ovarian hypofunction): o oligo-/dysmenorrhoea, amenorrhoea o libido dysfunctions o anovulatory cycles (infertility) o vaginal atrophy o androgenization o premenstrual syndrome with dysphoria and cognitive problems • Mastopathia, mastodynia • Galactorrhoea • Vision disorders, headache • Questionable increased risk of breast cancer in female
Males	• Hypogonadism (clinical manifestation of a testes hypofunction): o libido dysfunctions o erectile and/or ejaculatory dysfunctions o reduced spermatogenesis (oligospermia, infertility) • Gynaecomastia • Galactorrhoea • Vision disorders, headache
Females and males	• **Bones:** o reduced bone mineral density caused by a long-term relative or absolute oestrogen or testosterone deficiency with increased risk of osteoporosis • **Cardiovascular system** o increased risk of infarct and/or arteriosclerosis • **Other areas:** o affective disorders (eg depression) o cognitive dysfunctions o questionable increased risk of tardive dyskinesia
Girls and boys	• Delayed puberty • In boys among others reduced development of the skeletal muscles and disturbed bone growth • In girls, among others infertility, reduced libido, mammary atrophy and osteoporosis

Figure 3.35 Clinical short- and long-term consequences and complications related to increased prolactin.

Different pharmacological treatments are related to a varying risk of hyperprolactinaemia (Fig. 3.37). The following risk order could be made: combinations with PRL-elevating antipsychotics > amisulpride = risperidone = paliperidone > FGA (haloperidol) > olanzapine > quetiapine (IR or XR) = clozapine = aripiprazole = ziprasidone.

The most important causes of increased prolactin

Physiological or general causes

- Pregnancy, lactation
- Acute and chronic psychological and/or physical stress
- After orgasm
- After an epileptic seizure
- After intensive manipulation/sucking at the breast
- After albuminous meals and large intake of beer
- Physiological increase of prolactin in late sleep phase
- Excessive exercise

Pathological causes

- Autonomous production and secretion of prolactin
  - prolactinoma (micro- or macro-)
- Disturbed hypothalamic dopamine release or transport to the lactotrophic HVL cells
  - hypothalamic tumour (craniopharyngioma)
  - granulomatous diseases of the lining of the brain and spinal cord (eg sarcoidosis)
  - trauma
- Stimulation of the lactotrophic adenohypophyseal cells
  - hypothyroidism
- Pharmacological medications (eg)
  - dopamine receptor antagonist (eg some SGAs [risperidone, amisulpride, paliperidone], FGAs [benzamide, phenothiazine, butyrophenone])
  - antihypertensive drugs (eg reserpine)
  - monoamine synthesis inhibitor (-methyldopa)
  - monoamine uptake inhibitor (tricyclic antidepressants, eg imipramine and amitriptyline)
  - serotonin reuptake inhibitor (eg fluoxetine, sertraline, citalopram, fluvoxamine, paroxetine)
  - oestrogen (in higher dosage)
  - opiate
- Other causes
  - kidney failure
  - cirrhosis of the liver
  - diseases of the leading thorax septum (eg herpes zoster)
  - ectopic prolactin secretion
  - idiopathic functional prolactin elevation

Figure 3.36 The most important causes of increased prolactin. FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

There are several recommendations for good clinical practice (Fig. 3.38):

- Education and information for patients before start of antipsychotic treatment
- Antipsychotic-related risk of hyperprolactinaemia should be considered when prescribing antipsychotics
- Regular controls of the PRL level before start of antipsychotic treatment, if steady state is reached, and regular if the patient is treated with PRL-elevating antipsychotics or combination therapy (see Fig. 3.37)

Weighted effects of antipsychotics on prolactin levels

Antipsychotic	Prolactin response weighted score [a]	Hyperprolactinemia APA weighted risk [b]
Haloperidol	+++	+++
Amisulpride	+++	+++
Aripiprazole	0	0
Clozapine	+	0
Olanzapine	++/+	0
Paliperidone	ID, possibly comparable to risperidone	ID, possibly comparable to risperidone
Quetiapine IR and XR	+	0
Risperidone	+++	+++
Ziprasidone	+	+
Combination of prolactin-elevating antipsychotics	++++	++++

[a] +++ = robust elevation; ++ = moderate elevation; + = mild, transient elevation; 0 = no elevation.
[b] ++++ = frequently causes side effect with higher prevalence and higher prolactin elevation compared with monotherapy; +++ = frequently causes side effects at therapeutic doses; + = mild or occasionally causes side effects at therapeutic doses; 0 = no risk or rarely causes side effects at therapeutic doses. ID, insufficient data.

Figure 3.37 Weighted effects of antipsychotics on prolactin levels.

- Patients should be regularly assessed for sexual dysfunctions and should be given sufficient time to talk about their sexuality and any impairments, because most patients try to avoid this topic
- Treatment follows specialized algorithms (see Fig. 3.38) and, in case of chronically elevated PRL levels, several PRL-reducing medications could be used (Fig. 3.39).

3.3.8 Cardiovascular side effects

Antipsychotics have three main cardiovascular side effects:

1. Cardiac side effects, especially prolongation of the QTc interval
2. Hypotension and orthostatic hypotension
3. Tachycardia.

The most common cardiac side effect of antipsychotics is the prolongation of the QTc interval. The QTc interval represents the duration of ventricular repolarization corrected by the heart rate and is usually below 400–420 ms, depending on age, gender and time of day. A value >500 ms is considered a clinically relevant QTc prolongation because it is associated with a higher risk of torsades de pointes and transition to ventricular fibrillation.

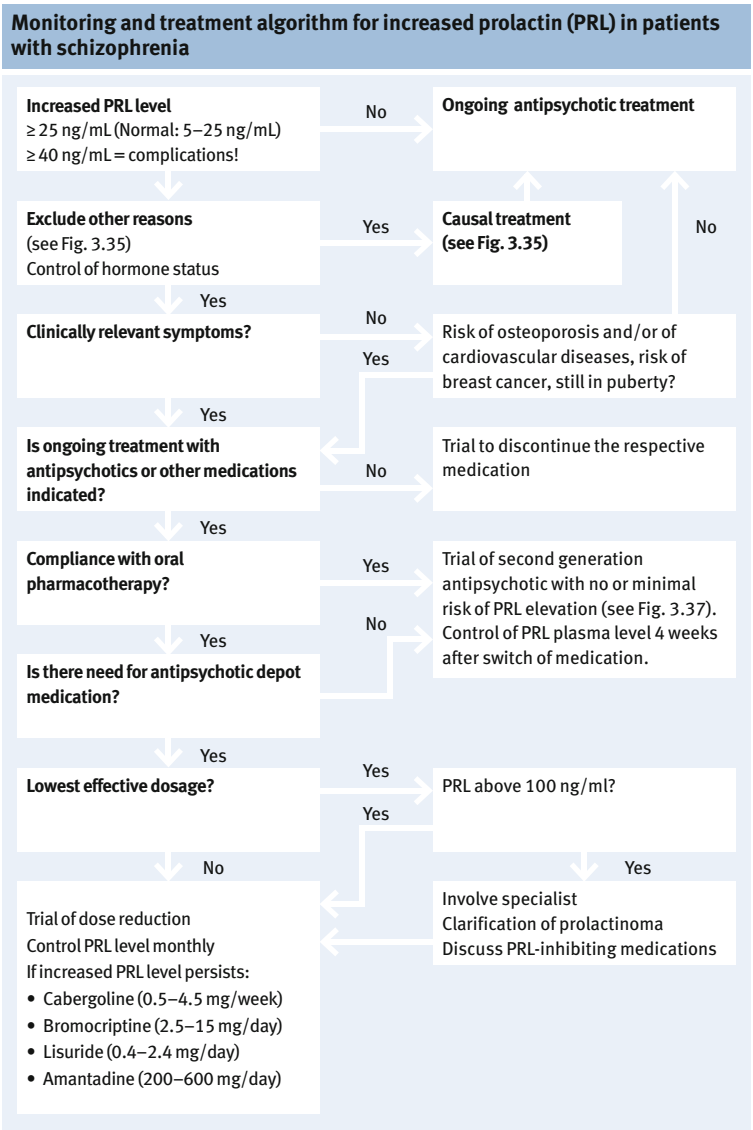


Figure 3.38 Monitoring and treatment algorithm for increased prolactin (PRL) in patients with schizophrenia.

Pharmacological and other treatments for increased prolactin
1. Causal treatment (eg)
a. Operation of a prolactinoma (micro- or macro-)
b. Treatment of hypothyroidism
2. Symptomatic treatment (normal dose to maximum dose)
a. Bromocriptine: 1.25 mg twice daily oral; up to 15 mg/day
b. Lisuride: 0.2 mg twice daily oral; up to 2.4 mg/day
c. Cabergoline: 0.5–1.0 mg/week oral; up to 4.5 mg/week
d. Amantadine: 200–300 mg/day oral; up to 600 mg/day

Figure 3.39 Pharmacological and other treatments for increased prolactin.

Risk factors for QTc prolongation and medications that prolong QTc interval	
Risk factors and patients at risk	
General risk factors	• Congenital long QT syndrome (inherited), personal history of syncope, family history of sudden death at an early age, hypokalaemia, hypomagnesaemia, other electrolyte imbalance, pre-existing cardiac disease or cardiovascular disease, bradycardia, female gender, older age
Patients at risk	• Individuals with severe and persistent mental illness, elderly, medically ill, overdose, concurrent drug use
Medications that can prolong QTc interval	
Antibiotics/ antivirals	• Erythromycin, quinine, chloroquine, amantadine
Antiarrhythmics	• Quinidine, procainamide
Antihistamines	• Terfenadine
Antipsychotics	• Tricyclic FGA of the phenothiazine type (eg chlorpromazine, promethazine, perazine, thioridazine and pimozide) • High-dose intravenous haloperidol • SGA: sertindole, ziprasidone
Other psychotropics	• Tricyclic antidepressants • Others: citalopram, chloral hydrate, lithium
Rare or uncertain for QTc prolongation, but other cardiac problems	• Clozapine (eg cardiomyopathy, cardiomyocarditis). Risk of myocarditis with clozapine is 1/500 to 1/10 000 treated patients. If the diagnosis is probable, clozapine should be stopped and the patient referred urgently to internal medicine

Figure 3.40 Risk factors for QTc-prolongation and medications that prolong QTc-interval. FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

Risk of cardiological side effects related to SGA and FGA

Antipsychotic	Tachycardia	Orthostatic hypotension	Orthostatic hypotension
High-potent FGA	(+)	(+)	(+)
Low-potent FGA	++	+++	+++
Amisulpride	0	0	0
Aripiprazole	0	0	0
Clozapine	++	+++	+++
Olanzapine	(+)	(+)	(+)
Quetiapine IR/XR	++	++	++
Risperidone/ paliperidone	(+)	+(+)	+(+)
Ziprasidone/sertindole	(+)	(+)	(+)

Figure 3.41 Risk of cardiological side effects related to SGA and FGA. Prevalence and severity of side effects derive from the pharmaceutical industry, from related research articles, and different guidelines (eg APA, CPA). 0, no risk, (+), rare, possibly no difference to placebo, +, mild (lower than 1%), ++, sometimes (lower than 10%), +++, often (>10%). FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

There is a variety of risk factors for QTc prolongation and medications known to prolong the QTc interval (Fig. 3.40). The risks with various antipsychotics are summarized in Fig. 3.41 and recommendations for monitoring cardiovascular side effects listed in Fig. 3.42.

Hypotension and orthostatic hypotension are related to the α-antiadrenergic effects of antipsychotics, known to occur, for example, with low-potency FGAs, clozapine or quetiapine (see Fig. 3.41). Patients who experience hypotension must be cautioned against getting up quickly and without assistance because falls can result in accidents, particularly in elderly patients.

Gradual dose titration, starting with a low dose, and monitoring of orthostatic signs minimize the risk of complications due to orthostatic hypotension.

Tachycardia is particularly relevant in pre-existing cardiac disease and in patients who are treated with certain antipsychotics, eg clozapine. It is caused by the anticholinergic effects of antipsychotics but may also occur as a result of postural hypotension (see Fig. 3.41).

3.4 The most recommended psychosocial interventions

Eóin Killackey

In the last few years there has been a growing realization of the failure of symptomatic recovery alone to lead to functional recovery. Thus individuals with illness make symptomatic recoveries due to the availability of better agents

Recommendations for monitoring cardiovascular side effects of antipsychotics

- ECG should be performed before initiating antipsychotic treatment in older patients and for those with the following risk factors:
  - concurrent treatment with medication that inhibits the metabolism of antipsychotics
  - concurrent treatment with medication that leads to QTc prolongation
  - positive family history for sudden death
  - syncope in the medical history
- Regular ECGs are recommended (see Fig. 4.6)
- Risk factors should be assessed and carefully monitored (eg diabetes, blood pressure, obesity, dyslipidaemia or previous cardiac side effects of antipsychotic treatment)
- If the QTc interval is >440 ms; medications that increase the QTc should be avoided and/or a cardiologist consulted
- If a QTc interval increases >500 ms, the antipsychotic should be discontinued

Figure 3.42 Recommendations for monitoring cardiovascular side effects of antipsychotics.

(and their more scientific use), but are left functionally disabled, not returning to school or work and becoming socially marginalized.

For these reasons the psychosocial treatment of schizophrenia is now considered to be as important and necessary as the pharmacological treatment. This has not always been the case. Several factors acted against the inclusion of psychosocial treatments as a core part of the treatment of schizophrenia in the past. These have included the largely prevalent kraepelinian concept of dementia praecox, which posited that schizophrenia was an illness of inevitable decline, and the fact that psychodynamic therapeutic interventions, which made up the larger part of psychosocial interventions in that era, were not effective.

General principles for use of psychosocial interventions in schizophrenia

- Psychosocial interventions should not be optional additions to treatment, but instead, wherever possible, should be part of the routine care of patients with schizophrenia.
- There is growing evidence that some of the psychosocial interventions, particularly cognitive–behavioural therapy (CBT), and vocational and family interventions, can have a major impact on the wellbeing of people with schizophrenia.
- Schizophrenia is an illness that affects people in many life domains and, as yet, medication does not address all of these deficits. Psychosocial and pharmacological interventions complement each other, and practitioners of each should work together to maximize outcomes for patients with schizophrenia.

- Patients with schizophrenia must be provided with psychosocial interventions relevant to their needs.
- When psychosocial interventions are provided, there is evidence that the quality of life and functioning of patients with schizophrenia is improved and that there is a positive effect on admission rates.
- Families feel more supported and informed and better able to look after a relative with schizophrenia when they are offered education, support and appropriate involvement in treatment.
- Psychosocial interventions work best in a system that is not wholly occupied with managing people through the acute episodes of illness and then discharging them to minimalist care (especially GPs or primary care practitioners, where the GP is the sole health worker).
- The nature of the psychosocial intervention has to be tailored to the individual and should focus specifically on issues of relevance to that patient.
- Psychosocial intervention requires highly trained clinicians with expertise in specific areas (rather than a model in which these interventions are devolved to less skilled practitioners and semi-skilled non-governmental organizations).

3.4.1 Family interventions

Family, broadly defined as those who have an emotional and practical relationship to the person with schizophrenia (parents, partner, siblings, etc), often play an important role in both caring for patients with schizophrenia and helping them care for themselves. However, this is a role that is often very stressful and has the potential to lead to strains on the relationships, if not to alienation. Family interventions in schizophrenia cover a wide variety of practices, which are conducted in a variety of situations. They can be: psychoeducational, therapeutic or skills based; conducted with or without the patient present, in multifamily groups or with one family alone; and brief in duration (eg single or few sessions) or conducted over an extended period.

A review of 13 studies of family interventions in patients with schizophrenia found the following:

- Family intervention has no effect on mortality
- The mental state of patients improves with family therapy; however, the improvement is greater when the level of skill of the therapy team is higher
- Drop-out rates are low, suggesting that family intervention is acceptable to patients
- There are no clear effects in the domain of social functioning, but there are positive trends towards employment and independent living

- The effect on families is to reduce the burden of illness, increase knowledge and decrease expressed emotion
- Family intervention leads to cost saving, with a drop of about 20% in total costs
- The number needed to treat (NNT) to have one person symptom free using family intervention is 6.5
- Family therapy reduces relapse rates by over 50% compared with medication and case management alone
- Another review of six randomized controlled trials of family intervention also found that there were significant effects on relapse rates at 6 and 9 months but not 24 months, and an NNT of between 2 and 5. There were also significant effects on expressed emotion and hospital admission but not on compliance.

Several reviews have examined studies of family interventions in schizophrenia and have reached the following conclusions:

- Family therapy is effective on a number of symptoms and is recommended
- Family intervention should be integrated at all stages and with all aspects of care
- Where possible, family interventions are more effective when they are more than 6 months in duration or include more than 10 planned sessions
- Family treatment should include a psychoeducational module
- Family intervention is effective in reducing relapse. It should be offered particularly where the family member has relapsed recently or is in danger of doing so
- Family psychoeducational interventions are effective in reducing problems in families with difficulties
- Multifamily groups may be better than single family groups; however, families may have a preference for single family groups and this should be respected where possible
- Local and national support groups are effective in supporting the family and referrals to consumer and carer networks are recommended.

3.4.2 Psychoeducation programmes

Psychoeducation is a means whereby the patient (and/or family) is educated about the illness and its treatment. In order that the patient may participate in decisions about treatment to the fullest degree possible, psychoeducation is a necessary process.

There have been a number of positive results with psychoeducation programmes in patients with schizophrenia. These include improving adherence

to treatment, better outcomes, better management of subsequent relapse, lower readmission rates and having a positive effect on patients' wellbeing.

Psychoeducation can be conducted separately, but it can also be included as part of other interventions, such as family interventions (see above). Psychoeducation in the early phases tends to focus on supporting and educating the individual or family about schizophrenia, generally from a biopsychosocial perspective. As the patient progresses in his or her recovery, the subject matter may devolve to more general topics, such as life skills and adapting to the changes necessary to manage the illness.

Information should also be given to other people who may not be direct primary carers, but who frequently come into contact with patients with schizophrenia. These may include workers at community agencies, local government employees and workers at supported accommodation residences, as well as the general public. The term for this process is mental health literacy rather than psychoeducation.

A Cochrane review of psychoeducation for patients with schizophrenia found that, compared with standard care alone, the addition of psychoeducation made a worthwhile contribution. A NICE review found that, although it is good practice to provide psychoeducation, there is not yet enough evidence of its effect on outcome to recommend it as a discrete treatment. Thus, in summary:

- Psychoeducation for patients possibly reduces relapse, through improved compliance. It also increases patients' satisfaction with treatment and improves their knowledge of schizophrenia
- However, the evidence of its ability to reduce relapse is not yet conclusive enough to recommend its use as a discrete intervention
- Psychoeducation for families is also effective and should be offered routinely.

3.4.3 Cognitive interventions

Although Aaron Beck used cognitive therapy techniques to treat psychotic symptoms in at least one patient in the early 1950s, the development of further work in this area really began in earnest only after the reconceptualization of schizophrenia from a single syndrome to a cluster of separate symptoms, each of which varied and could be addressed individually. There are two strands to the cognitive interventions: one is what may be called the CBT strand, which seeks to use the techniques of CBT to reduce distress and symptoms; the second is the cognitive remediation strand, which seeks to address directly the cognitive deficits that are evident in patients who have or are experiencing schizophrenia. Each of these is dealt with separately below.

Cognitive–behavioural therapy interventions

CBT interventions involve the therapist and patient exploring the links between thoughts (which may be delusional) and feelings. They may also

challenge the validity of some thoughts and perceptions, testing them against other possible hypotheses that could explain the experience. A Cochrane review of CBT for schizophrenia found that the NNT for one person to become symptom free was 6. It also found that CBT in combination with standard care was better at reducing relapse compared with standard care alone. Furthermore, for CBT to be effective, those who administer it need to be skilled in its application.

A review conducted in the preparation of the NICE guidelines, which incorporated part of the Cochrane review and some more recent studies, found that CBT intervention had better effects when the intervention was for more than 6 months or had at least 10 planned sessions. It also found that CBT intervention showed good efficacy with those who had persistent psychotic symptoms. Recommendations for CBT are given in Fig. 3.43.

Cognitive remediation

Another cognitive intervention used in the treatment of schizophrenia is cognitive remediation (sometimes known as cognitive rehabilitation). The aim of cognitive remediation is to address the cognitive impairments of patients with schizophrenia, eg distractibility, memory problems, lack of vigilance, attentional deficits, and limitations in planning and decision-making. It is hoped that, by addressing these issues, patients will be more able to take advantage of other interventions and better able to function in social and other domains. So far, results in controlled trials of cognitive remediation have been equivocal. Consequently, the NICE guidelines, along with other international guidelines, have concluded that there is not enough evidence currently to recommend cognitive remediation as an evidence-based intervention at this point in time.

Recommendations for use of cognitive–behavioural therapy (CBT) in schizophrenia

- Individual CBT is highly effective in improving the mental state and global functioning of a patient as it is associated with reduced risk of relapse over standard care alone
- CBT in the acute phase can accelerate recovery and hasten discharge when added to standard care
- CBT can be helpful in reducing symptoms of TRS
- CBT should be offered particularly to those who have persistent symptoms
- CBT should be available to all people with schizophrenia
- CBT is an intervention that requires a skilled practitioner

Figure 3.43 Recommendations for use of cognitive–behavioural therapy (CBT) in schizophrenia. TRS, treatment-resistant schizophrenia.

3.4.4 Social skills training

Schizophrenia most commonly occurs for the first time in young people (children, adolescents and young adults) and, as a result, patients with schizophrenia quite often miss out on engaging in many of the normal developmental tasks of late adolescence and early adulthood. These tasks include developing such things as social skills, intimate relationships, occupational skills and independent living skills. In addition, those who develop schizophrenia later in life often develop deficits in these areas. Social skills training (also called 'life skills training') is a widely practised intervention and seeks to address these deficits.

Evidence shows that social skills training improves social adjustment, enlarges or enhances the social network of the patient with schizophrenia, and contributes significantly to the development of independent living skills. In 1997, there was a report that a small number of studies have shown that skills taught in programmes tend to generalize and do not teach to an individual's specific needs, although this is an area that is in need of more research. Although the benefit of social skills training has been demonstrated in a number of independent studies, both the Cochrane and NICE reviews of social skills training found no evidence to determine whether it was of benefit. There is, therefore, a need for well-planned and -conducted studies to examine the effectiveness of social skills training, although the NICE guidelines suggest that social and physical activities should be a required part of the care plan for all patients with schizophrenia.

3.4.5 Vocational rehabilitation

One of the associated features of schizophrenia is low socioeconomic status. In high-income societies unemployment rates among severely mentally ill patients are estimated at 75–92%. Apart from being a fundamental right, being occupied in a paid or voluntary capacity can have a clinical impact by increasing self-esteem, alleviating psychiatric symptoms, and reducing dependency and relapse. An intervention that aims to address the issue of employment for patients with schizophrenia is vocational rehabilitation.

Sheltered workshops were the original vocational rehabilitation model. However, these did not lead to many people getting competitive employment. Currently, there are two main models of vocational rehabilitation: prevocational training, in which a period of preparation is engaged in before seeking competitive employment; and supported employment, in which people are placed in competitive employment with the provision of on-the-job support. It was found in the Cochrane review of vocational rehabilitation that supported employment was a more effective programme than prevocational training. A total of 34% of

people engaged in the supported employment programme were still working at 12 months compared with 12% in the prevocational training conditions. The most defined form of supported employment is known as individual placement and support (IPS). There is emerging evidence that early intervention on the vocational domain using IPS for young people with a first-episode illness leads to even better outcomes.

Based on these findings, patients with schizophrenia should be encouraged, where possible, to find a meaningful occupation in either a paid or a voluntary capacity. In addition, patients with schizophrenia should be put in contact with agencies that provide such services early in the course of illness:

- Becoming vocationally involved is likely to have positive psychosocial consequences
- People with mental illnesses, including those with schizophrenia, want to find work, but, at present, there is an extremely disproportionate number of patients with mental illnesses who are unemployed
- Various models of vocational rehabilitation have had different levels of success in placing people in competitive positions
- Supported employment programmes are much more successful than other types of programmes
- Vocational rehabilitation programmes can reduce re-hospitalization and improve insight
- Vocational rehabilitation enhances vocational functioning.

3.4.6 Compliance therapy

One of the problems that faces clinicians working with people experiencing schizophrenia is the issue of compliance. There are many reasons why patients are not compliant, but, when the lifestyle change involved in regularly taking medicine (which often has unpleasant side effects), the difficulty that most people have in adhering to a 2-week course of, say, antibiotics and the amotivation and low insight that often accompany schizophrenia are considered, non-compliance should be no surprise. Being aware of the link between compliance and a favourable outcome, a therapy was developed that specifically addresses compliance.

Compliance therapy has been found to be effective in increasing compliance with treatment in one randomized controlled trial. Compliance therapy uses motivational interviewing and cognitive–behavioural techniques to help clients explore issues around compliance. Compliance therapy may be useful when applied in both early and later phases of recovery. However, further research is needed to confirm the validity of this intervention.

3.4.7 Summary of psychosocial interventions

The most important recommendations for the use of psychosocial interventions are given in Fig. 3.44. After decades of receiving little, if any, consideration, psychosocial interventions are making a comeback and are being viewed as a necessary complement to the ever-advancing sophistication of pharmacotherapy. Some interventions, such as CBT, vocational and family interventions, already have a good deal of evidence to support them; others are currently being tested.

Increasingly, the role of managing patients with schizophrenia is being devolved to primary care doctors in many countries around the world. It is important, therefore, that doctors make themselves aware of the psychosocial interventions that are evidence based and available in their area, if for no other reason than to share the burden of care. Where there are no such services, doctor and consumer groups should use the available evidence to lobby for the provision of such services.

Recommendations for use of psychosocial interventions in schizophrenia

- Can address a range of important domains not always addressed by medication
- Have a positive impact on the quality of life of patients with schizophrenia and their carers
- Where possible should be offered as part of a package that has a pharmacotherapeutic basis but includes some or all of:
  - Psychological therapy (CBT) – vocational interventions
  - Family interventions
  - Psychoeducation
  - Compliance therapy
- Must be administered by people trained in their application

Figure 3.44 Recommendations for use of psychosocial interventions in schizophrenia. CBT, cognitive–behavioural therapy.

Chapter 4

Quick reference

4.1 Epidemiology, aetiology and course of illness

4.1.1 Epidemiology

Prevalence

With a worldwide lifetime prevalence of 0.6–1% schizophrenia represents one of the most serious global health challenges. The 1-year incidence of schizophrenia is 0.2–1.0 per 100 (pooled rate 0.34), lifetime incidence 0.4–2.2 per 100 (pooled rate 0.55) and annual incidence 3.6–200 per 100 000 (pooled rate 11.1). Services with the capacity for early detection have reported even higher annual rates of 16.7 per 10 000 in men and 8.1 per 10 000 in women among 15- to 20-year-old individuals.

Age at onset

Childhood onset (defined as onset by the age of 12 years) is rare: up to 1% of all schizophrenia spectrum disorders manifest before the age of 10 years, 5% before the age of 15 years and almost 20% below the age of 18 years. In most cases (30–40%), onset is in early adulthood, in the age range 18–25 years. However, some people experience a later onset: so-called late-onset schizophrenia (patients aged >40 years) and very-late-onset schizophrenia-like psychosis (onset after age 60 years).

Gender differences

The lifetime risk for schizophrenia seems to be equal in both sexes. It was previously reported that women tend to have a later age of onset (by 3–4 years) and a second peak of onset around the menopause. With respect to age at onset, newer epidemiological studies with early detection and after a period of community education have not found gender differences. Moreover, women experience a possibly more benign course, especially in the short term, better premorbid functioning, including social and intellectual abilities, more affective and less negative symptoms, and lower rates of comorbid substance abuse.

The risk of schizophrenia and affective disorders due to the presence of these illnesses in families was described as higher in women than in men, but there was less evidence of obstetric complications in their mothers and less structural brain abnormality.

4.1.2 Aetiology

Overview

Evidence suggests that schizophrenia is probably not related to a single biological defect. Rather, it is suggested that an interaction of different pathological mechanisms, including intrinsic and extrinsic (risk) factors, is more likely. These risk and/or premorbid factors may be associated with an increased vulnerability for schizophrenia. The pathways between risk factors and the diagnosis and course of schizophrenia are not fully assessed and many questions remain unanswered about the diagnostic specificity and aetiological significance of these associations. Risk factors include, among others (Fig. 4.1):

- an illness that is combined with severe central nervous system (CNS) dysfunctions (eg multiple sclerosis)
- CNS dysfunctions caused by various substances (eg amphetamine psychosis)
- genetic predisposition (eg positive family history for psychosis)
- intrauterine and/or birth complications (eg viral infections or hypoxia), certain patterns of family interaction and life events (eg expressed emotion)
- extrinsic (environmental) factors, such as substance abuse or developmental stress.

Most of these risk factors may operate early in life (eg during the perinatal period), creating a disruption in the development of the brain followed by an increased vulnerability for stress (eg environmental stress, toxins, or neuronal dysfunction and damage). It seems to be clear that environmental factors both add to and interact with genetic factors to produce the onset of the clinical disorder.

Genetic findings

Repeated studies of families, twins and adopted individuals have demonstrated that genetic factors are of major relevance in schizophrenia (Fig. 4.2). Lifetime prevalence differs markedly between relatives of those without and those with schizophrenia (0.2–2% compared with 0.5–16%). Children of a parent diagnosed with schizophrenia have a 10-fold increased risk of developing the disorder. Studies of twins suggest the importance of genetic factors, demonstrating higher rates of concordance for the disorder in monozygotic (MZ) twins (44.3%) than in dizygotic (DZ) twins (12.1%), proved by consistent MZ:DZ ratios across the studies. Studies of adopted individuals provide further evidence for genetic vulnerability, showing an association between

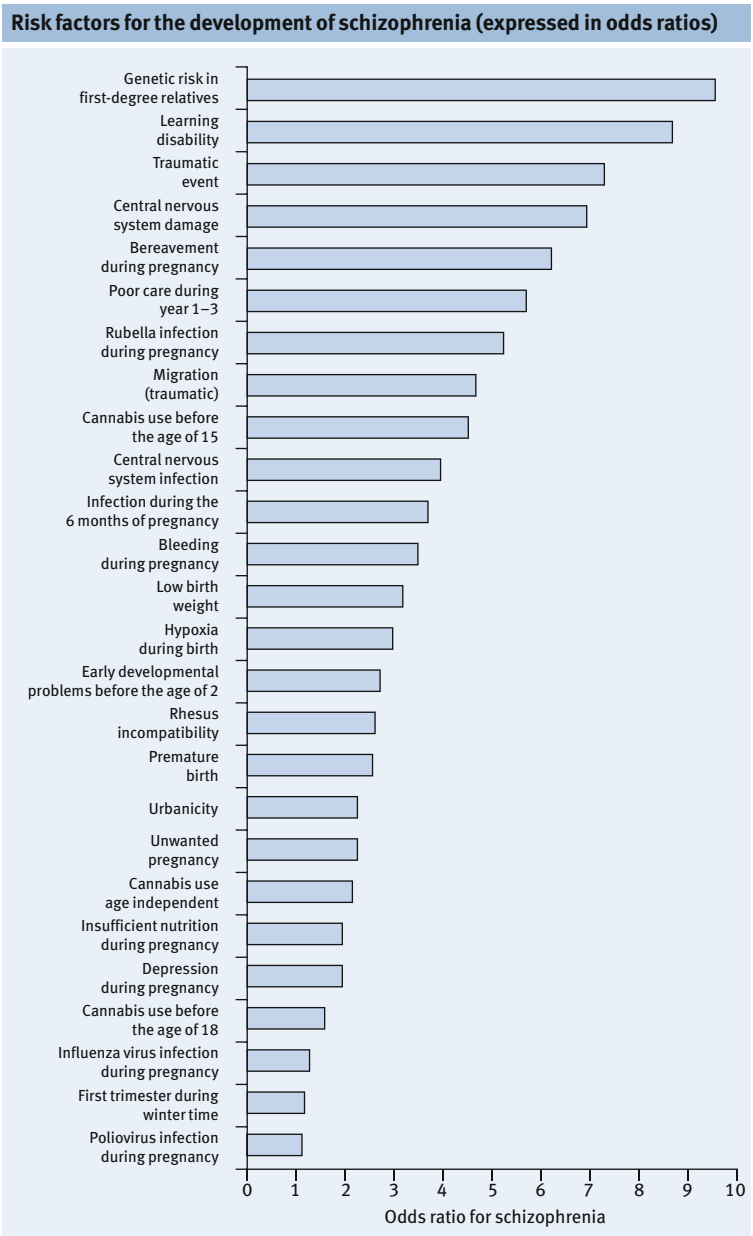


Figure 4.1 Risk factors for the development of schizophrenia (expressed in odds ratios). Note that these risk factors were explored and assessed in different studies with varying methodologies. As such, it is not possible to compare the sizes of the shown odds ratios.

biological relatives separated at birth (10-fold increased risk). Moreover, schizophrenia spectrum disorders have a significant familial relationship with schizophrenia.

Structural and functional brain abnormalities

There is a large body of evidence that indicates that people with schizophrenia display abnormalities on electroencephalography (EEG), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) scanning, eye tracking, neurological signs, cognitive impairment and psychophysiology. However, the mechanisms of the associations are not known. There is no singular pathology or laboratory test to confirm the presence of schizophrenia.

Lifetime risk for schizophrenia according to genetic and family relationship to patient with schizophrenia

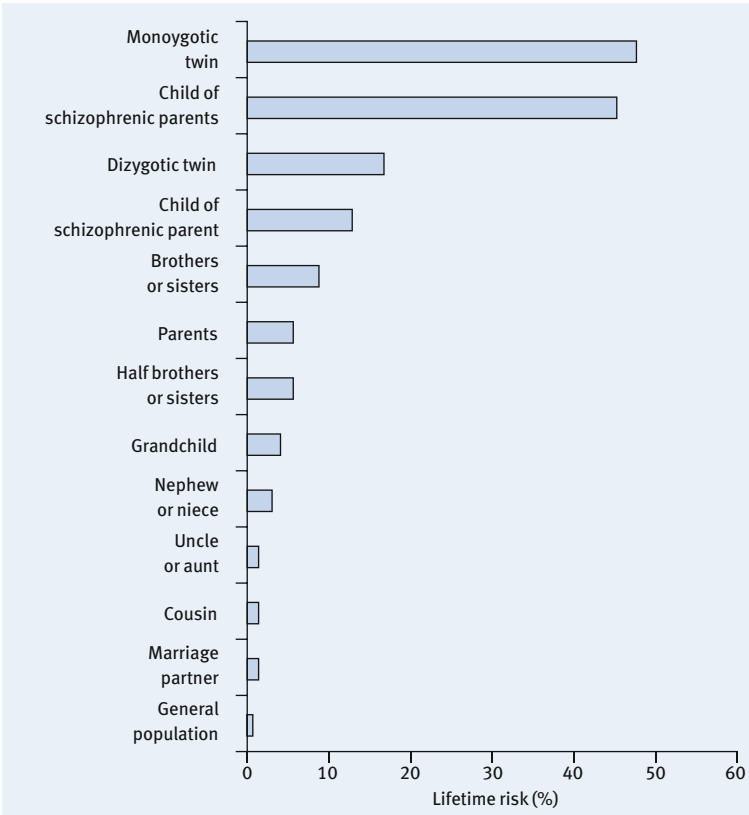


Figure 4.2 Lifetime risk for schizophrenia according to genetic and family relationship to patient with schizophrenia

4.1.3 Course of illness

Prodromal phase

A prodrome in schizophrenia could be defined as:

- the earliest form of psychosis
- a syndrome conferring increased vulnerability to psychosis.

Most of these symptoms are not specific for psychosis and also exist in other psychiatric disorders. In the main, they are subtle, self-experienced disturbances of affect and cognition, possibly accompanied by unusual perceptions. The duration of the prodromal phase can be extremely variable and its onset and separation from the phase of duration of untreated psychosis or non-psychotic psychiatric disorders may be difficult. Common prodromal changes could be separated into symptomatic and behavioural deteriorations (see Fig. 3.2, page 42). Results of various studies underline the hope that early detection can help to identify people with a vulnerability to the development of psychosis or schizophrenia. These studies conclude that the rates of transition from normal or prodrome to psychosis are 33–58% in a time frame of up to 12 months. However, even though these findings are encouraging, caution must be taken to avoid stigmatization and false-positive interventions.

Duration of untreated psychosis (DUP)

For patients first presenting with schizophrenia, the DUP (time between the onset of positive psychotic symptoms and the initiation of treatment) and the duration of untreated illness (DUI: time between onset of first prodromal symptoms and the initiation of treatment) vary widely, from a few weeks to several years. Measured in different countries, DUP ranges between 1 and 2 years. Determinants for delayed initial treatment include, among others, denial of illness, self-withdrawal from social networks, negative psychopathology, age at onset, poor premorbid functioning, and insight about self-care and treatment. Some studies report a significant inverse negative correlation between long DUP or long DUI and symptomatic outcome; others have not found this correlation. Other psychosocial variables have shown a negative association with a longer phase of active psychosis. Early detection can help to reduce DUP and influence patient characteristics positively at initial treatment.

Psychotic acute phase

In terms of the positive/negative distinction, negative symptoms are the initial psychopathology in 70% of the cases of schizophrenia, mixed negative and positive symptoms in 20% and positive symptoms in only 10%. The initial psychopathological syndrome includes combined delusions and hallucinations in 43% of patients and

is undifferentiated in 30% of patients, and there were negative symptoms in 13% of patients. In approximately 70% of patients the illness starts slowly and chronically, only 15–20% starting with an acute episode. With regard to the type of first psychopathology, delusions are reported to be the most common initial psychotic symptoms (up to 50% of patients), followed by hallucinations (up to 30% of patients). Besides psychotic symptoms, many patients with schizophrenia demonstrate cognitive impairments, already evident before the initial treatment (see section 2.2, Chapter 2, page 4).

Agitation is another frequent problem in the acute phase of schizophrenia and is often combined with violent and destructive behaviour, personal distress and suffering, self-harm, and harm to caregivers and others (see section 3.2.2, Chapter 3, page 44). Authors who studied the consequences of agitation found that:

- an average of eight assaults per year occur in a typical psychiatric service
- mechanical restraints are used in 8.5% of patients with a mean duration of 6.1 hours
- approximately 50–150 deaths per year occur in the context of physical restraints.

These rates may vary across mental health systems and services. Psychiatric comorbidity is also frequent in schizophrenia. Approximately 80–90% of patients with schizophrenia have at least one comorbid psychiatric condition. This has negative consequences for prognosis and contributes to the high rate of morbidity and mortality. Substance abuse disorders are associated with poor outcome (up to 70% of patients, depending on the availability of drugs) and depression is associated with suicide (in up to 75% of patients with depression), the leading cause of premature death in patients with schizophrenia. Other relevant comorbid psychiatric disorders are post-traumatic stress disorder, panic (anxiety) disorder(s), obsessive–compulsive disorder and social phobia, all of which may worsen prognosis. Moreover, comorbid medical conditions, including cardiac and pulmonary disease, infectious diseases, diabetes, hyperlipidaemia, hypogonadism and osteoporosis, are not often sufficiently recognized and are undertreated.

Long-term phase and outcome

In outcome there is a large variation between patients, but in many cases schizophrenia is a long-term illness with persistent symptoms and impairment of role functioning. According to one study symptomatic evolution data show that 22% of patients who have one episode of schizophrenia do not experience long-term disability and 35% of those who have repeated episodes do so without disability. Eight per cent of patients have repeated episodes with stable disability and 38% have several episodes with increasing long-term disability. It was also shown that, in a 23-year follow-up period in one study, only 9% of

the patients had one psychotic episode, 32% were found to experience two or three episodes, and 36% had four or more episodes. Long-term hospitalization was required for 24% of the patients. The average number of episodes in the 23-year assessment period was 3.5.

In the long-term, episodes with predominant positive symptoms decrease, whereas episodes with negative symptoms increase. Symptoms, such as delusions or hallucinations, may persist, but they become attenuated over the course of the illness. Repeated episodes can be triggered by several factors, mainly comorbidity, medication non-compliance and life events. On average, 10–20% of patients with schizophrenia have a positive outcome and 40–50% a negative outcome in a follow-up period of 40 years from the first episode. Full remission without any disability is rare, with only 10–20% of patients showing complete remission in 5 years and 7% in 25 years. However, this course can be tempered greatly by the degree and quality of intervention provided.

4.2 Presentations and diagnosis

4.2.1 Clinical presentation

Schizophrenia is probably one of the most complex psychiatric disorders. Even in the early stages of the disorder (eg prodromal phase or first episode) many patients present with a variety of different symptoms, comorbid psychiatric and somatic disorders, and interrelated social and psychological dysfunctions (Fig. 4.3).

Patients usually present with positive, negative and disorganized symptoms (Figs 4.3 and 4.4):

- **Positive symptoms** include, most importantly, hallucinations (false perceptions in any of the senses) and delusions (false beliefs held with great certainty, preoccupying the individual's mind, which are socioculturally inappropriate).
- **Negative symptoms** typically include the reduction of social and/or personal interests, anhedonia, blunted or inappropriate emotions, and inactivity. People with schizophrenia often display negative symptoms long before the first positive symptoms emerge and, in the long term, so-called residual symptoms.
- **Disorganized symptoms** include disorganized thought, speech and behaviour. There is some controversy over whether the disorganized symptoms are a separate set of symptoms of schizophrenia or whether, as they are seen in other presentations (eg manic phase of bipolar disorder), they should not be considered diagnostic of schizophrenia on their own.

Currently, schizophrenia is mainly defined by the presence of positive symptoms. However, there are those who see it as more of a cognitive disorder with the presence of neurocognitive deficits being a marked feature of the presentation of many people with schizophrenia (see Fig. 4.3).

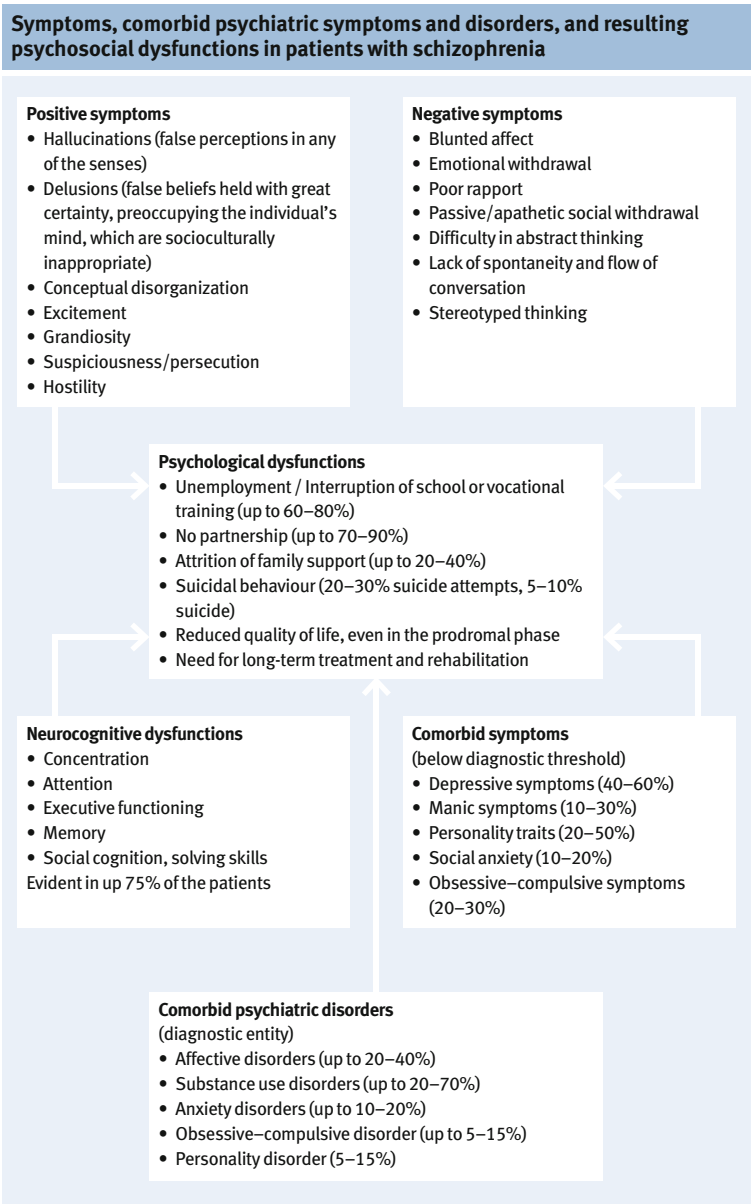


Figure 4.3 Symptoms, comorbid psychiatric symptoms and disorders, and resulting psychosocial dysfunctions in patients with schizophrenia.

Model of positive and negative symptoms and value of symptoms during the course of schizophrenia

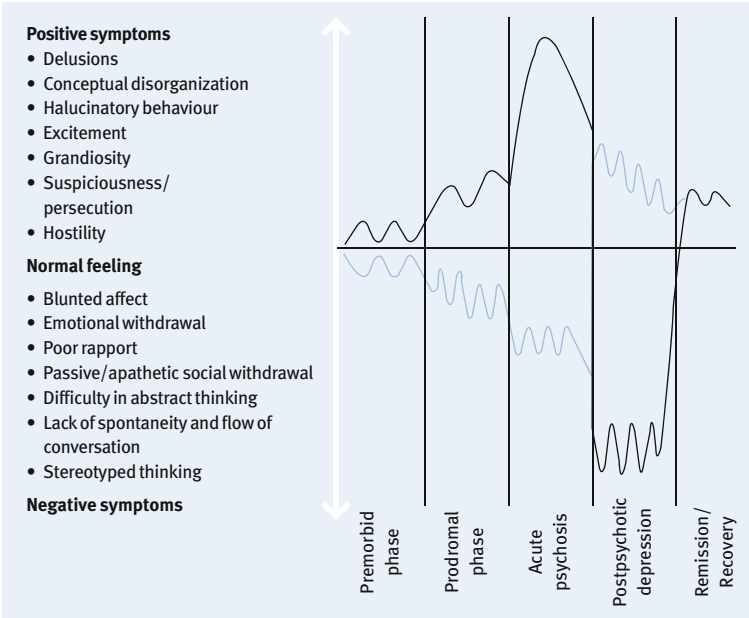


Figure 4.4 Model of positive and negative symptoms and value of symptoms during the course of schizophrenia. (According to J Bäum.)

4.2.2 Psychosocial assessment

In line with the complexity of the disorder, the psychosocial assessment in schizophrenia includes a Mental State Examination (MSE), a risk assessment, an assessment of the personal and psychiatric history and comorbid psychiatric disorders, and an assessment of possible social problems (Fig. 4.5).

4.2.3 Neuromedical assessment

A full neuromedical examination should be undertaken (Fig. 4.6). This examination is important to detect somatic comorbidities and risk factors for future somatic diseases, especially cardiovascular disease, including obesity, smoking, hypertension, dyslipidaemia and type 2 diabetes. Furthermore, the medical assessment gives information on the potential existence of an organic cause of psychosis and whether there are risk factors for incomplete remission or treatment resistance (eg wide ventricles on magnetic resonance tomography). It also establishes a baseline against which possible future side effects and complications of pharmacological treatment can be measured.

Overview of major aspects of the psychosocial assessment in schizophrenia

Assessment	Content
Mental State Examination	• Positive symptoms (eg hallucinations, systematized delusions) • Negative symptoms (eg primary deficit syndrome, secondary negative symptoms) • Disorganization, thought disorder • Manic or depressive syndromes, anxiety • Cognitive dysfunctions • Insight
Risk assessment	• Suicidal risk (eg actual thoughts or plans, past suicide attempts, actual depression, delusion-related anxiety, actual substance use, command hallucinations, tragic loss) • Violent/aggressive behaviour (eg previous violent behaviour, agitation, disorganization, suspiciousness/delusions, dysphoric and/or manic symptoms, antisocial personality, catatonic excitement, drug intoxication) • Risk of victimization by others (eg disorganization, manic–psychotic mental state) • Risk of treatment non-adherence (eg insufficient therapeutic alliance, persistent comorbid substance abuse disorder, lack of insight, negative attitude towards medication, negative subjective wellbeing under antipsychotics, lack of social support) • Risk of service disengagement and unauthorized absconding from hospital (eg young age, male, persistent substance use disorder, antisocial personality, lack of insight)
Personal and psychiatric history	• Biography (eg developmental milestones, school/work status and functioning, peer relationships) • Psychiatric history of family (eg psychiatric disorders in relatives, expressed emotion, genetic risk) • Pregnancy and obstetric complications (eg intrauterine infection, hypoxia, premature birth) • Early developmental events (eg delayed speaking and walking) • Functional problems during early childhood (eg in kindergarten or elementary school) • Premorbid functioning • Trauma in early childhood or youth and other psychosocial stressors • Prodromal symptoms (including Brief Limited Intermittant Psychotic Symptoms (BLIPS), Attenuated Positive Symptoms (APS), reduced functioning level in the last 12 months, duration of prodrome, time point of ongoing positive symptom manifestation) • Duration of untreated psychosis (DUP; including symptoms and symptomatic development) • Forensic history • Pathways to care • Psychodynamic context

Figure 4.5 Overview of major aspects of the psychosocial assessment in schizophrenia.
PTSD, post-traumatic stress disorder.

Overview of major aspects of the psychosocial assessment in schizophrenia (*continued*)

Assessment	Content
Comorbid psychiatric disorders	• Comorbid psychiatric disorder (premorbid, during prodrome, during DUP and at initial presentation) • In case of comorbid substance abuse disorder, • Substance abuse disorder (eg type, abuse or dependency, onset, actual use, reasons for use, previous treatment, previous drug-induced psychosis, motivation to change) • Major depression (eg onset, course, previous treatment, actual severity) • Anxiety disorder (eg onset, course, previous treatment, actual severity; especially social phobia and PTSD) • Obsessive–compulsive disorder (eg onset, course, previous treatment, actual severity) • Personality disorder/traits (eg onset, course, previous treatment, actual severity; especially antisocial and avoidant personality disorder) • Learning disability • Attention deficit hyperactivity disorder
Social assessment	• Actual situation and problems at school or work • Living situation • Financial situation, debts • Family situation

Figure 4.5 Overview of major aspects of the psychosocial assessment in schizophrenia (*continued*). PTSD, post-traumatic stress disorder.

4.2.4 Neuropsychological assessment

Approximately 75% of patients with schizophrenia display cognitive dysfunctions in a wide variety of domains (see section 2.2, Chapter 2, page 4). Cognitive assessment is important because empirical evidence has shown that cognitive deficits are determinants of functional outcome. Furthermore, they are linked to other clinical variables such as insight or the ability to take medication as prescribed. Moreover, undisturbed cognitive abilities are important for patients to benefit successfully from psychotherapeutic interventions. The assessment should be undertaken when the patient is not floridly psychotic and has been stabilized. A repeated assessment is recommended about 6 months after the first neuropsychological test.

4.2.5 Assessment of psychotic and comorbid psychiatric disorders

The diagnostic categorization of schizophrenia is hampered by several factors, eg diagnostic instability, a large range of differential diagnoses (Fig. 4.7) and a high rate of comorbid psychiatric disorders.

Recommendations for biomedical examinations in patients with schizophrenia

Examination	Beginning of treatment	Follow-up examination
Medical history	√	No
Physical examination	√	When clinically indicated, otherwise in intervals as proposed for healthy populations
Neurological examination	√	When clinically indicated, otherwise in intervals as proposed for healthy populations
Vital signs (blood pressure, pulse, temperature)	√	Regularly during drug adjustment, especially after dose escalation
Body weight, body mass index (BMI), height, binge-eating behaviour	√	Body weight and BMI weekly during drug adjustment; then every 4 weeks; after 12 weeks every 3 months Monitor binge-eating behaviour, especially during the first 3 days, then regularly
Haematology (blood count; if indication differential blood count, eg clozapine)	√	Yearly and in case of clinical indication For clozapine treatment differential blood count before start of therapy, weekly for 18 weeks, then monthly
Blood chemistry – electrolytes, enzymes (especially liver function tests, thyroid and renal function tests)	√	Yearly and in case of clinical indication Higher frequency in case of risk or pre-existing medical illness
Lipid metabolism (fasting, including triglycerides, total cholesterol, HDL- and LDL-cholesterol)	√	Yearly and in case of clinical indication Higher frequency in case of treatment with drugs with special risk for lipid metabolism alterations, combination therapy, in patients with genetic risk or in patients with pre-existing medical illness
Metabolic syndrome [a]	√	Yearly and when clinically indicated Higher frequency in case of treatment with drugs with special risk, combination therapy, in patients with genetic risk or in patients with pre-existing medical illness
Screening for diabetes (fasting glucose and HbA1c)[b,c]	√	Fasting glucose and HbA1c every 2–4 months after beginning of drug therapy, then yearly For patients with positive family history, BMI ≥25, increased hip size and/or deviation of lipid metabolism every 4 months

Prolactin (in case of sexual dysfunctions oestrogen or testosterone)	√	When clinically indicated higher frequency in case of treatment with drugs with special risk (eg amisulpride, risperidone, paliperidone, FGA) or combination therapy
Electrocardiogram	√	When clinically indicated Regular in patients with pre-existing risk factors (eg drugs with higher risk for QTc prolongation, pre-existing disorders such as cardiovascular disease)
Electroencephalogram	When clinically indicated	When clinically indicated In first-episode patients or patients treated with antipsychotics with higher risk of seizures (eg clozapine or zotepine)
Cranial computed tomography (CCT) or magnetic resonance tomography (MRT)	When clinically indicated	Indication for first-episode patients without previous CCT or MRT When clinically indicated
Pregnancy test	When clinically indicated	When clinically indicated
Screening for extrapyramidal motor symptoms	√	In each visit
Tardive dyskinesia	√	First-generation antipsychotics (FGAs) every 3–6 months (patients at risk: every 3 months) Second-generation antipsychotics (SGAs) every 6–12 months (patients at risk: every 6 months)
Ophthalmological check	When clinically indicated	When clinically indicated

[a]Metabolic syndrome defined by presence of three or more of the following: (1) abdominal obesity with increased hip size: male ›102 cm, female ›88 cm; (2) triglycerides ≥150 mg/dL; (3) HDL-cholesterol decreased: male ‹40 mg/dL, female ‹50 mg/dL; (4) blood pressure ≥130/85 mmHg; (5) fasting glucose ≥110 mg/dL.
[b]Pathological values: fasting glucose ≥126 mg/dL; plasma glucose ≥200 mg/dL; HbA1c ›6.1%; fasting glucose 100–126 mg/dL = pre-diabetes.
[c]Risk factors for diabetes: obesity (BMI ≥ 27 kg/m^2), diabetes in first-degree relatives, hypertension (≥140/90 mmHg or antihypertension therapy), hyperlipidaemia (HDL ≤35/0.9 and/or triglycerides ≥250/2.8 mg/dL), manifest metabolic syndrome, females with gestation diabetes, macrovascular diseases, albuminuria.

Figure 4.6 Recommendations for biomedical examinations in patients with schizophrenia.

Differential diagnosis of schizophrenia according to ICD-10 or DSM-IV

ICD-10/DSM-IV	Differential diagnosis
F0/290, 293, 294 Organic, including symptomatic mental disorders	• Encephalitis (eg herpes encephalitis, AIDS encephalitis, Creutzfeldt–Jakob, neurosyphilis) • Traumatic cerebral injury • Cerebral tumours • Epilepsy • Hormonal disorders (eg Cushing's syndrome, hyperthyroidism) • Neurodegenerative disorders (such as dementia, Friedreich's ataxia, Huntington's disease, Parkinson's disease) • Endocrine disorders (such as acute intermittent porphyria, Wilson's disease, uraemia, vitamin B_{12} insufficiency, zinc insufficiency) • Rheumatic disorders (eg lupus erythematosus) • Multiple sclerosis • Others (narcolepsy, pregnancy, heart disorders, endocrinopathies, postoperative states)
F1/291–305 Mental and behavioural disorders due to psychotropic substances	• **Drug-induced psychotic disorder** • Intoxication • Withdrawal syndrome with or without delirium
F2/293–298 Schizophrenia spectrum disorders	• **Brief psychotic episode** • **Schizophreniform disorder** (ICD-10: ≤1 month; DSM-IV: ≤ 6 months) • **Schizoaffective disorder** (manic, mixed and depressive type) • **Delusional disorder** • **Drug-induced psychotic disorder** (for subtype see F1 or 291–305) • **Psychotic disorder NOS** (not otherwise specified) • Schizotypal disorder • Acute transient delusional disorder • Induced delusional disorder
F3/293–296 Affective disorders	• **Bipolar affective disorder** (manic, mixed and depressive type) • **Severe depressive episode** with psychotic symptoms • **Recurrent depressive disorder, presently severe depressive episode, with psychotic symptoms**
F4/300.01–309.9 Neurotic, stress and somatioform disorders	• Dissociative stupor • Depersonalization and derealization syndrome
F6/301.0–301.9 Personality and behavioural disorders	• Paranoid personality disorder • Schizoid personality disorder • Emotionally unstable personality disorder (borderline type) • Artificial disorders
F8 Development disorders	• Asperger's syndrome • Autistic spectrum disorders

Figure 4.7 Differential diagnosis of schizophrenia according to ICD-10 or DSM-IV (most important are in bold type).

Formulation of the diagnosis of schizophrenia includes the assessment of specific symptoms and their duration, as well as the exclusion of other psychotic disorders. The most important differential diagnoses are schizoaffective or bipolar disorder type I, delusional disorder, psychosis NOS ('not otherwise specified'), borderline personality disorder and major depression with psychotic features. The differential diagnosis of a schizophreniform disorder differs in duration of psychotic symptoms but not in type of symptoms. Psychotic episodes shorter than 1 month (ICD-10) or 6 months (DSM-IV) are diagnosed as schizophreniform disorder. Other types of psychoses must be considered as well. However, since the introduction of the 6-month duration criterion with DSM-III, schizophrenia is reported to be the most stable diagnosis (about 90%) over a period of 6 months–40 years.

The diagnosis should be made using modern operationalized systems, such as the ICD-10 or DSM-IV. Both systems require exactly defined criteria to be met for the diagnosis of schizophrenia. The diagnosis of schizophrenia can be made only if specifically defined symptoms have been present for a predefined period and other aetiologies have been excluded. As schizophrenia is a heterogeneous disorder, generally, subtypes are differentiated. These are not disorders themselves, but rather descriptions of predominant psychopathology. The subtypes of schizophrenia differ from each other according to the predominant psychopathology and certain time criteria. The most common subtype is the paranoid subtype, but a change of subtypes in the course of illness as a result of changing psychopathology is often diagnostically possible.

If the type of psychotic disorder or the existence and type of comorbid disorders remain unclear, both can be assessed with structured diagnostic interviews when the patient is stabilized (eg Structured Clinical Interview for DSM-IV – SCID). For first-episode psychosis patients such an interview should be repeated 12 months after the initial episode. This recommendation is based on studies that show that up to 40% of initial diagnoses need to be changed within 12 months. With the exception of substance abuse disorders, the diagnostic evaluation of co-morbid psychiatric disorders is often difficult (see Fig. 4.5). As untreated comorbid psychiatric disorders can worsen the course of schizophrenia, they should be consequently assessed and treated. Helpful in this respect are, again, SCIDs, eg for DSM-IV (SCID-I or -II).

Resources

Psychiatric associations	
American Psychiatric Association (APA)	www.psych.org/index.cfm
Canadian Psychiatric Association (CPA)	www.cpa-apc.org/
German Association of Psychiatry, Psychotherapy and Neurology (DGPPN)	www.dgppn.de
National Institute for Health and Clinical Excellence (NHS)	www.nice.org.uk www.nice.org.uk/Docref.asp?d=62331 www.nice.org.uk/cat.asp?c=32878
Information for patients and relatives	
Information on schizophrenia	www.schizophrenia.com www.psychose.de (in German) www.psychosis-bipolar.com (in English) www.psihos.ru (in Russian) www.psychose.de/tr (in Turkish) www.sane.org.uk www.mind.org.uk www.psychnet-uk.com www.rcpsych.ac.uk www.schizophrenia-world.org.uk www.sane.org/information/factsheets
Other major websites	
Canadian Mental Health Association (CMHA)	www.cmha.ca/bins/index.asp
National Institute for Mental Health (NIMH)	www.nimh.nih.gov/index.shtml
National Library of Medicine for articles about schizophrenia	www.ncbi.nih.gov/entrez/query.fcgi
Relatives' associations	www.eufami.org www.gamian.org
Schizophrenia International Research Society	www.schizophreniaresearchsociety.org/index.html

Major national websites	
UK and Ireland	www.nice.org.uk www.psychnet-uk.com www.rcpsych.ac.uk www.rethink.org
USA and Canada	www.psych.org/index.cfm www.cpa-apc.org www.schizophrenia.com www.schizophrenia.ca www.mentalhealth.com/dis/p20-ps01.html www.cmha.ca/bins/index.asp
Germany	www.psychose.de www.kompetenznetz-schizophrenie.de www.psychiatrie-aktuell.de/disease/detail.jhtml?itemname=schizophrenia www.psychose-netz.de/news.php www.psychosenetz.de
Australia	www.orygen.org.au/clinicalprogram/index.html www.orygen.org.au/clinicalprogram/eppicserv.html www.sane.org/information/factsheets/schizophrenia.html

Useful assessment scales

The following scales are useful tools for the assessment of general psychopathology, comorbidity, global functioning, outcome, quality of life and subjective wellbeing for patients on antipsychotic treatments.

Positive, negative, and general symptoms

- Positive and Negative Syndrome Scale (PANSS)
- Brief Psychiatric Rating Scale (BPRS)
- Scale for Assessment of Positive Symptoms (SAPS)
- Scale for Assessment of Negative Symptoms (SANS)

Severity of illness

- Clinical Global Impression Scale (CGI)
- Clinical Global Impression Scale – Schizophrenia version (CGI-Sch)

Level of functioning

- Global Assessment of Functioning Scale (GAF)
- Scale of Occupational and Functional Assessment (SOFAS)
- Role Functioning Scale (RFS)

Specific comorbid symptoms

- Calgary Depression Symptoms Scale (CDSS)
- Beck Depression Inventory (BDI)
- Beck Hopelessness Scale (BHS)

Quality of life

- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18)
- MOS 36-item short-form health survey (SF-36)
- Drug Attitude Inventory (DAI)

Subjective wellbeing under neuroleptic treatment

- Subjective Wellbeing under Neuroleptic Treatment (SWN-K), short form

Service engagement, satisfaction with care, medication adherence

- Service engagement scale (SES)
- Client satisfaction Questionnaire (CSQ-8)
- Satisfaction with Antipsychotic Medication scale (SWAM)
- Medication Adherence Rating Scale (MARS)

Further reading

The following list comprises the key literature on schizophrenia. To facilitate easy access to the most important articles and reviews, the list is sorted alphabetically according to different topics.

Acute treatment

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