Ashraf Mozayani · Lionel Raymon
Editors

Handbook of Drug Interactions

A Clinical and Forensic Guide

Second Edition

Humana Press

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Preface

Adverse drug reactions and drug interactions remain a major issue in 2011. During the second edition of our book, FDA reported greater than 370,000 serious adverse events in 2009 and more than 100,000 for the first quarter of 2010. The Adverse Event Reporting System is a database that gives computerized statistics used to support FDA's post-marketing safety surveillance for all approved drugs. A serious event is defined as requiring hospitalization, being life-threatening, causing disability or congenital anomalies, for example. Importantly, more than 63,000 deaths were recorded in 2009, and more than 20,000 occured during the first quarter of 2010.

The second edition of *Handbook of Drug Interactions: A Clinical and Forensic Guide* has been updated to reflect new information and also includes new chapters of interest. In this respect, it is a continuation of the first edition and part of the ongoing story of drug–drug interactions.

Pharmacogenomics is a rapidly growing field covering the genetic basis for individual variability in drug responses. This new section allows the reader to review important polymorphisms in drug metabolizing enzymes and applies the findings to forensic interpretation through interesting cases involving opiates.

Although the section relating to central nervous system drugs encompasses a number of potential drugs with illicit use such as benzodiazepines and opiates, a chapter dealing exclusively with drugs of abuse has been added to the second edition. Cocaine, amphetamines, cannabis, flunitrazepam and GHB are now discussed. Alcohol and nicotine are still covered in the section related to environmental and social pharmacology.

The existing chapters from the first edition have, in most cases, been updated and edited to reflect new data or bring out better tables and diagrams. More recent drugs and formulations are included. Recent references have been added for completeness.

This volume emphasizes explanations when possible and covers both pharmacokinetic and pharmacodynamic drug interactions. The result, we hope, will continue to prove useful to health and forensic professionals as well as students.

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Part I
Pharmacogenomics

Chapter 1
Pharmacogenetics in Clinical and Forensic Toxicology: Opioid Overdoses and Deaths

Saeed A. Jortani, Elaine Stauble, and Steven H. Wong

Abstract Factors considered in the observed variability in drug response within a population are intrinsic, extrinsic, or a combination of both. The intrinsic factors are differences in the demographics of a given individual (e.g., age or gender), disease or physical condition (e.g., renal function or BMI), and pharmacogenetics (see below). The extrinsic factors are composed of environmental factors (e.g., diet) as well as drug interactions or polypharmacy.

In recent years, the role of genetic variation in drug metabolism and response has been increasingly recognized. Since various pharmacokinetic and pharmacodynamic mediators of drug efficacy and toxicity involve peptides and proteins, polymorphisms in the genes responsible for encoding their amino acid sequence create a fundamental mechanism for the observed variations. In this chapter, we will briefly discuss the sources of variability in drug metabolism and response. The role of pharmacogenetics in pharmacokinetics and pharmacodynamics will then be discussed. Special attention will be paid to the consequence of polymorphisms on the forensic applications of toxicology, such as postmortem investigations.

Keywords Pharmacogenetics • Variability • Polymorphisms • Forensic applications

Pharmacogenetics and Pharmacogenomics

The terms pharmacogenomics and pharmacogenetics are generally used interchangeably, denoting the study of genetic variation on an individual's ability to metabolize a drug or respond to it. More specifically, pharmacogenetics is concerned with the effects of variation in one or a handful of genes whereas pharmacogenomics

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Table 1.1 Drugs used in pain management as analgesics or as adjutants

Drug class	Examples
Analgesics	
NSAIDs	
Traditional	Aspirin, ibuprofen
Coxibs	Celecoxib, rofecoxib
Opioids	
Strong opioids	Fentanyl, morphine, hydromorphone
Partial agonists	Buprenorphine, pentazocine
Weak opioids	Codeine, hydrocodone, propoxyphene
Local anesthetics	Lidocaine
Neuroleptics	Phenothiazines, clozapine
Tricyclic antidepressants	Nortriptyline, despiramine
SSRIs	Lamotrigine, citalopram, sertraline
Antiepileptics	Barbiturates, carbamazepine
NMDA antagonists	Ketamine, methadone[a]

SSRIs selective serotonin reuptake inhibitors

[a]Methadone and tramadol elicit their pharmacological actions through opioid receptors and by an additional mechanism such as NMDA antagonism or inhibition of reuptake of norepinephrine and serotonin

involves the entire genome [1]. The field of clinical pharmacogenetics was initiated approximately a decade ago [2, 3] with a slow but steady adaptation in various fields of medicine such as oncology [4], psychiatry [5, 6], and cardiology [7–9]. In fact, the role of pharmacogenetics in warfarin management has led to clinical testing for polymorphisms in Cytochrome P450 2C9 (CYP2C9) and Vitamin K Oxido-Reductase Complex 1 (VKOR C1) genes [10–12]. This has also involved the development of several clinical decision tools that now make it possible for clinicians to incorporate genotyping results in their decisions regarding warfarin therapy [13, 14]. Such progress has led to recommendations by regulators and guidelines by various authoritative bodies [10, 15–17]. The significant role of pharmacogenetics in oncology has also been noticeable involving multiple drugs such as Erbitux (cetuximab) and K-Ras mutation [18], tamoxifen and CYP2D6 testing [19], and Irinotecan and UGT1A1 testing [20, 21]. In pain management, pharmacogenetics has been implicated for various non-steroidal anti-inflammatory drugs (NSAIDs) such as Celecoxib [22] and opioids such as fentanyl, hydrocodone, and codeine [23–27]. Table 1.1 lists various classes of drugs used either directly or as adjuvants in pain management [28, 29]. Opioids constitute a major class of analgesics with many of the members being influenced by pharmacogenetic variables. Codeine, hydrocodone, and oxycodone are substrates for CYP2D6 whereas the pharmacokinetics of buprenorphine and fentanyl are influenced by CYP3A4 and CYP3A5 enzymes [30, 31]. Oftentimes, the same enzymes are responsible for the metabolism of additional drugs also given to the patients for various reasons. Our discussion in this chapter will demonstrate the use of pharmacogenetics for forensic applications focusing primarily on opioids. Through the review of several cases, we

will highlight the importance of considering genetic variations in interpretation of postmortem drug concentrations in the field of forensic toxicology. Obviously, there is a steep learning curve for general toxicologists and pharmacologists trying to bring genetic information into their applied practices. Wong and colleagues first coined the term molecular autopsy, which best signifies the role of incorporating pharmacogenetics in forensic toxicology [25]. It is our hope that this chapter will catalyze the adaptability of this novel approach to describe the mechanistic role of pharmacogenetics in personalized medicine as well as in personalized justice. This latter emerging practice would include the use of molecular diagnostics such as pharmacogenomics in legal proceeding to explain the possible genetic contribution to drug therapy and efficacy, and therefore performance and side effect. This might be applied in the settings of drug influence of drugs (DUID) and working under the influence of drugs (WUID). According to Wong, the inevitable check and social balance relationship to personalized medicine would enhance both practices in the future [70, 71]).

Variability in Response to Medications

Forensic toxicologists are among the professionals facing the interpretive challenges brought about by variability in drug response and efficacy. Frequently, such variabilities are co-presented in settings affected by additional confounders such as postmortem redistribution, polypharmacy, unknown drug exposures, and homicidal or suicidal poisonings. In this section, we will briefly discuss physician variability and genetic differences in drug handling and response that are considered two of the main factors affecting interpretation of clinical and forensic toxicology results.

Physician Variability

To demonstrate the issue of physician variability, we will focus on the use of medications in the area of pain management. Differences among practitioners in this medical discipline have led to either inadequate pain management for patients, accusation of drug diversion or non-compliance, as well as considerable morbidity and death. Various tools such as drug screening, patient contracts, and counseling have been developed to cope with these challenges.

Much attention in the lay press, as well as the medical literature, has focused on pain control in the last several years. In emergency rooms, only 44% of patients rate their pain control as “very good” [32]. This is especially interesting in light of the fact that after Lipitor, hydrocodone (Lortab) is the second most commonly dispensed prescription medication in this country [33]. What are the factors that influence clinical decision-making on the part of physicians prescribing opioid narcotics? The decision to prescribe narcotics is quite complex. It varies depending on the characteristics of the physician and the presenting condition, as well as patient characteristics.

There is a large body of research focusing on physician variables, as well as on the different clinical conditions with which patients present. Studies reveal that there is an inherent dichotomy between beneficence of the physician versus the physician who acts as gatekeeper to forestall narcotic addiction. Every physician approaches a problem from his or her own perspective. The decision to prescribe opioids depends on the physician's personal experience (i.e., cultural, surgical). It must depend on the clinical content of the situation (i.e., the chief complaint, their experience investigating the chief complaint, stereotyping), as well as the context (role expectation, available resources). Patient expectations and demands also affect the decision to prescribe narcotics. Some physicians prescribe more, others less, when the patient requests "something strong" for the pain. The effectiveness of the communication between the patient and doctor also plays a role. Language barriers make the physician–patient interaction cumbersome; interpreters for a specific dialect are not always readily available. Male and female medical students have been shown to respond differently to identical clinical vignettes depicting chest pain [34]. Their responses also varied depending on the patient's race and gender. Each physician's training and philosophy of prescribing narcotics develops depending on what medical school they attended, how long ago they graduated, and their surgical experience. The specialty of the physician (i.e., ER physician versus general practitioner) also influences the prescribing of opioid narcotics. General practitioners may respond differently to patients with chronic non-cancer pain than the ER physician, who is accustomed to treating acute pain. The general practitioner often has more continuity with the patient, knows their family history in depth, and has more information with which to make a decision regarding prescriptions. In contrast, the ER physician makes decisions in a vacuum, relatively speaking. This may permit judgmental issues to be more influential, especially at the beginning of an encounter with a patient for whom the physician has a paucity of objective data. When ER physicians were faced with clinical scenarios of three common medical conditions in a study designed by Tamayo-Sarver et al. [35], patient race and ethnicity had no effect on whether the physician prescribed narcotics or not. When information about high socioeconomic status or socially desirable occupations was provided with the same scenario, the physician prescribed more opioid narcotics. In another series of cases from a pain clinic, the severity and duration of the pain experienced by the patient did not affect narcotic prescribing as much as observed pain behaviors (distorted posture, audible expressions of distress, and avoidance of activity) [36]. The communication skills possessed by the clinician have a large influence on his/her decision to prescribe medication for pain control. Physicians look for features compatible with their expectation about a specific clinical condition [35]. When ER physicians viewed identical case scenarios, they had highly variable rates of prescribing narcotics. Physician prejudice and stereotyping also plays a role and occasionally may threaten the patient–physician relationship.

Therefore, the complexity of a clinical decision to prescribe opioid narcotics for pain control is apparent. It may be that better curricula must be developed early on in medical schools, to standardize the prescribing of opioids for certain clinical

conditions, so as to "level the playing field," and to better control pain for all patients with the same condition, no matter how differently they present.

In summary, from a physician's standpoint, effective pain management is complicated by multiple factors, including strict regulatory requirements and concerns about addiction or diversion, and also because both the experience and treatment of pain are subject to a broad degree of interindividual variability. Setting policy and procedural issues aside, the very subjective nature of pain is at the heart of the problem for practitioners. Research has found that the experience of pain and patients' response to therapy (with regard to adverse reactions and therapeutic benefit), are subject to wide interindividual variability caused by a number of factors, including patient age, BMI, organ function, co-medication, underlying disease, and genetics. In the remainder of this chapter, we will focus on the genetic variability influencing toxicology and interpretation of drug response.

Genetic Differences in Drug Handling and Response

The effect of physician variability is theoretically minimized by a scenario in which the same clinician is prescribing a given medication for two different patients. An example is pain medication administered to these two individuals with similar extrinsic factors. It is widely recognized that even under these circumstances, variability in response remains unlikely. Since proteins and peptides are responsible for the action of therapeutics, alterations in the genetic sequence responsible for encoding them creates an inherent source of variability. The association between drug response and toxicity and inherited genetic variations was recognized over 50 years ago [37]. Several different types of variations exist in the DNA sequence which range from single nucleotide polymorphisms (SNPs) to larger structural alterations such as copy number variants (CNVs), deletions, and inversions [38, 39]. Polymorphisms are defined as genetic variants occurring in at least 1% of the population. By the year 2007, over 3.2 million SNPs in the human genome have been reported [40]. The functional consequences of SNPs range from having no effect on the transcribed protein's function to a total loss of its activity. Since SNPs can alter a drug's pharmacokinetics and pharmacodynamics, they serve as an objective measure of a potentially significant source of variability in drug response. In fact, clinical pharmacogenetics has now made it possible for incorporating the effect of such variability in dosing decision-making and personalized drug therapy [20].

Polymorphisms in Drug Metabolizing Enzymes

A significant part of genetically caused variations in drug handling arise from the mediators of pharmacokinetics such as the drug metabolizing enzymes. These enzymes are classified into two main groups based on their function as phase

I–oxidative or phase II–conjugative [41]. In the clinical pharmacogenetic practice, many of the phase I and phase II enzymes are currently genotyped for assessing an individual's variability in drug metabolism. Within this group, CYP450 and several phase II enzymes such as urindine diphosphate glucuronosyltransferase 1A1 (UGT1A1) take part in the metabolism of the majority of drugs approved in the USA. Zanger et al. have studied the elimination routes for the 200 drugs available mainly by prescription in the USA [31]. Approximately 80% of drugs for which hepatic metabolism is indicated, polymorphisms in CYP450 genes of the families 1, 2, and 3 are considered to be the main sources of variability. Contribution by CYP3A4/5 was shown to be responsible for metabolism of 37% of the drugs studied. The extent of involvement by other CYP enzymes was reported to be 17% for CYP2C9, 15% for CYP2D6, 10% for CYP2C19, 9% for CYP1A2, 6% for CYP2C8, and 4% for CYP2B6 [31]. The Food and Drug Administration (FDA) has long recognized the importance of incorporating pharmacogenetic knowledge and testing in clinical practice. The FDA has made significant efforts in relabeling products where drug efficacy or toxicity has been linked to polymorphisms (Wu et al. Future medicine 2009). Genotyping tests for several enzymes, including CYP2D6, CYP2C9, CYP2C19, and UGT1A1 as well as a drug target (i.e., VKORC1), have been approved by the FDA as clinical laboratory tests. There are many articles and book chapters devoted to presenting pharmacogenetics of various classes of drugs and genes for clinical applications [8, 14, 16]. Since covering all of these is beyond the scope of this chapter, we will focus on the CYP2D6 and opioid analgesics in the setting of pain management and the associated forensic cases. Special attention will be paid on drugs more likely to be implicated in postmortem cases and issues related to forensic toxicology.

CYP3A4 and CYP3A5

The CYP3A subfamilies are overall the most abundant drug metabolizing enzymes, taking part in the metabolism of approximately 40% of the drugs [31]. In this subfamily of enzymes, the CYP3A4 and CYP3A5 are the two most important ones in the hepatic tissue. Many drugs of interest to forensic toxicologists are the semisynthetic or synthetic opioids which are either in part or primarily metabolized by the CYP3A4 enzyme. These include methadone, propoxyphene, buprenorphine, tramadol, and fentanyl [42, 43]. Generation of norfentanyl from fentanyl by CYP3A4 has previously been reported in several forensic cases [25]. Another example of variability is N-dealkylation of buprenorphine to norbupronorphine [43] by CYP3A4 [44]. Although buprenorphine has low respiratory depressive properties, its metabolite is the one that primarily contributes to its toxicity [43, 45]. Another issue to be considered by toxicologists while interpreting drug levels is the coadministration of opioid analgesics with drugs known to alter the activities of CYPA4/5 enzymes. To demonstrate this point, consider taking itraconazole or ketoconazole and even drinking grapefruit juice which are all known to inhibit the CYP3A4 activity in patients also

on fentanyl or buprenorphine. These inhibitors are expected to enhance fentanyl's toxic effects by reducing its elimination whereas they can decrease the toxic buildup of the metabolite of buprenorphine! Another example is benzodiazepines such as midazolam which are known to be metabolized by CYP3A4 enzyme. Its administration to patients taking semisynthetic and synthetic opioids can create a source of variability in toxicity and response. This situation is far more common than generally recognized. In fact, anesthetics and drugs routinely administered during the preoperative and perioperative periods can include lists containing midazolam and fentanyl. Potential drug interactions can then be expected in patients who are concurrently receiving inhibitors and substrates of CYP3A4 (e.g., ketoconazole, posaconazole), benzodiazepines (e.g., midazolam) and opioids [1, 46]. The contribution of CYP3A5 for metabolism of various drugs is also significant. In many cases, both CYP3A4 and CYP3A5 contribute to metabolism of the same drugs such as fentanyl. Therefore, it is possible that a patient has wild-type alleles for one enzyme and polymorphism in the other. This creates a challenge in interpretation of the genotyping results for the CYP3A4/5 families. Despite this concern, specific polymorphisms denoted as CYP3A4*1B and CYP3A5*3 have been found to be helpful in certification of postmortem fentanyl toxicity cases [25]. It is therefore recommended that for similar situations, both CYP3A4 and CYP3A5 be genotyped and their results be interpreted as an adjunct considering all other case evidence accordingly.

CYP2D6

Only 2–4% of the overall cytochrome composition in human hepatic tissue belongs to the CYP2D6 enzyme. Nevertheless, this enzyme, which is highly polymorphic, is responsible for metabolizing approximately 35% of all the drugs on the market [47]. The role of CYP2D6 in pharmacokinetics of many drugs of interest to forensic toxicologists has already been established [26, 30, 48, 49]. According to the Human Cytochrome P450 Allele Nomenclature Committee, there are over 120 reported base substitutions or polymorphisms reported by June 2009 [50]. Genotyping for these is routinely performed by commercially available kits capable of testing for 20 or less of these polymorphisms. Routinely, multiplexing or array-type techniques are best suited for CYP2D6 genotyping [51, 52]. Overall, the allele variants are designated by a * and a number. For example a *1 allele variant generally refers to the wild-type genotype. An allele variant of *2 is also expected to have normal activity whereas *3 through *8 and *11 through *15 genotypes denote no enzymatic activity. Partial activity is expected from those with allele designations of *9, *10, *11, and *41. Traditionally, four major genetically derived phenotypic designations have been described for this CYP2D6. Extensive metabolizers (EM) represent the norm for metabolic capacity. Genotypes consistent with the EM phenotype include two active CYP2D6 alleles (for example, *1/*1 or *1/*2) or one active and one partially active CYP2D6 allele. In general, extensive metabolizers can be administered drugs which are substrates of the CYP2D6 enzyme following standard dosing practices.

Increased caution may be appropriate for individuals having one partially active allele. Intermediate metabolizers (IM) may require lower than average drug dosages for optimal therapeutic response. Genotypes consistent with the IM phenotype are those with one active and one inactive CYP2D6 allele, one inactive and one partially active CYP2D6 allele, or two partially active CYP2D6 alleles. Poor metabolizers (PM) are at increased risk of drug-induced side effects due to diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug. Genotypes consistent with the PM phenotype are those with no active CYP2D6 genes. Ultrarapid metabolizers (UM) exhibit higher than average rates of metabolism. Genotypes consistent with the UM phenotype include three or more active CYP2D6 alleles due to duplication of an active allele. UMs are at increased risk of therapeutic failure as a result of increased drug elimination. Thus they may require an increased dosage of medications that are inactivated by CYP2D6. Alternatively, UMs may also be at increased risk of drug-induced side effects because of increased exposure to active drug metabolites. In this case, they may require lower than average doses.

In addition to the above-mentioned enzymes, there are several other genes such as the CYP2C19 and UGT subfamily which may be worth looking into during a case investigation. The National Academy for Biochemistry (NACB) has developed recommendations for the use of pharmacogenetics in forensic applications which are now closed for further comments and about to be published [53]. In addition, during the past couple of years, the College of American Pathologists has had proficiency testing surveys available for pharmacogenetic testing [54]. The remainder of this chapter will focus on the CYP3A4/5 and CYP2D6 genes by presentation of several cases illustrating the use of their genotypic information in working up toxicology cases.

Forensic Applications of Pharmacogenetics

In the discipline of forensic toxicology, results of drug screening activities as well as postmortem investigations are influenced by genetic differences in drug metabolism and elimination. We will focus on these areas in more detail below.

Interpretation of Urine Drug Screening Results

Toxicology screens have become very popular in both clinical and forensic toxicology disciplines. For clinical purposes, drug screens play an important role in the evaluation and treatment of the potentially poisoned patient. Other clinical applications include pain management, drug addiction treatment, and compliance testing. The forensic applications of drug screening are commonly used in workplace testing utilized by both private and governmental organizations. The consequences of

these results affect hiring practices, quality assurance, termination policies, and medical compensation for work-related injuries. Drug screening for other purposes such as driving under the influence and testing in athletes, students, and prisoners is also very popular. Obviously, the legal and social repercussions of a given test result are potentially devastating to the subject. In addition, the illicit drug use suggested by toxicological screens leads to employers routinely denying medical compensation to workers injured on the job should their hospital evaluation include a positive screening result. In many forensic situations, medical review officers (MRO) certify the drug screening results without any knowledge or evidence for an individual's ability to metabolize the drug in question. Added to this challenge is the fact that many drug screens are performed using immunoassays utilizing antibodies with differential cross-reactivities to the parent drug versus its metabolites. Otton et al. have demonstrated that the clearance of hydrocodone in the form of hydromorphone was 28.1 ± 10.3 mL/h/kg for patients with EM and 3.4 ± 2.4 mL/h/kg for those with PM genotypes for the CYP2D6 enzyme [55]. Therefore, in addition to the therapeutic efficacy of hydrocodone, the proportion excreted as its O-demethylated metabolite may have consequences on the urine opioid screening results [55, 56]. Another example is the metabolism of diazepam which is dependent on CYP2C19 activity [57]. Individuals with the PM genotype have prolonged half-lives for diazepam which are twice as long as those with the wild-type phenotype (88.3 ± 17.2 versus 40.8 ± 14.0 h, respectively). Obviously, benzodiazepine immunoassays with preferential cross-reactivities for the metabolites may have a reduced chance of detecting exposure to the drug. Combining analytical and pharmacogenetic screening was used in a case of an individual on oxycodone with continued negative drug screening results in the urine. Apparently, this individual had been on rifampin, which is a known inducer of CYP450 activity causing a very rapid half-life for the drug [58]. With the stated examples, it is apparent that alterations in metabolic capacity of drugs either due to polymorphisms or drug interactions can have consequences on the urine drug screening test results.

Pharmacogenetics in Forensic Investigations

Through presentation of several cases involving various different opioids, we will demonstrate the use of pharmacogenetic testing in establishing (or excluding) genetic differences in drug metabolism as a potential contributing factor to the cause of death. The field of forensic toxicology is in a great position to contribute to pharmacogenetics and its use in personalized medicine. When drugs are taken in "therapeutic" doses, toxicity and ultimately death are not generally expected. In cases where a patient dies after taking conventional doses of a drug or a combination of drugs, death investigation needs to be highly "individualized." This is best achieved by assessing the person's ability to metabolize the drugs through genotyping the DNA responsible for transcribing the relevant proteins and enzymes. Often, in individuals with reduced metabolic ability such as the IM or PM genotypes, the toxicity

is attributed to the parent drug. Alternatively, in those with the UM genotype, a higher than expected production of active metabolites can be the mechanism of toxicity. We will present several published and unpublished cases in which pharmacogenetics information was useful in determination of cause of toxicity or death.

Case Reports

We will initially focus on codeine and present several cases in which patients with various genotypes were investigated. We will then present an example for each of the other opioids, namely, oxycodone, fentanyl, and methadone.

Codeine is considered to be a weak opioid agonist, and is generally used for its analgesic and antitussive properties. The O-demethylation of codeine to morphine is by the CYP2D6 enzyme, and is considered to be important for its analgesic efficacy. Despite this, in PM subjects, respiratory depression and other side effects of opioid toxicity have been observed which are thought to be due to codeine itself. Therefore, it cannot be assumed that lack of CYP2D6 metabolic activity (by which codeine is converted to morphine) also results in the absence of side effects. The following cases demonstrate codeine toxicity in patients with different genotypes. In each of these, genotyping contributed to either the determination of the cause of death or was helpful in confirmation of the cause of death. Codeine is also metabolized by the CYP3A4 enzyme by *N*-demethylation to norcodeine which is equipotent to codeine.

Case 1: Codeine Intoxication in a Breast-fed Infant

This is the case of a newborn male infant who had developed lethargy at 7 days of age [59]. On day 11 after birth, the infant had been noted to have altered skin color and had reduced milk intake. The baby was finally transported to a hospital on day 13 for being cyanotic with no vital signs. Resuscitation efforts that had been initiated at home were unsuccessful and the patient was pronounced dead at the hospital. After ruling out various inborn errors of metabolism for conditions such as organic acidemias, fatty acid oxidative disorders, and thyroid issues, toxicological examinations were also performed. The postmortem blood sample had 70 ng/mL of morphine and 5.9 μg/mL of acetaminophen. The source of this blood sample was not mentioned in the report. This morphine concentration is approximately 6–7 times the therapeutic concentration seen in neonates receiving morphine for analgesia. The breast milk which he was being fed contained a morphine concentration of 87 ng/mL. This milk sample had been collected during the time his mother was taking half of the prescribed codeine dose during which she was somnolent and constipated. Pharmacogenetic analysis involved genotyping for CYP2D6 and UGT2B7 (catalyzing the morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) formation). The mother was considered to be an ultrarapid metabolizer since she

had CYP2D6 gene duplication (heterozygous with CYP 2D6*2A allele and a CYP 2D6*2×2 alleles). The father of the infant and the infant himself were EM with CYP2D6 *1/*2 genotypes. In addition, both the infant and his mother were homozygous for the UGT 2B7*2 gene known to be associated with increased M6G to morphine ratio. M6G is known be an active metabolite of morphine. Considering the genotype for the mother, it is apparent that she was converting more of the codeine to morphine due to her enhanced CYP2D6 activity. Additional morphine in her blood had led to her own somnolence and constipation. As a result, her milk also contained increased morphine which was fed to the infant. The clinical presentation of the infant prior to his death is consistent with opioid intoxication, also confirmed by the fact that the postmortem morphine values were in the toxic range.

Case 2: Codeine Intoxication in Twin Boys (Set A)

Codeine is widely used in the pediatric population for its antitussive as well as its analgesic properties. Compared to other opioids, it is generally regarded to have fewer side effects; therefore, it is frequently prescribed to younger children and neonates. This case involves codeine-induced toxicity in a recently published case of 3-year-old monozygotic twin brothers [48, 60]. They had been prescribed 10 mg of codeine to treat their cough following the diagnosis of upper respiratory infection. They were both administered codeine for 6 days. On the 6th day, 5 h after administration of the last dose, one of the twins was found to be apneic and had vomited. Their mother began resuscitation and the child was transferred to the pediatric intensive care unit. He was tachycardic, hypotensive, and had a Glasgow Coma Scale of 3. He had elevated leucocytes and was diagnosed with a tracheal viral infection. His aspiration pneumonia was treated by administration of antibiotics, and catecholamines were used to raise his blood pressure. After a few days, he eventually recovered with no further complications. Gas chromatography-mass spectrometry analysis of a serum sample collected 7.5 h after the last codeine dose resulted in total and free codeine concentrations of 489 and 179 ng/mL, respectively. The total and free morphine in the same sample were 312 and 33 ng/mL, respectively. The therapeutic serum concentration for codeine was listed as 56–129 ng/mL in small children. The concentration of morphine after codeine therapy has been mentioned to be 4.5 ± 2.1 ng/mL [60]. This particular case is consistent with codeine (and morphine) overdose leading to apnea, vomiting, and hypotension. Unfortunately, the second twin brother had been found dead in his bed at home shortly after the first twin was initially discovered to be in distress. Autopsy on the second twin revealed aspiration of gastric contents. Analysis of codeine and morphine were performed on several postmortem tissues and fluids on the second twin [60]. A serum sample obtained from the femoral vein resulted in a free codeine concentration of 547 ng/mL and a free morphine value of 150 ng/mL, respectively. The total and free codeine and morphine levels were also high in the cardiac blood. It is probable that respiratory depression and aspiration secondary to codeine (and the resulting morphine) overdoses led to the death of this twin brother. Genotyping

for CYP2D6 was used to investigate the reason for the elevation of both codeine and morphine. As expected, both twins had the same CYP2D6 genotypes which were considered to be wild types with no gene duplication. Therefore, they were categorized as extensive metabolizers thus ruling out the possibility of reduced metabolism due to genetic variation (i.e., being poor or intermediate metabolizer phenotypes). Accumulation of morphine was not attributed to CYP2D6 gene duplication since the children were not ultrarapid metabolizers. The pharmacogenetic data raises the suspicion that too much codeine had been administered to these children. Indeed, case investigation further revealed that the prescribed dose was 0.5 mL of the codeine solution resulting in 10 mg of the drug per dose. Sadly, their mother had administered the codeine to them by "drops." Each time, she administered 10 "drops" which were experimentally shown to range from 494 to 940 mg of codeine per dose. Authors had concluded that variations in "drop" size and imprecision in its measurements could have created the unfortunate overdose situation for these twins.

Case 3: Codeine Intoxication in Twin Boys (Set B)

The case of a second set of 3-year-old twin boys who had both died of respiratory depression following administration of codeine is presented. These children had undergone adenotonsillectomy operations within an hour of one another for severe obstructive sleep apnea syndrome (OSAS). Their operations had gone well with no complication. Both children had awakened, were extubated, and were stable. To control their surgical pain, each had received 5 mL of a codeine elixir containing 12 mg of codeine sulfate prior to discharge. Later on the same day, each child had further received two additional doses of the same codeine elixir at home. The recommended dose in children 3–6 years of age is 5 mL to be administered 3–4 times per day to be given every 3–4 h as needed (PRN). Interestingly, these children were being awakened to take their medication every 4 h. Several hours later, the first twin was noticed to be in respiratory distress and "choking," which eventually lead to acute cardiopulmonary arrest. CPR was initiated and the child was taken to the hospital. Resuscitation efforts were not successful and he was pronounced dead. While at the hospital with the first twin, the parents became concerned about the second twin who had been left in the care of a neighbor. The second twin was later on found to be unresponsive, had no pulse, and was cyanotic. He was resuscitated and eventually had his pulse reinstated. Ultimately, after 2–3 days of intensive care, the second twin also passed away. Autopsy performed on the first twin the morning after his death indicated that he had cerebral edema and airway froth. Toxicological analyses were performed on postmortem femoral blood, urine, vitreous fluid, and brain collected at autopsy from the first twin. Analysis of the peripheral blood sample resulted in total and free codeine concentrations of 740 and 540/mL, respectively. The total and free morphine levels in the same sample were 190 and 60 ng/mL, respectively. The concentrations of total and free codeine in the brain tissue were 530 and 500 ng/mL, respectively. Vitreous fluid contained primarily free codeine (300 ng/mL) and its

morphine concentration was <10 ng/mL. CYP2D6 genotyping on these twins showed that each had one functional allele (*2) and one nonfunctional allele (*4). Therefore, it is concluded that they were both intermediate metabolizers. It is clear that the codeine concentrations in twin A, and by extrapolation in twin B, were elevated at the time of cardiopulmonary arrest. Additional investigation into this case revealed that the mother had administered the correct amount of the drug to each child at each dosing time. The volume of unused elixir corroborated this conclusion. The twins had inherited the *4 from their mother and *2 from their father, since the mother was a carrier of *4 allele and the father was wild type carrying the *2 allele. Therefore, carrying a nonfunctional CYP2D6 allele more probably than not contributed in part to the reduced metabolism of codeine reflected by the toxic concentrations measured in the first twin at autopsy. Contribution of the extent of postoperative respiratory compromise or other variables to the demise of these children is not known.

Cases 4: Codeine in an Ultrarapid Metabolizer Child

In CYP2D6 rapid metabolizers, opioid toxicity after ingestion of codeine, hydrocodone, and oxycodone is possible due to the generation of too much morphine, hydromorphone, and oxymorphone, respectively. These metabolites are more potent than their parent counterparts. In a reported case, codeine elixir was used for managing pain in a 2.5-year-old boy who had undergone tonsillectomy operation [61]. He apparently had received four doses of codeine on postoperative day 1 and one more dose the next evening. Four hours later, the mother found the child unresponsive and apneic. The emergency team administered naloxone which led to some improvement; however, the child became apneic at the hospital and was intubated. After a couple of weeks, he was extubated and discharged in stable condition. CYP2D6 genotyping revealed that he had a copy of *1 allele and multiple copies of the *2 allele. Both *1 and *2 have enzymatic activity and having more than two copies renders the individual an ultrarapid metabolizer. In this case, use of pharmacogenetic information was found to be useful in implicating morphine as the cause of respiratory depression. However, the authors had not verified this finding by measuring the concentrations of codeine and morphine in this child.

Cases 5: Codeine in an Ultrarapid Metabolizer Adult

Another case of toxicity in individuals with multiple copies of CYP2D6 involves a 62-year-old gentleman with a history of leukemia who had presented with cough, fever, and dyspnea [62]. Since this patient was considered to be immunocompromised, bronchoalveolar lavage had been performed which revealed the presence of yeast. He was treated with two antibiotics (ceftriaxone and clarithromycin), an antifungal agent (voriconazole) and oral codeine (25 mg three times a day) for cough. His condition deteriorated on hospital day 4 and he became unresponsive. The last dose

had been administered 12 h prior to the changes in his level of consciousness. The patient's pupils were miotic and he had a Glasgow Coma Scale of 6 (no eye opening, no verbal response, and limb withdrawal after pain stimulation) on his initial neurologic examination. Administration of naloxone (0.4 mg repeated two times) resulted in a dramatic improvement in his level of consciousness. His plasma codeine concentration was 114 μg/L. The reference range for CYP2D6 extensive metabolizers has been reported to be 13–75 μg/L [62]. He was genotyped for CYP2D6 and CYP3A4, both of which are implicated in the metabolism of codeine. In addition, relative activities of CYP2D6 and CYP3A4 were assessed by administration of dextromethorphan and subsequent measurement of deconjugated dextrorphan excreted in the urine. The results of genotyping indicated that he had >3 copies of CYP2D6 which was confirmed by the phenotyping results assessed by the ratio of dextromethorphan and deconjugated dextrorphan. This patient was on a macrolide and an azole derivative to treat his infections. Both of these agents are known inhibitors of CYP3A4. It is believed that more of the codeine metabolized through the CYP2D6 route since CYP3A4 was inhibited, in this situation since there were multiple copies of CYP2D6 present to convert codeine to morphine. It is clear from this case that genotyping was useful in directing the investigation by focusing on codeine as a cause of decreased neurological function and opioid toxicity.

Case 6: Oxycodone in a Poor Metabolizer

The decedent was a 49-year-old white male, prescription drug abuser with a history of depression and posttraumatic stress disorder [49]. For treating his chronic back pain following surgery, OxyContin and Percocet were prescribed. He was an alcoholic. He attempted suicide once. Of the 60 oxycodone pills prescribed, only 12 had remained. His roommate, who saw him in the morning, found the decedent unresponsive after returning from work. Toxicological analysis showed subclavian blood, obtained within 24 h after death, with a concentration of oxycodone 0.437 mg/L, and without detection of alcohol and other drugs. Autopsy showed hepatic cirrhosis which might have impaired his drug metabolism. Molecular autopsy showed he was CYP 2D6*4 homozygous, corresponding to the poor metabolizer phenotype. This deficiency might have contributed to impaired metabolism of oxycodone, along with hepatic cirrhosis. Death certification was: cause of death, oxycodone overdose; and manner of death, accident.

Cases 7: Methadone in a Poor Metabolizer

The decedent was a 51-year-old white male with a 25-year history of heroin addiction for which he was enrolled in a methadone maintenance program [63]. On Friday, he was accompanied by his friend to the methadone clinic where he ingested his prescribed dose, and was given an extra dose for the weekend. He also bought illicit drugs near the clinic. His girlfriend confirmed that he was alive

at 7 a.m. on Sunday, and she found the decedent on Monday at 8 a.m., with a bottle of methadone nearby. The decedent had hepatitis C and hepatic cirrhosis. Toxicology showed the iliac blood methadone concentration to be 1.6 mg/L. Based on the case history, acute ingestion of methadone was likely, followed by postmortem interval of <24 h. Thus, the high methadone concentration was not due to postmortem redistribution. Molecular autopsy showed CYP 2D6*3 and *4 compound heterozygosity, corresponding to a poor metabolizer of methadone. Other toxicological findings included benzoylecgonine, 0.871 mg/L; propoxyphene, 0.32 mg/L; and diazepam, 0.12 mg/L. Autopsy finding included end-stage alcoholic liver disease. Death certification was: cause of death, mixed drug toxicity attributed to methadone, cocaine abuse, propoxyphene, and diazepam; and manner of death, accident.

Cases 8: Fentanyl in a Poor Metabolizer

The decedent was a 44-year-old white female, with a history of drug abuse (cocaine, marijuana, and pain medications), suicidal ideation, and psychiatric disorders [25]. In a previous attempt to obtain medications, she had cut her arm. After a rummage sale, she complained to her boyfriend about her knee pain, and obtained some narcotic patches. Later that evening, she seemed "goofy." She was found dead 24 h later. One Duragesic patch was attached to her arm, and another adhered to a blanket. Toxicology showed subclavian blood concentrations of : fentanyl and norfentanyl, 19 and 7.6 μg/L with a total of 26.6 μg/L; cyclobenzapine, 0.16 mg/L; tramadol, 0.06 mg/L; diphenhydramine, 0.08 mg/L; citalopram, 0.22 mg/L; and olanzapine, positive. Pharmacogenetic testing (i.e., molecular autopsy) showed: CYP3A4*1B heterozygous and CYP3A5*3 heterozygous. In these individuals, a reduced rate of fentanyl metabolism is expected. Therefore, according to the toxicology results and the genetic testing information, the death certification was issued as: cause of death, mixed drug toxicity attributed to fentanyl, diphenhydramine, citalopram, cyclobenzaprine, and tramadol; the manner of death was indicated to be an accident.

Techniques and Methods

Genetic variations in the genes which encode the drug-metabolizing enzymes may lead to normal, deficient, or higher enzyme activities. Such genetic variations can include SNPs, gene deletion, or gene duplications. For several enzymes such as CYP2D6, CYP2C9, and CYP2C19, there are several FDA-approved methodologies and kits available [64, 65]. In many of the techniques used for genotyping drug-metabolizing enzymes, DNA is initially isolated from blood or tissues and is amplified using PCR-based techniques. The variation in the gene sequence is then queried, using a variety of different methods. Restriction fragment length polymorphism (RFLP) has been considered to be the traditional approach in identifying known

mutations. This approach is limited by the fact that targeted polymorphisms have to be able to lead to alterations capable of forming a restriction site. The restriction sites will determine changes in the DNA fragmentation (restriction digestion) pattern which is identified on the gel [66]. In allele-specific amplification using real-time PCR, the product is amplified by PCR and its formation is detected [67]. Another approach is the multiplex PCR in which the target DNA sequence is amplified, and based on allele-specific primer extension technique, the simultaneous detection of multiple CYP2D6 variants is achieved [52]. There are many other methods such as HPLC, mass spectrometry, and sequencing which can detect variations in the DNA sequence. The detailed discussion of these methods is beyond the scope of this chapter and the reader is referred to other sources for more information [51, 66, 68].

Frequently, the question of "what sample type should be used for pharmacogenetic testing" comes up in forensic applications. DNA has been isolated from many different types of samples, ranging from dried blood spots or whole blood to various organs such as the liver. For some genes, sample condition is less of an issue than others. For example, many of the PCR products of CYP2D6 are large, and therefore sample integrity and DNA quality in the original sample is important. In the clinical environment, blood drawn in EDTA plasma tubes is recommended since DNA can be readily isolated from the buffy coat. On the other hand, collection of samples during autopsy is limited to getting a whole blood specimen or tissue. Since whole blood has been used with success for DNA isolation, it is the preferred specimen. However, if needed, tissue can also be used for isolation of DNA for pharmacogenetic testing.

Since many medical examiner offices and state laboratories do not routinely perform pharmacogenetic testing, it is recommended that they use referral laboratories for this type of determination. It is also crucial to consider the needed knowledge and skill set in order to properly interpret the results for forensic settings. As previously indicated, the drug-metabolizing gene testing is done as an adjunct to the overall process of case investigation. Most ideally, the interpretations should be performed by individuals with toxicology knowledge who have been specifically trained in pharmacogenetics. Obviously, molecular diagnostics experts often lack the pharmacology and toxicology background needed for forensic toxicology issues. If too much emphasis is put on the pharmacogenetic data without considering the fundamentals of forensic toxicology, the case can be easily misinterpreted. Therefore, understanding the drug concentrations and utilizing the pharmacogenetic data are best done by considering both items simultaneously. It is recommended that toxicologists consult with the pharmacogenetics experts and use the information as a piece of a larger puzzle.

In summary, when assessing therapeutic and toxic effects of opioids such as codeine which are often implicated in forensic cases, two distinct issues need to be considered. In the CYP2D6 poor metabolizers, not only opioid toxicity can be caused by the drug (e.g., codeine) itself, adequate pain relief mediated by its metabolite (e.g., morphine) is less likely [24, 69]. In a recent study, CYP2D6 genotyping was shown to predict only 50% of ultrarapid metabolizers subjects who carried gene duplication [27]. These subjects were better identified by dextromethorphan-based

phenotyping, which was able to distinguish 68% of the subjects on codeine with high morphine formation. When genotyping and phenotyping were combined, 88% of the high morphine formation subjects after administration of codeine were identified. On the other hand, CYP2D6 genotyping by itself was adequate enough to be able to predict insufficient morphine formation subjects. The point to consider when interpreting postmortem codeine cases is that determining the metabolic category for the patient is useful in establishing the underlying cause. For example, in twin set A (Case 2 discussed above), being an extensive metabolizer correlated with the finding that imprecision in "drop size" potentially leads to too much drug being administered. On the other hand, in twin set B (Case 3), carrying an inactive CYP2D6 allele explains toxic concentrations of codeine measured postmortem even if the correct dosing has been proven. Therefore, it is advised that genotyping be used as an additional piece of the puzzle when forensic toxicity cases are being investigated.

References

1. Weinshilboum, R.M., and L. Wang. 2006. Pharmacogenetics and pharmacogenomics: development, science, and translation. *Annu Rev Genomics Hum Genet* 7:223–245.
2. Linder, M.W., R.A. Prough, and R. Valdes, Jr. 1997. Pharmacogenetics: a laboratory tool for optimizing therapeutic efficiency. *Clin Chem* 43(2):254–266.
3. Spielberg, S.P. 1996. N-acetyltransferases: pharmacogenetics and clinical consequences of polymorphic drug metabolism. *J Pharmacokinet Biopharm* 24(5):509–519.
4. Huang, R.S., and M.J. Ratain. 2009. Pharmacogenetics and pharmacogenomics of anticancer agents. *CA Cancer J Clin* 59(1):42–55.
5. de Leon, J., M.J. Arranz, and G. Ruano. 2008. Pharmacogenetic testing in psychiatry: a review of features and clinical realities. *Clin Lab Med* 28(4):599–617.
6. Hamdani, N., and P. Gorwood. 2008. [Role of genetics in psychiatric treatment]. *Presse Med* 37(5 Pt 2):902–911.
7. Brugts, J.J., A.H. Danser, M.P. de Maat, C.A. den Uil, E. Boersma, R. Ferrari, and M.L. Simoons. 2008. Pharmacogenetics of ACE inhibition in stable coronary artery disease: steps towards tailored drug therapy. *Curr Opin Cardiol* 23(4):296–301.
8. Marin, F., V. Roldan, R. Gonzalez-Conejero, and J. Corral. 2005. Pharmacogenetics in cardiovascular antithrombotic therapy. *Curr Med Chem Cardiovasc Hematol Agents* 3(4):357–364.
9. Roepke, T.K., and G.W. Abbott. 2006. Pharmacogenetics and cardiac ion channels. *Vascul Pharmacol* 44(2):90–106.
10. Gage, B.F., and L.J. Lesko. 2008. Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. *J Thromb Thrombolysis* 25(1):45–51.
11. Takahashi, H., G.R. Wilkinson, E.A. Nutescu, T. Morita, M.D. Ritchie, M.G. Scordo, V. Pengo, M. Barban, R. Padrini, I. Ieiri, K. Otsubo, T. Kashima, S. Kimura, S. Kijima, and H. Echizen. 2006. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance dose of warfarin in Japanese, Caucasians and African-Americans. *Pharmacogenet Genomics* 16(2):101–110.
12. Wu, A.H., P. Wang, A. Smith, C. Haller, K. Drake, M. Linder, and R. Valdes, Jr. 2008. Dosing algorithm for warfarin using CYP2C9 and VKORC1 genotyping from a multi-ethnic population: comparison with other equations. *Pharmacogenomics* 9(2):169–178.
13. Langley, M.R., J.K. Booker, J.P. Evans, H.L. McLeod, and K.E. Weck. 2009. Validation of clinical testing for warfarin sensitivity: comparison of CYP2C9-VKORC1 genotyping assays and warfarin-dosing algorithms. *J Mol Diagn* 11(3):216–225.

14. Zhu, Y., M. Shennan, K.K. Reynolds, N.A. Johnson, M.R. Herrnberger, R. Valdes, Jr., and M.W. Linder. 2007. Estimation of warfarin maintenance dose based on VKORC1 (–1639 G>A) and CYP2C9 genotypes. *Clin Chem* 53(7):1199–1205.
15. Flockhart, D.A., D. O'Kane, M.S. Williams, M.S. Watson, D.A. Flockhart, B. Gage, R. Gandolfi, R. King, E. Lyon, R. Nussbaum, D. O'Kane, K. Schulman, D. Veenstra, M.S. Williams, and M.S. Watson. 2008. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. *Genet Med* 10(2):139–150.
16. Thompson, C.A. 2007. FDA encourages genetics-aided warfarin dosing. *Am J Health Syst Pharm* 64(19):1994–1996.
17. Vladutiu, G.D. 2008. The FDA announces new drug labeling for pharmacogenetic testing: is personalized medicine becoming a reality? *Mol Genet Metab* 93(1):1–4.
18. Albitar, M., C. Yeh, and W. Ma. 2009. K-ras mutations and cetuximab in colorectal cancer. *N Engl J Med* 360(8):834; author reply 835–836.
19. Rae, J.M., M.J. Sikora, N.L. Henry, L. Li, S. Kim, S. Oesterreich, T.C. Skaar, A.T. Nguyen, Z. Desta, A.M. Storniolo, D.A. Flockhart, D.F. Hayes, and V. Stearns. 2009. Cytochrome P450 2D6 activity predicts discontinuation of tamoxifen therapy in breast cancer patients. *Pharmacogenomics J*.
20. Jada, S.R., R. Lim, C.I. Wong, X. Shu, S.C. Lee, Q. Zhou, B.C. Goh, and B. Chowbay. 2007. Role of UGT1A1*6, UGT1A1*28 and ABCG2 c.421 C>A polymorphisms in irinotecan-induced neutropenia in Asian cancer patients. *Cancer Sci* 98(9):1461–1467.
21. Sai, K., J. Sawada, and H. Minami. 2008. [Irinotecan pharmacogenetics in Japanese cancer patients: roles of UGT1A1*6 and *28]. *Yakugaku Zasshi* 128(4):575–584.
22. Ahlstrom, M.M., M. Ridderstrom, and I. Zamora. 2007. CYP2C9 structure-metabolism relationships: substrates, inhibitors, and metabolites. *J Med Chem* 50(22):5382–5391.
23. de Leon, J. 2008. CYP2D6 genotyping and codeine. *Paediatr Anaesth* 18(3):274–275; author reply 275–276.
24. Foster, A., E. Mobley, and Z. Wang. 2007. Complicated pain management in a CYP450 2D6 poor metabolizer. *Pain Pract* 7(4):352–356.
25. Jin, M., S.B. Gock, P.J. Jannetto, J.M. Jentzen, and S.H. Wong. 2005. Pharmacogenomics as molecular autopsy for forensic toxicology: genotyping cytochrome P450 3A4*1B and 3A5*3 for 25 fentanyl cases. *J Anal Toxicol* 29(7):590–598.
26. Kaplan, H.L., U.E. Busto, G.J. Baylon, S.W. Cheung, S.V. Otton, G. Somer, and E.M. Sellers. 1997. Inhibition of cytochrome P450 2D6 metabolism of hydrocodone to hydromorphone does not importantly affect abuse liability. *J Pharmacol Exp Ther* 281(1):103–108.
27. Lotsch, J., M. Rohrbacher, H. Schmidt, A. Doehring, J. Brockmoller, and G. Geisslinger. 2009. Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* 144(1–2):119–124.
28. Kong, V.K., and M.G. Irwin. 2009. Adjuvant analgesics in neuropathic pain. *Eur J Anaesthesiol* 26(2):96–100.
29. Onal, S.A. 2006. [Adjuvant analgesics in pain management]. *Agri* 18(4):10–23.
30. Reynolds, K.K., B. Ramey-Hartung, and S.A. Jortani. 2008. The value of CYP2D6 and OPRM1 pharmacogenetic testing for opioid therapy. *Clin Lab Med* 28(4):581–598.
31. Zanger, U.M., M. Turpeinen, K. Klein, and M. Schwab. 2008. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem* 392(6):1093–1108.
32. Lanser, P., and S. Gesell. 2001. Pain management: the fifth vital sign. *Healthc Benchmarks* 8(6):68–70, 62.
33. Lamb, E. 2009. Top 200 Drugs of 2008. *Pharmacy Times* Published Online: May 15, 2009
34. Rathore, S.S., L.A. Lenert, K.P. Weinfurt, A. Tinoco, C.K. Taleghani, W. Harless, and K.A. Schulman. 2000. The effects of patient sex and race on medical students' ratings of quality of life. *Am J Med* 108(7):561–566.
35. Tamayo-Sarver, J.H., N.V. Dawson, S.W. Hinze, R.K. Cydulka, R.S. Wigton, J.M. Albert, S.A. Ibrahim, and D.W. Baker. 2003. The effect of race/ethnicity and desirable social characteristics on physicians' decisions to prescribe opioid analgesics. *Acad Emerg Med* 10(11):1239–1248.

36. Turk, D.C., and A. Okifuji. 1997. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? *Clin J Pain* 13(4):330–336.
37. Kupiec, T.C., V. Raj, and N. Vu. 2006. Pharmacogenomics for the forensic toxicologist. *J Anal Toxicol* 30(2):65–72.
38. Feuk, L., J.R. MacDonald, T. Tang, A.R. Carson, M. Li, G. Rao, R. Khaja, and S.W. Scherer. 2005. Discovery of human inversion polymorphisms by comparative analysis of human and chimpanzee DNA sequence assemblies. *PLoS Genet* 1(4):e56.
39. Khaja, R., J. Zhang, J.R. MacDonald, Y. He, A.M. Joseph-George, J. Wei, M.A. Rafiq, C. Qian, M. Shago, L. Pantano, H. Aburatani, K. Jones, R. Redon, M. Hurles, L. Armengol, X. Estivill, R.J. Mural, C. Lee, S.W. Scherer, and L. Feuk. 2006. Genome assembly comparison identifies structural variants in the human genome. *Nat Genet* 38(12):1413–1418.
40. Levy, S., G. Sutton, P.C. Ng, L. Feuk, A.L. Halpern, B.P. Walenz, N. Axelrod, J. Huang, E.F. Kirkness, G. Denisov, Y. Lin, J.R. MacDonald, A.W. Pang, M. Shago, T.B. Stockwell, A. Tsiamouri, V. Bafna, V. Bansal, S.A. Kravitz, D.A. Busam, K.Y. Beeson, T.C. McIntosh, K.A. Remington, J.F. Abril, J. Gill, J. Borman, Y.H. Rogers, M.E. Frazier, S.W. Scherer, R.L. Strausberg, and J.C. Venter. 2007. The diploid genome sequence of an individual human. *PLoS Biol* 5(10):e254.
41. Iyanagi, T. 2007. Molecular mechanism of phase I and phase II drug-metabolizing enzymes: implications for detoxification. *Int Rev Cytol* 260:35–112.
42. Armstrong, S.C., G.H. Wynn, and N.B. Sandson. 2009. Pharmacokinetic drug interactions of synthetic opiate analgesics. *Psychosomatics* 50(2):169–176.
43. Kobayashi, K., T. Yamamoto, K. Chiba, M. Tani, N. Shimada, T. Ishizaki, and Y. Kuroiwa. 1998. Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metab Dispos* 26(8):818–821.
44. Elkader, A., and B. Sproule. 2005. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 44(7):661–680.
45. Megarbane, B., N. Marie, S. Pirnay, S.W. Borron, P.N. Gueye, P. Risede, C. Monier, F. Noble, and F.J. Baud. 2006. Buprenorphine is protective against the depressive effects of norbuprenorphine on ventilation. *Toxicol Appl Pharmacol* 212(3):256–267.
46. Krishna, G., A. Moton, L. Ma, I. Savant, M. Martinho, M. Seiberling, and J. McLeod. 2009. Effects of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: a phase I, randomized, open-label, crossover study in healthy volunteers. *Clin Ther* 31(2):286–298.
47. Vandel, P., J.M. Talon, E. Haffen, and D. Sechter. 2007. Pharmacogenetics and drug therapy in psychiatry--the role of the CYP2D6 polymorphism. *Curr Pharm Des* 13(2):241–250.
48. Hermanns-Clausen, M., W. Weinmann, V. Auwarter, N. Ferreiros, R. Trittler, C. Muller, A. Pahl, A. Superti-Furga, and R. Hentschel. 2009. Drug dosing error with drops: severe clinical course of codeine intoxication in twins. *Eur J Pediatr* 168(7):819–824.
49. Jannetto, P.J., S.H. Wong, S.B. Gock, E. Laleli-Sahin, B.C. Schur, and J.M. Jentzen. 2002. Pharmacogenomics as molecular autopsy for postmortem forensic toxicology: genotyping cytochrome P450 2D6 for oxycodone cases. *J Anal Toxicol* 26(7):438–447.
50. CYP-Committee. 2009. Home Page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee http://www.cypalleles.ki.se/.
51. de Leon, J., M.T. Susce, M. Johnson, M. Hardin, L. Maw, A. Shao, A.C. Allen, F.A. Chiafari, G. Hillman, and D.M. Nikoloff. 2009. DNA microarray technology in the clinical environment: the AmpliChip CYP450 test for CYP2D6 and CYP2C19 genotyping. *CNS Spectr* 14(1):19–34.
52. Melis, R., E. Lyon, and G.A. McMillin. 2006. Determination of CYP2D6, CYP2C9 and CYP2C19 genotypes with Tag-It mutation detection assays. *Expert Rev Mol Diagn* 6(6):811–820.
53. Jortani, S.A., Wong S. H. 2009. Guidelines and Recommendations for Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice (Applications in Forensics). *Laboratory Medicine Practice Proposed Guidelines (NACB)*.
54. Check, W. 2009. PGx tests for warfarin dosing—how soon? *CAP Today* January - 2009.

55. Otton, S.V., M. Schadel, S.W. Cheung, H.L. Kaplan, U.E. Busto, and E.M. Sellers. 1993. CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. *Clin Pharmacol Ther* 54(5):463–472.
56. Hutchinson, M.R., A. Menelaou, D.J. Foster, J.K. Coller, and A.A. Somogyi. 2004. CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol* 57(3):287–297.
57. Lennestal, R., H.A. Lakso, M. Nilsson, and T. Mjorndal. 2008. Urine monitoring of diazepam abuse- new intake or not? *J Anal Toxicol* 32(6):402–407.
58. Lee, H.K., L.D. Lewis, G.J. Tsongalis, M. McMullin, B.C. Schur, S.H. Wong, and K.T. Yeo. 2006. Negative urine opioid screening caused by rifampin-mediated induction of oxycodone hepatic metabolism. *Clin Chim Acta* 367(1–2):196–200.
59. Madadi, P., G. Koren, J. Cairns, D. Chitayat, A. Gaedigk, J.S. Leeder, R. Teitelbaum, T. Karaskov, and K. Aleksa. 2007. Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician* 53(1):33–35.
60. Ferreiros, N., S. Dresen, M. Hermanns-Clausen, V. Auwaerter, A. Thierauf, C. Muller, R. Hentschel, R. Trittler, G. Skopp, and W. Weinmann. 2009. Fatal and severe codeine intoxication in 3-year-old twins-interpretation of drug and metabolite concentrations. *Int J Legal Med*.
61. Voronov, P., H.J. Przybylo, and N. Jagannathan. 2007. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. *Paediatr Anaesth* 17(7):684–687.
62. Gasche, Y., Y. Daali, M. Fathi, A. Chiappe, S. Cottini, P. Dayer, and J. Desmeules. 2004. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 351(27):2827–2831.
63. Wong, S.H., M.A. Wagner, J.M. Jentzen, C. Schur, J. Bjerke, S.B. Gock, and C.C. Chang. 2003. Pharmacogenomics as an aspect of molecular autopsy for forensic pathology/toxicology: does genotyping CYP 2D6 serve as an adjunct for certifying methadone toxicity? *J Forensic Sci* 48(6):1406–1415.
64. Babic, N., E.V. Haverfield, J.A. Burrus, A. Lozada, S. Das, and K.T. Yeo. 2009. Comparison of performance of three commercial platforms for warfarin sensitivity genotyping. *Clin Chim Acta*.
65. Jain, K.K. 2005. Applications of AmpliChip CYP450. *Mol Diagn* 9(3):119–127.
66. Jannetto, P.J., E. Laleli-Sahin, and S.H. Wong. 2004. Pharmacogenomic genotyping methodologies. *Clin Chem Lab Med* 42(11):1256–1264.
67. Nguyen, D.L., J. Staeker, B. Laika, and W. Steimer. 2009. TaqMan real-time PCR quantification strategy of CYP2D6 gene copy number for the LightCycler 2.0. *Clin Chim Acta* 403(1–2):207–211.
68. Misra, A., J.Y. Hong, and S. Kim. 2007. Multiplex genotyping of cytochrome p 450 single-nucleotide polymorphisms by use of MALDI-TOF mass spectrometry. *Clin Chem* 53(5): 933–939.
69. Eckhardt, K., S. Li, S. Ammon, G. Schanzle, G. Mikus, and M. Eichelbaum. 1998. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain* 76(1–2):27–33.
70. Wong, SHY. 2011. Pharmacogenomics as molecular autopsy- an adjunct to forensic pathology/ toxicology: from gregor mendel to personalized medicine and personalized justice. In *Clarke's analysis of drugs and poisons 4th edition*, Moffat, D Osselton and B Widdop, Eds. Royal pharmaceutical society publishing, London. pp. 401–16.
71. Wong, SHY, C. Happy. 2009. Personalized justice, translational pharmacogenomics and personalized medicine – relevant to the forensic sciences? tox talk, (Newsletter of the society of forensic toxicologists). 33(1):22–3.

Part II
CNS Drugs

Chapter 2
Drug Interactions with Benzodiazepines: Epidemiologic Correlates with Other CNS Depressants and In Vitro Correlates with Inhibitors and Inducers of Cytochrome P450 3A4

David E. Moody

Abstract The benzodiazepines are a class of a relatively large number of drugs that share a common chemical structure and have anxiolytic to sedative action on the central nervous system (CNS). They are chemically diverse, but share a classic structure that consists of a benzene fused to a seven-membered diazepine ring. Benzodiazepines are noted to have both pharmacodynamic and pharmacokinetic drug interactions. The former can be most devastating, and usually arise from co-exposure to another CNS depressant (e.g., ethanol, opioids, barbiturates, anesthetics). These have been associated with enhanced impairment and mortality, usually from respiratory depression. Pharmacodynamic interactions occur with all benzodiazepines and are not related to their structure. Pharmacokinetic interactions, on the other hand are highly structure dependent, as most arise from either inhibition or induction of the cytochrome P450s involved in the metabolism of the benzodiazepine. Numerous examples of pharmacokinetic interactions that alter the pharmacokinetics of the benzodiazepine have been reported and these are herein described for an assortment of drug. These interactions may have sufficient changes to significantly reduce efficacy (induction of metabolism), but toxicity from inhibition of metabolism was rarely seen at the therapeutic doses used in clinical studies. These consequences, however, could be magnified in the overuser. Numerous drug interactions between benzodiazepines and other drugs do occur; those with other CNS depressants are of greatest concern.

Keywords Benzodiazepines • Drug interactions • Drug metabolism • Respiratory depression

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General Information About Benzodiazepines

Introduction

The purpose of this chapter is to examine the drug interactions that occur with benzodiazepines and discuss the relevance of these interactions to the field of medicine in general with an emphasis on forensic toxicology. Because of the diverse nature of the benzodiazepines, some time has been taken to introduce this class of drugs. This introductory material has drawn upon some basic reference material and reviews [1–8], and is not otherwise referenced, except for specific points that did not come from these references. The primary literature will be more thoroughly cited in latter sections presenting evidence of interactions with other central nervous system (CNS) depressants and specific enzyme involvement in the metabolism of benzodiazepines and drug interactions.

The benzodiazepines are a class of a relatively large number of drugs that share a common chemical structure and have anxiolytic to sedative action on the CNS. Chlordiazepoxide was first introduced in the 1960s, followed by diazepam, flurazepam, and oxazepam. Since that time, a number of benzodiazepines have been introduced. In the 1999 edition of Martindale [7], at least 43 benzodiazepines were listed (Table 2.1). Most were found in the section on anxyolytic sedatives hypnotics and antipsychotics; one, clonazepam, was listed in the antiepileptics section. Of these 43 benzodiazepines only 15 have, or had, US manufacturers listed in the more recent online version of Martindales (Table 2.1) [9].

Most benzodiazepines are now made by more than one pharmaceutical house, or more than one subsidiary of a pharmaceutical house and therefore have more than one trade name. A single example of trade names has been listed in Table 2.1, along with an associated manufacturer.

To understand the importance of drug interactions with benzodiazepines, a basic understanding of their pharmacodynamic action is required, along with the related therapeutic use. In addition, because many of the drug interactions are of a pharmacokinetic nature, the chemical structure and metabolism of the benzodiazepines must be appreciated.

Pharmacodynamics (Briefly), Uses, and Adverse Effects of Benzodiazepines

Most of the effects of benzodiazepines arise from their action on the CNS. Within the CNS, the major molecular targets of the benzodiazepines are inhibitory neurotransmitter receptors directly activated by the amino acid, gamma-aminobutyric acid (GABA). Benzodiazepines have been shown to bind and modulate the major GABA receptor in the brain, $GABA_A$, while $GABA_B$ receptors are not altered by benzodiazepines. The $GABA_A$ receptor is an integral membrane chloride channel that mediates most of the rapid inhibitory

Table 2.1 Benzodiazepines listed in Martindales

Generic name	Representative trade name	Representative manufacturer	CAS #
Adinazolam	None	Upjohn, USA	37115-32-5
Alprazolam[a]	Xanax (others)	Upjohn, USA	28981-97-7
Bentazepam	Tiadipona	Knoll, Spain	29462-18-8
Bromazepam	Lexotan (others)	Roche, UK	1812-30-2
Brotizolam	Lendormin	B.I., Germany	57801-81-7
Camazepam[b]	Albego	Daker Farmasimos, Spain	36104-80-0
Chlordiazepoxide[a]	Librium (others)	Roche, USA	438-41-5
Cinolazepam	Gerodorm	Great, Australia	75696-02-5
Clobazam	Frisium	Hoechst, UK	22316-47-8
Clonazepam[a]	Klonopin (others)	Roche, USA	1622-61-3
Clorazepate[a]	Tranxene (others)	Abbott, USA	20432-69-3
Clotiazepam	Clozan (others)	Roerig, Belgium	33671-46-4
Cloxazolam	Akton (others)	Excel, Belgium	24166-13-0
Delorazepam	En	Ravizza, Italy	2894-67-9
Diazepam[a]	Valium (others)	Roche, USA	439-14-5
Estazolam[a]	Prosom (others)	Abbott, USA	29975-16-4
Ethyl Loflazepate	Victan (others)		29177-84-2
Etizolam	Depas (others)	Fournier, Italy	40054-69-1
Fludiazepam	Erispan	Sumitomo, Japan	3900-31-0
Flunitrazepam	Rohypnol (others)	Roche, UK	1622-62-4
Flurazepam[a]	Dalmane (others)	Roche, USA	1172-18-5
Halazepam[a,b]	Paxipam (others)	Schering, USA	23092-17-3
Haloxazolam	Somelin	Sankyo, Japan	59128-97-1
Ketazolam	Solatran (others)	SmithKline Beecham, Sweden	27223-35-4
Loprazolam	Dormonoct (others)	Hoechst Marian Russell, Belgium	61197-73-7
Lorazepam[a]	Ativan (others)	Biovail, USA	846-49-1
Lormetazepam	Loramet (others)	Wyeth, Greece	848-75-9
Medazepam	Rudotel	AWD, Germany	2898-12-6
Metaclazepam[b]	Talis	Organon, Germany	65517-27-3
Mexazolam	Sedexil	Medibial, Portugal	31868-18-5
Midazolam[a]	Versed	Roche, USA	59467-96-8
Nimetazepam[b]	Ermin	Suitomo, Japan	2011-67-8
Nitrazepam	Mogadon (others)	ICN, UK	146-22-5
Nordazepam	Nordaz (others)	Boucharo-Recordati, France	1088-11-5
Oxazepam[a,c]	Serafax (others)	Wyeth, India	604-75-1
Oxazolam	Serenal	Sankyo, Japan	24143-17-7
Pinazepam	Domar (others)	Teoforma, Italy	52463-83-9
Prazepam[a,c]	Centrax (others)	Parke-Davis, Germany	2955-38-6
Quazepam[a]	Doral (others)	Questcor, USA	36735-22-5
Temazepam[a]	Restoril (others)	Novartis, USA	846-50-4
Tetrazepam	Myolastan (others)	Sanofi Aventis, France	10379-14-3
Tofisopam	Grandaxin	Hung	22345-47-7
Triazolam[a]	Halcion	Pharmacia Upjohn, USA	28911-01-5

Note: Benzodiazepines listed in the 32nd edition of "Martindale: The Complete Drug Reference (1999)" [7]. When more than one trade name was listed (noted as "other"), either the USA or most common one was chosen; a representative manufacturer was selected for listing. Listed in latest online edition [9] as: [a]having a US manufacturer; [b]manufacturing suspended; [c]manufacturing suspended in USA, but still made in other countries

Table 2.2 Uses of benzodiazepines

1. Anxiety (27)[a]
2. Insomnia (26)
3. Presurgery/sedation (8)
4. Epilepsy/seizures (7)
5. Alcohol withdrawal (4)
6. Muscle spasms (3)
7. Panic disorder (2)
8. Depression (2)

[a] The number in parentheses represents the number of benzodiazepines listed in Martindale that are used to treat this disorder

neurotransmission in the CNS. Benzodiazepines, unlike barbiturates that also bind $GABA_A$, act only in the presence of GABA. Typical benzodiazepine agonists increase the amount of chloride current generated by $GABA_A$ activation, potentiating the effect of GABA throughout the CNS. Bicuculline, an antagonist of $GABA_A$, reduces the behavioral and electrophysiological effects of benzodiazepines, and a benzodiazepine analog, flumazenil, that potently and selectively blocks the benzodiazepine binding site, is used clinically to reverse the effects of high doses of benzodiazepines [4].

These CNS depressive effects result in anxiolytic, muscle relaxant, hypnotic, anti-grade amnesia, anticonvulsant, and sedative effects that define the therapeutic uses of benzodiazepines (Table 2.2). While the proper dose of any one benzodiazepine will produce many of these effects, some benzodiazepines are more appropriate for certain uses than others. In large part, this is dictated by the therapeutic half-life of the drug. Benzodiazepines are generally classified as short- (0–6 h), intermediate- (6–24 h), or long-acting (>24 h); some texts, however, will just use short- (0–24 h) and long-acting (>24 h) designations. Benzodiazepines used as anticonvulsants are long acting and have rapid entry into the brain. Short- to intermediate-acting benzodiazepines are favored for the treatment of insomnia. Short-acting benzodiazepines are used as preanesthetic agents for sedation prior to surgery. Long-acting or multidose shorter-acting benzodiazepines are generally used as anxiolytics. The use of benzodiazepines listed in Martindale, along with their half-life, route(s) of administration, and normal range of doses is presented in Table 2.3.

Drowsiness, sedation, and ataxia are the most frequent adverse effects of benzodiazepine use. They generally decrease on continued administration and arise from the CNS depressive effects of benzodiazepines. Less common adverse effects include vertigo, headache, mental depression, confusion, slurred speech, tremor, changes in libido, visual disturbances, urinary retention, gastrointestinal disturbances, changes in salivation, and amnesia. Rare events include paradoxical excitation leading to hostility and aggression, hypersensitivity reactions, jaundice, and blood disorders. With very high doses, hypotension, respiratory depression, coma, and occasionally death may occur.

Table 2.3 Uses of benzodiazepines listed in Martindale

Generic name	Half-life (h)[a]	Route(s) of administration	Usual dose (mg)	Uses[b]
Adinazolam	Short	–	–	1, 8
Alprazolam	11–15	Oral	0.75–1.5	1, 8
Bentazepam	–	Oral	25	1, 2
Bromazepam	12–32	Oral	3–18	1, 2
Brotizolam	4–8	Oral	0.25	2
Camazepam	–	Oral	10	2
Chlordiazepoxide	5–30, 48–120[c]	Oral, iv, im	25–100	1, 2, 3, 5, 6
Cinolazepam	–	–	–	2
Clobazam	18, 42[c]	Oral	20–30	2, 4
Clonazepam	20–40	Oral, iv	0.25–1	4, 7
Clorazepate	48–120[c]	Oral, iv, im	15–90	1, 4, 5
Clotiazapam	4–18	Oral	5–60	1, 2
Cloxazolam	Long	Oral, im	8–12	1, 3
Delorazepam	Long	Oral, im	0.5–6	1, 2, 3, 4
Diazepam	24–48, 48–120[c]	Oral, iv, im	5–30	1, 2, 3, 4, 5, 6
Estazolam	10–24	Oral	1–2	2
Ethyl Lorazepate	Long	Oral	1–3	1
Etizolam	Short	Oral	3	1, 2
Fludiazepam	Short	Oral	–	1
Flunitrazepam	16–35	Oral, iv	0.5–2	2, 3
Flurazepam	47–100	Oral	15–30	2
Halazepam	Short	Oral	20	1
Haloxazolam	Short	Oral	5	2
Ketazolam	Long	Oral	15–60	1
Loprazolam	4–15	Oral	1–2	2
Lorazepam	10–20	Oral, iv, s.l.	1–6	1, 2, 3, 4
Lormetazepam	11	Oral	0.5–1.5	2
Medazepam	Long	Oral	10–20	1
Metaclazepam	Short	Oral	15	1
Mexazolam	–	Oral	0.5	1
Midazolam	2–7	iv, im	2.5–7.5	3
Nimetazepam	Short	Oral	3	2
Nitrazepam	24–30	Oral	5–10	2, 4
Nordazepam	48–120	Oral	15	1, 2
Oxazepam	4–15	Oral	15–30	1, 2, 5
Oxazolam	Long	Oral	10	1
Pinazepam	Long	Oral	5–20	1, 2
Prazepam	48–120[c]	Oral	30–60	1
Quazepam	39, 39–73[c]	Oral	15	2
Temazepam	8–15	Oral	10–40	1, 3
Tetrazepam	–	Oral	25–50	6
Tofisopam	–	Oral	150	1
Triazolam	1.5–5.5	Oral	0.125–5	2

[a]If half-lives were not given, they were often referred to as short- or long-acting
[b]See Table 2.2 for the number corresponding to different uses
[c]Half-life for active metabolite

Daily benzodiazepine use has been associated with dependence, tolerance, and after discontinuation, withdrawal symptoms in many individuals. Tolerance to the effects of benzodiazepines is a highly debated topic. It appears to occur in some individuals and may not occur in others. The likelihood of dependence appears higher in individuals with a history of drug or alcohol dependence and personality disorders. High doses and intravenous injection are used for their euphoric effects. Because development of dependence cannot be easily predicted, abrupt discontinuation of use is not recommended. Rather the dose should be tapered. Symptoms of withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension. If long-term use of benzodiazepines occurs, professional assisted withdrawal is recommended.

Basic Pharmacokinetics

The benzodiazepines are generally lipophilic drugs. Within the class, however, lipophilicity measured as the oil:water coefficient can differ over a 50-fold range. Due to their lipophilicity the benzodiazepines have relatively high plasma protein binding (70–99%) and relatively large volumes of distribution (0.3–22 L/kg) (Table 2.4). In general, the percent plasma protein binding and the volume of distribution increase as does the oil:water partition coefficient.

The differences in lipophilicity can have a major impact on the pharmacokinetics of the benzodiazepine. Diazepam is regarded as a long-acting benzodiazepine. When diazepam is given as a single dose, however, it rapidly redistributes to non-plasma (lipid) compartments, which is referred to as the α elimination phase. It then slowly distributes back into the plasma compartment at subtherapeutic concentrations with a long terminal elimination half-life. Therefore, single doses of diazepam can be used as a preanesthesia medication, while daily dosing will result in accumulation during the terminal elimination phase and provide long-acting therapy.

The benzodiazepines are well absorbed from the gastrointestinal tract, which allows for oral dosing of benzodiazepines (Table 2.3). As described in more detail in the Section on metabolism, most will also undergo extensive first-pass metabolism, some to such an extent that parent drug is only detected at very low concentrations in blood (or blood-derived) samples. The plasma concentration of benzodiazepines, or their primary pharmacodynamically active metabolites, correlates well with the dose of benzodiazepine administered (Fig. 2.1).

As a class, the benzodiazepines share many properties. There are structural differences between them, and these differences will effect the manner in which the benzodiazepine is metabolized, and thereby have an impact on their individual susceptibility to drug interactions.

Table 2.4 The percent of plasma protein binding and volume of distribution (V_d) of some benzodiazepines

Benzodiazepine	% Bound	V_d (L/kg)	Source
Alprazolam	71	0.7	a
Bromazepam	70	0.9	b
Chlordiazepoxide	96	0.3	a
Clobazam	85	1.0	b, c
Clonazepam	86	3.2	a
Clotiazepam	99	–	c
Diazepam	99	1.1	a
Estazolam	93	–	c
Flunitrazepam	78	3.3	a
Flurazepam	97	22.0	a
Halazepam	–	1.0	b
Lorazepam	91	1.3	a
Midazolam	95	1.1	a
Nitrazepam	87	1.9	a
Nordazepam	98	0.8	a
Oxazepam	98	0.6	a
Prazepam	–	13.0	b
Quazepam	95	–	c
Temazepam	98	1.1	a
Triazolam	90	1.1	a

The source of information was a [5]; b [6]; and c [7]

Chemistry and Metabolism of Benzodiazepines

Chemistry of Benzodiazepines

The classic structure of benzodiazepines (Fig. 2.2) consists of a benzene (A ring) fused to a seven-membered diazepine (B ring). In all but two of the commercially available benzodiazepines, the nitrogens in the diazepine ring are in the 1,4-position. Clobazam has nitrogens in the 1,5-position of the diazepine ring; tofisopam has nitrogens in the 2,3-position of the diazepine ring (Fig. 2.3). In addition, most commercially available benzodiazepines have an aryl substituent (C ring) at the 5-position of the diazepine ring. Therefore, with the exception of clobazam and tofisopam, these are 5-aryl-1,4-benzodiazepines.

Following the initial synthesis of chlodiazepoxide by Sternbach in 1957, and its introduction as a therapeutic agent in 1961, a number of benzodiazepines have been introduced onto the market. The initial modifications involved changes in the substituents on the diazepine ring. Modifications along this line first led to the development of diazepam, flurazepam, and oxazepam. These have continued through the years, leading to a number of 1,4-benzodiazepines (Table 2.5). Substitution of the benzene with a thieno group produced the 1,4-thienodiazepines

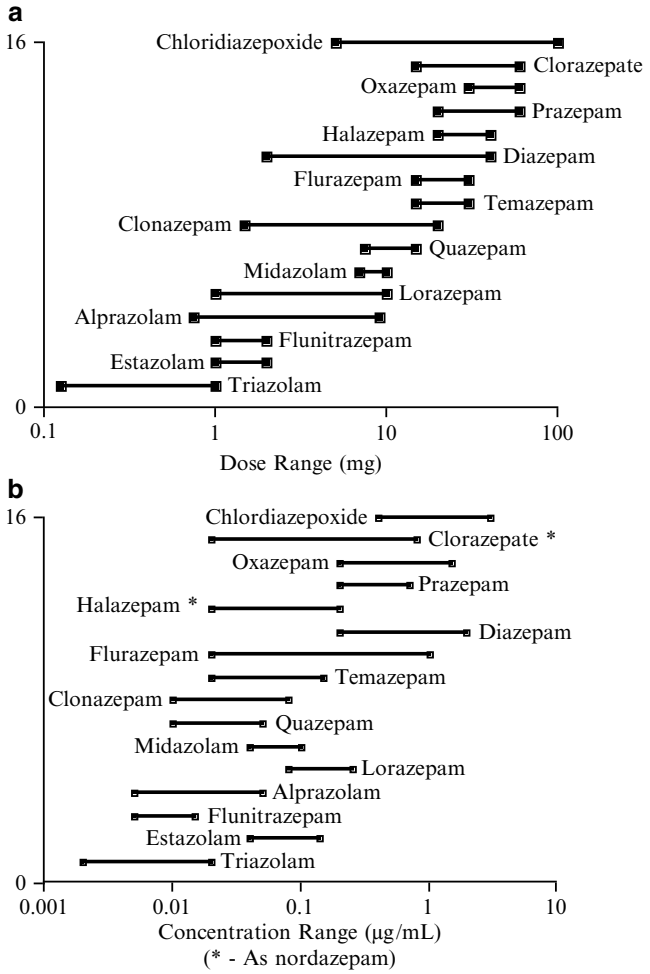

Fig. 2.1 The range of therapeutic doses (**a**) and plasma concentrations (**b**) of selected benzodiazepines. *In (**b**), these concentrations are for the primary metabolite, nordiazepam

(Figs. 2.2 and 2.3, Table 2.6). Annelation of an oxazolo (Fig. 2.2, Table 2.6) or oxazino group (ketazolam in Fig. 2.3, Table 2.6) at the 4,5-position of the diazepine has been used and the newer benzodiazepines have 1,2 annealed triazolo or imidazo groups (Fig. 2.2, Table 2.6). While most benzodiazepines have a phenyl substituent at the 5-position of the diazepine ring, bromazepam has a 2-pyridinyl substituent, and tetrazepam has a 1-cyclohexen-1-yl substituent at this position (Fig. 2.3, Table 2.6). Bentazepam, with a benzylthieno group fused to the diazepine ring, and brotizolam with both the thieno and triazolo groups are unique 1,4-thienodiazepines (Fig. 2.3, Table 2.6).

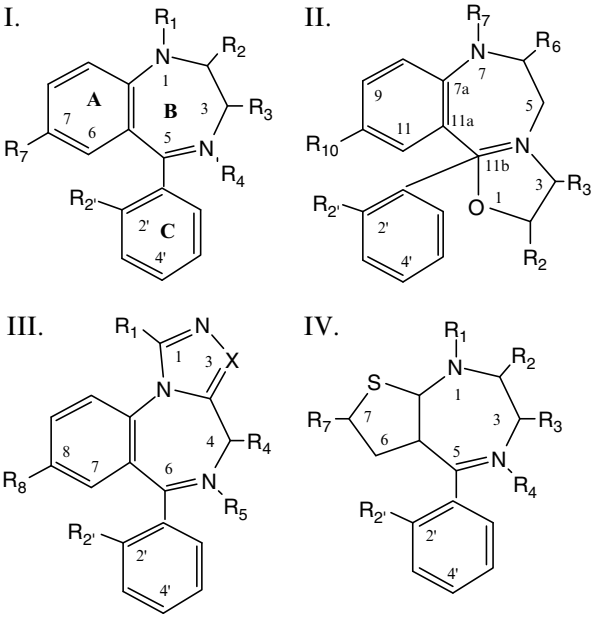

Fig. 2.2 Basic structure of the 5-aryl-1,4-benzodiazepines (I), 4,5-oxazolo-benzodiazepines (II), 1,2-triazolo- or 1,2-imidazo-benzodiazepines (III), and 1,4-thienodiazepines (IV)

Structure activity studies have demonstrated some essential requirements for the benzodiazepine-mediated CNS effects. An electron-withdrawing group is required at the 7-position of the benzene (or thieno) group (R10 for oxazolo and R8 for triazolo or imidazo). These are generally the halides chloride, and occasionally bromide, or a nitroso group. An electron-withdrawing group at the 2′ position of the 5-phenyl substituent is associated with increased potency and decreased half-life. Chloride or fluoride substituents have been used for this purpose.

Basic Metabolism of Benzodiazepines

Most of the 5-aryl-1,4-benzodiazepines are metabolized by N-dealkylation at the N-1 position and hydroxylation at the 3-position (Fig. 2.4). The N-dealkylation results in an active metabolite with a longer therapeutic half-life. In many cases, the N-dealkyl metabolite is nordiazepam (N-desmethyldiazepam, nordiazam) (Fig. 2.4). Hydroxylation at the 3-position also results in an active metabolite. The 3-hydroxyl group is then conjugated, usually with glucuronide, resulting in an inactive metabolite. For benzodiazepines with a 3-hydroxyl group, such as temazepam, oxazepam (Fig. 2.4), lorazepam, and lormetazepam (not shown), conjugation of the 3-hydroxyl group is the major route of metabolism, even when other routes, such as N-dealkylation may occur. These 3-hydroxyl benzodiazepines are consistently intermediate-acting

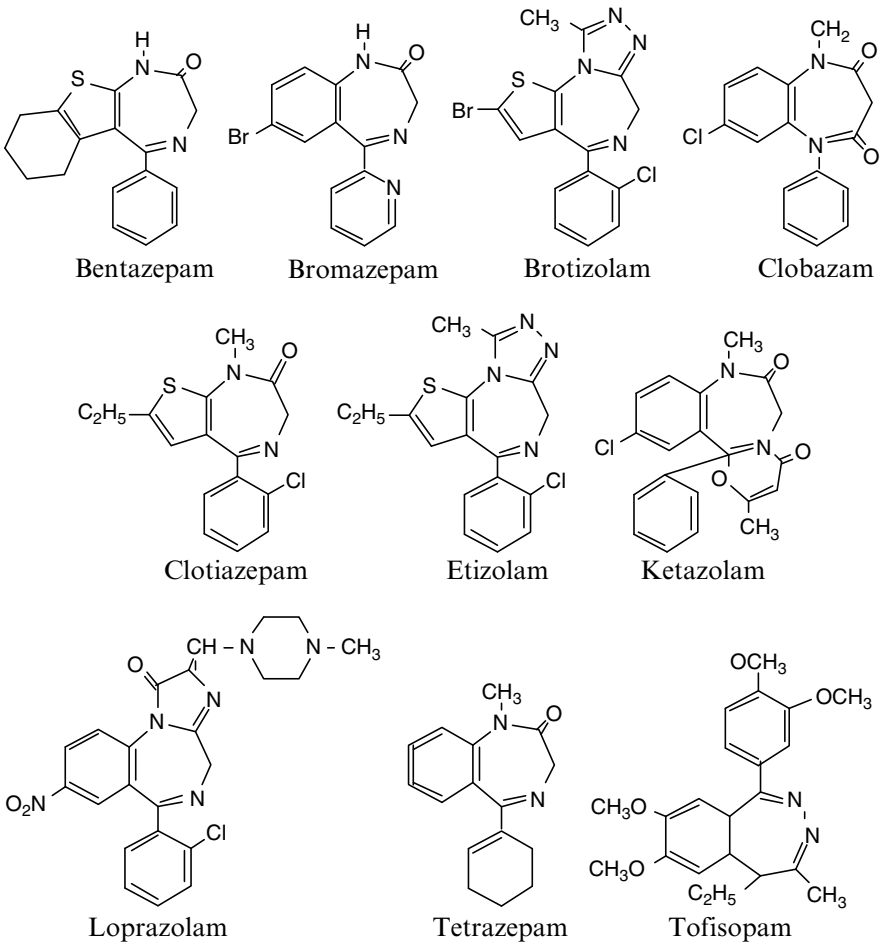

Fig. 2.3 Structure of "odd" benzodiazepines that could not easily be described in Tables 2.5 or 2.6

drugs. Clorazepate is nonezymatically decarboxylated to nordiazepam at the low pH of the stomach. The 4,5-oxazolo-benzodiazepines, such as ketazolam, oxazolam, and mexazolam have the 4,5-oxazolo cleaved. It has been postulated by Ishigami et al. [10] that P450-mediated hydroxylation of the oxazolo-ring is followed by nonenzymatic cleavage of the ring, as shown for mexazolam (Fig. 2.5).

The 1,2-triazo- and 1,2-imidazo-benzodiazepines, alprazolam, triazolam, and midazolam are metabolized by hydroxylation at the alpha (1) methyl group and at the 4-position (same as 3-position for other benzodiazepines). These metabolites are active until they are conjugated. 1-Hydroxylation is the primary route for triazolam and midazolam, while 4-hydroxylation is the primary route for alprazolam. Cleavage of the diazo ring of alprazolam has also been described (Fig. 2.6).

Table 2.5 Structures of the 1,4-benzodiazepines

Benzodiazipine	R_1	R_2	R_3	R_4	$R_{2'}$	R_7
I. *1,4-Benzodiazepines*						
Camazepam	$-CH_3$	=O	$-OCON(CH_3)_2$	–H	–H	–Cl
Chlordiazepoxide	–H	$-NHCH_3$	–H	–>O	–H	–Cl
Cinazolam	$-CH_2CH_2CN$	=O	–OH	–H	–F	–Cl
Clonazepam	–H	=O	–H	–H	–Cl	$-NO_2$
Clorazepate	–H	=O	$-COO^-$	–H	–H	–Cl
Delorazepam	–H	=O	–H	–H	–Cl	–Cl
Demoxepam	–H	=O	–H	–>O	–H	–Cl
Diazepam	$-CH_3$	=O	–H	–H	–H	–Cl
Ethyl Lorazepate	–H	=O	$-COOC_2H_5$	–H	–F	–Cl
Fludiazepam	$-CH_3$	=O	–H	–H	–F	–Cl
Flunitrazepam	$-CH_3$	=O	–H	–H	–F	$-NO_2$
Flurazepam	$-C_2H_4N(C_2H_5)_2$	=O	–H	–H	–F	–Cl
Flutoprazepam	$-CH_2CH=(CH_2CH_2)$	=O	–H	–H	–F	–Cl
Halazepam	$-CH_2CF_3$	=O	–H	–H	–H	–Cl
Lorazepam	–H	=O	–OH	–H	–Cl	–Cl
Lormetazepam	$-CH_3$	=O	–OH	–H	–Cl	–Cl
Medazepam	$-CH_3$	–H	–H	–H	–H	–Cl
Metaclazepam	$-CH_3$	$-CH_2OCH_3$	–H	–H	–Cl	–Br
Nimetazepam	$-CH_3$	=O	–H	–H	–H	$-NO_2$
Nitrazepam	–H	=O	–H	–H	–H	$-NO_2$
Nordazepam	–H	=O	–H	–H	–H	–Cl
Oxazepam	–H	=O	–OH	–H	–H	–Cl
Pinazepam	$-CH_2C=CH$	=O	–H	–H	–H	–Cl
Prazepam	$-CH_2-$	=O	–H	–H	–H	–Cl
Quazepam	$-CH_2CF_3$	=S	–H	–H	–F	–Cl
Temazepam	$-CH_3$	=O	–OH	–H	–H	–Cl

Adinazolam is successively N-demethylated at the 1-dimethylaminomethyl constituent to N-desmethyladinazolam and didesmethyladinazolam. The first N-demethyl product has a higher area under the curve (AUC) than the parent drug and higher affinity for the central benzodiazepine receptors. Deamination of N-desmethyladinazolam with eventual 1-hydroxylation to 1-hydroxyalprazolam or side chain cleavage to estazolam have been described in the mouse, but does not appear important in humans [11, 12]. Estazolam is hydroxylated to 1-oxo-estazolam and to 4-hydroxyestazolam. While both metabolites have minor activity, they are not formed in sufficient amounts to contribute to the pharmacologic activity of estazolam.

The 7-nitroso-benzodiazepines, clonazepam, flunitrazepam, and nitrazepam are metabolized by successive reduction of the nitroso-group to the amine and subsequent N-acetylation of the amine to the corresponding acetamido-group (Fig. 2.7). These are often the major metabolites present in urine and plasma and are devoid of activity at benzodiazepine receptors. N-Dealkylation at the 1 position of the diazo ring is also a prominent route of metabolism for flunitrazepam. Clonazepam and

Table 2.6 Structures of the *oxazolo*-, 1,2-triazo-, and 1,2-imidazo- benzodiazepines

II. Oxazolo-benzodiazepines	R_7	R_6	R_2	R_3	$R_{2'}$	R_{10}
Cloxazolam	–H	=O	–H	–H	–Cl	–Cl
Flutazolam	$–CH_2CH_2OH$	=O	–H	–H	–F	–Cl
Haloxazolam	–H	=O	–H	–H	–F	–Br
Metazolam	–H	=O	–H	$–CH_3$	–Cl	–Cl
Mexazolam	–H	=O	$–CH_3$	–H	–Cl	–Cl
Oxazolam	–H	=O	$–CH_3$	–H	–H	–Cl
III. 1,2-Triazo- or 1,2-imidazo-annelated-benzodiazepines	R_1	X	R_4	R_5	$R_{2'}$	R_8
Adinazolam	$–CH_2N(CH_3)_2$	–N–	–H	–H	–H	–Cl
Alprazolam	$–CH_3$	–N–	–H	–H	–H	–Cl
Clinazolam	$–CH_3$	–CH–	–H	–H	–Cl	–Cl
Estazolam	–H	–N–	–H	–H	–H	–Cl
Midazolam	$–CH_3$	–CH–	–H	–H	–F	–Cl
Triazolam	$–CH_3$	–N–	–H	–H	–Cl	–Cl

V. Odd structures (see Fig. 2.3)	
Bentazepam	Has thieno-cyclohexyl ring in place of benzyl A ring
Bromazepam	2-Pyridynyl ring at 5-position
Brotizolam	Has thieno ring in place of benzyl A ring along with 1,2-triazo fused ring
Clobazam	A 5-aryl-1,5-benzodiazepine
Clotiazepam	Has thieno ring in place of benzyl A ring
Etizolam	Has thieno ring in place of benzyl A ring along with 1,2-triazo fused ring
Ketazolam	Has a non-oxazolo 4,5-fused ring
Loprazolam	Has a imidazo fused ring with different N configuration/also 7-nitroso
Tetrazepam	Nonaromatic 6-membered ring at 5-position
Tofisopam	A 1-aryl-2,3-benzodiazepine

flunitrazepam can also be hydroxylated at the 3-position of the diazo ring. With nitrazepam, oxidative metabolism at the diazo ring results in ring cleavage; this can be followed by hydroxylation of the phenyl (B) ring (Fig. 2.7).

The routes of metabolism of other benzodiazepines, bromazepam (ring cleavage and 3-hydroxylation), clobazem (N-dealkylation and c-ring hydroxylation), clotiazepam (N-dealkylation and side chain hydroxylation), and loprazolam (N-dealkylation and spontaneous hydrolysis to polar compounds) have been described (Fig. 2.8). Metaclazepam has a methyl ether at the 2-position of the diazo ring. This appears to block hydroxylation at the 3-position, with N- and O-demethylations forming the primary metabolites (Fig. 2.9) [13]. Camazepam has a dimethylcarbamyl group at the 3-position of the diazo ring. Successive hydroxylations of the methyl groups followed by N-dehydroxymethylations account for most of the metabolites, along with N-demethylation (Fig. 2.9) [14]. Tofisopam (tofizopam) is an unusual 2,3-diazopine with hydroxymethyl groups at

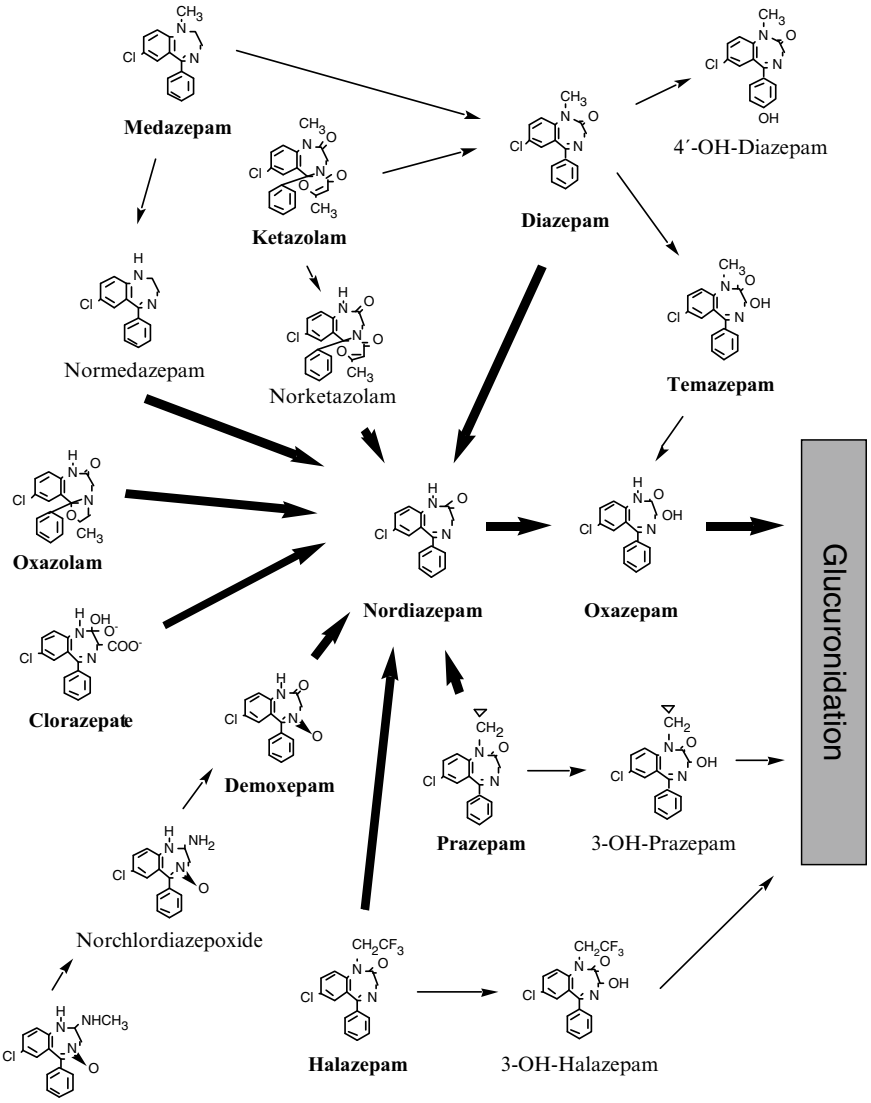

Fig. 2.4 Common metabolic pathways of 5-aryl-1,4-benzodiazepines. The compounds in *bold type* are pharmaceutical benzodiazepines. From [433], reproduced from the *Journal of Analytical Toxicology* by permission of Preston Publications a division of Prenton Industries, Inc

4 positions. O-Demethylation at the R1 and R4 positions has been described as the major routes of tofisopam's metabolism (Fig. 2.9) [15]. The metabolism of a number of other benzodiazepines has not been described. Based upon the principles discussed above, however, one can speculate on putative pathways of their metabolism (Table 2.7).

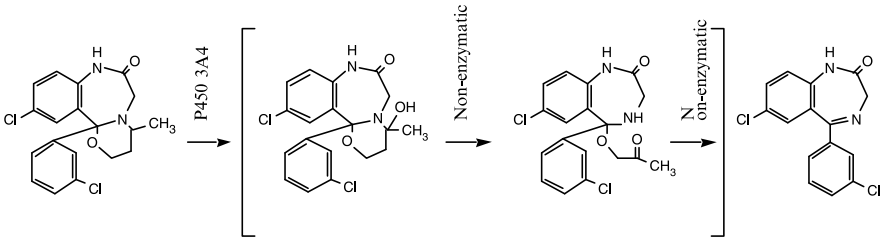

Fig. 2.5 Metabolism of the 4,5-oxazolone ring as postulated for mexazolam by Ishigami et al. [10]

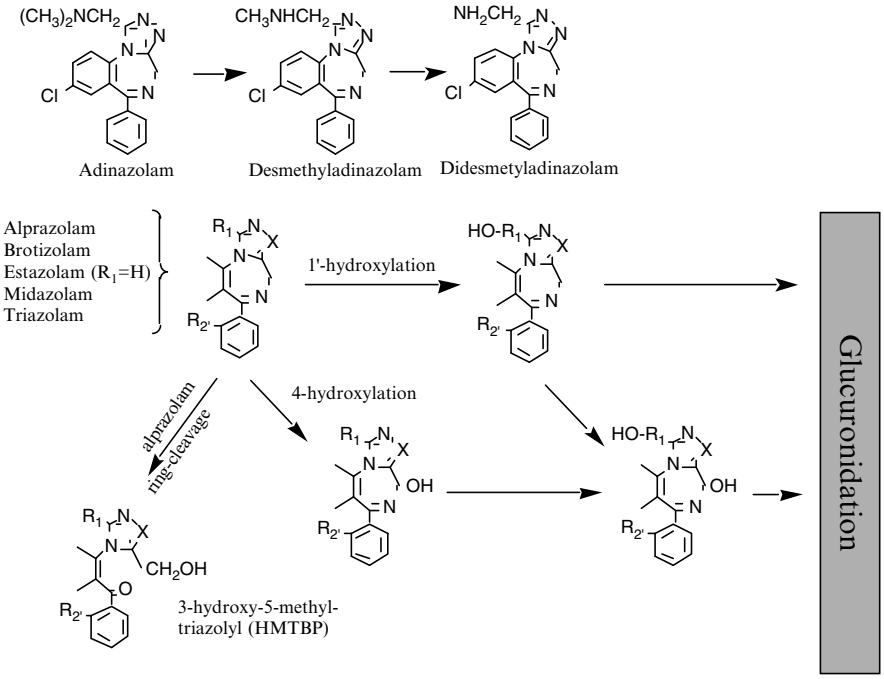

Fig. 2.6 Metabolic pathways for triazolo- and imidazobenzodiazepines

The Role of Specific Enzymes in the Metabolism of Benzodiazepines

Methods Used to Determine Enzyme Involvement in the Metabolic Pathway

The methods for determination of the role of a specific enzyme in the pathway of a drug's metabolism have been developed most thoroughly for the cytochrome P450s (P450s) [16–20]. Studies are done using human liver tissue that is now usually

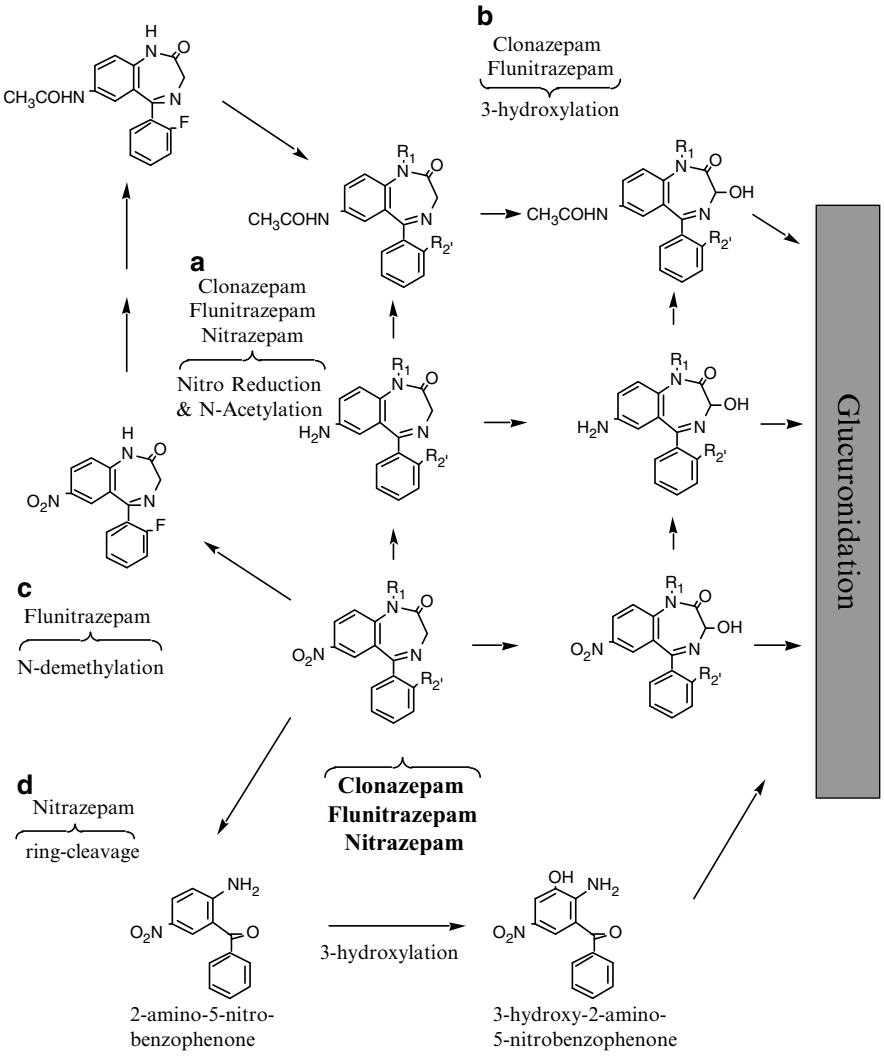

Fig. 2.7 Common metabolic pathways for 7-nitrobenzodiazepines. From [433], reproduced from the *Journal of Analytical Toxicology* by permission of Preston Publications a division of Prenton Industries, Inc

procured from donor tissue that is deemed unsuitable for transplantation. Most often, studies utilize the microsomal cell fraction prepared from differential centrifugation of homogenates of liver tissue [21], but cultured hepatocytes and liver slices are also being used. The methods used include the use of selective inhibitors, selective antibodies, correlation between P450 activities or contents in a number of human liver microsome (HLM) preparations with the pathway in question, and activities with cDNA-expressed P450s (Table 2.8). Each of these methods has

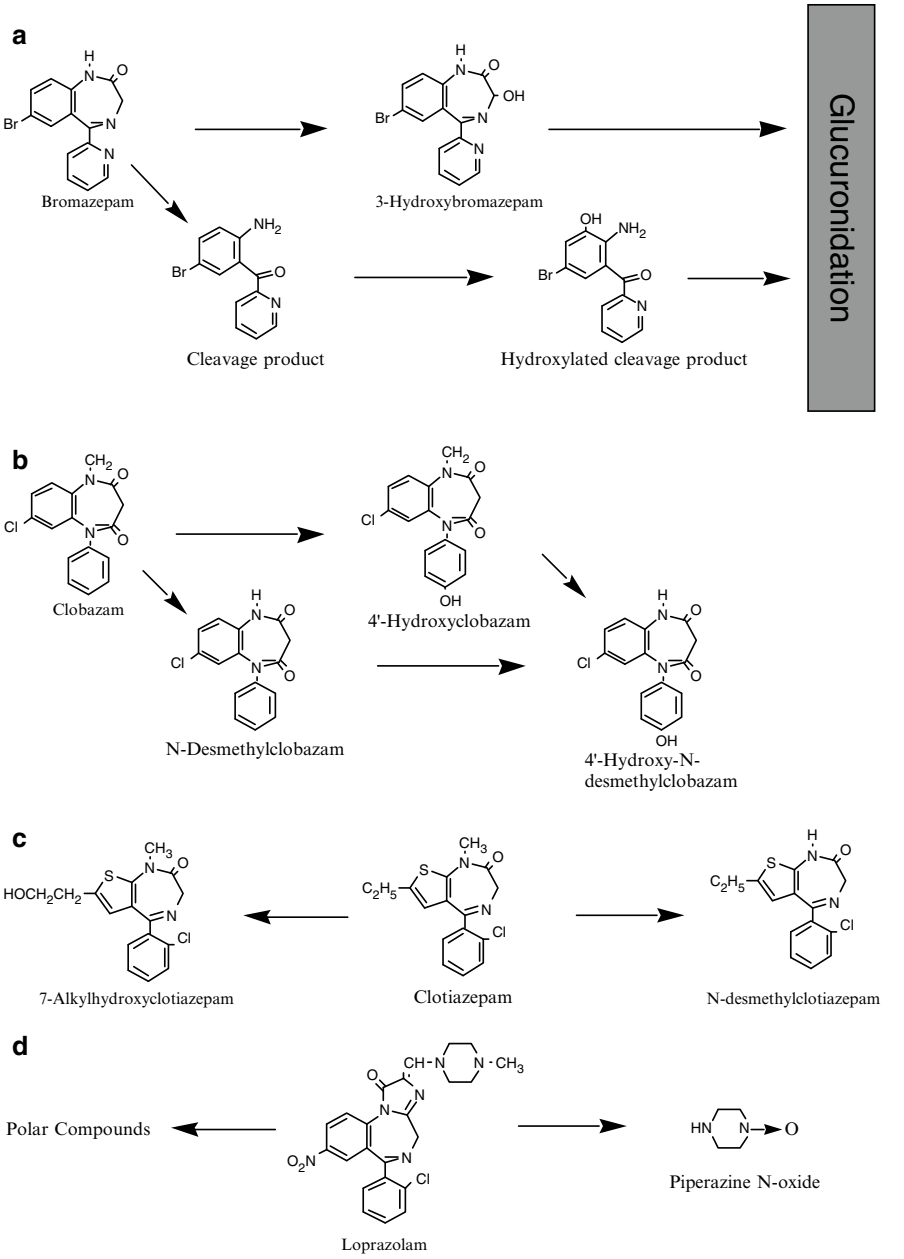

Fig. 2.8 Metabolic pathways for some other benzodiazepines: bromazepam (**a**), clobazam (**b**), clotiazepam (**c**), and loprazolam (**d**). From [433], reproduced from the *Journal of Analytical Toxicology* by permission of Preston Publications a division of Prenton Industries, Inc

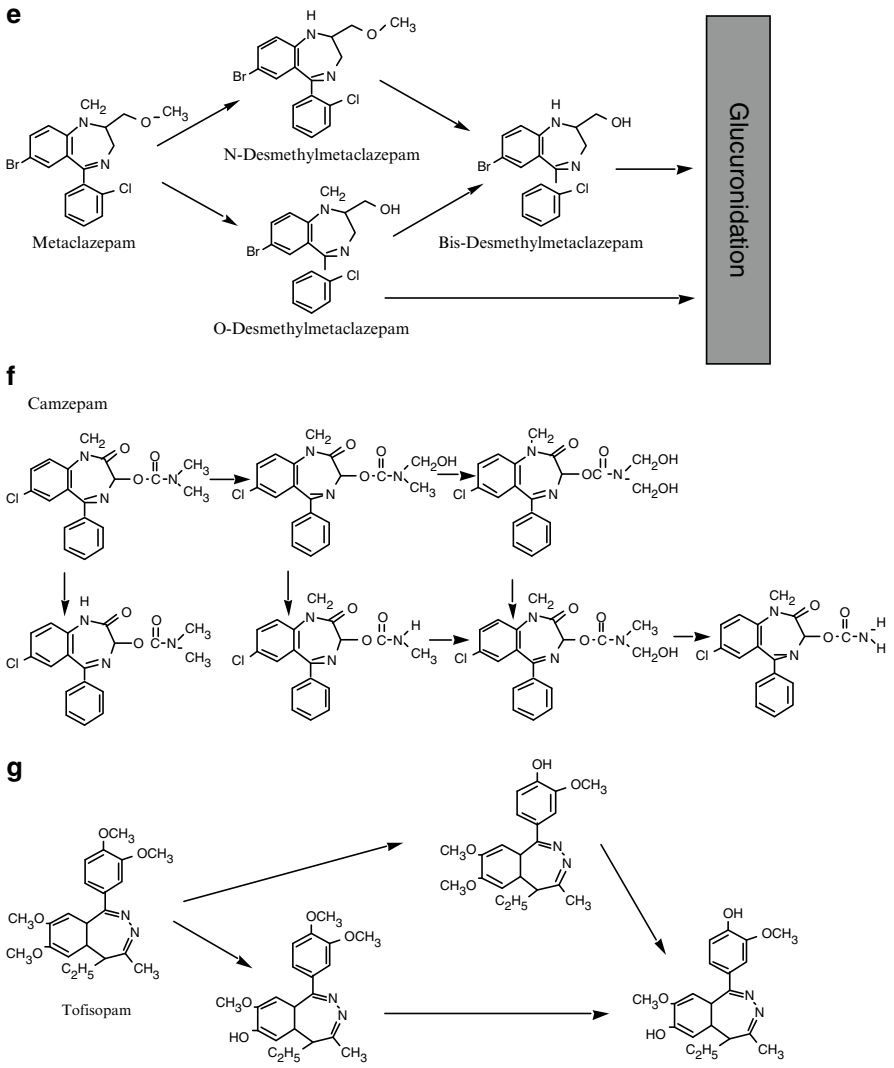

Fig. 2.9 Metabolic pathways for some other benzodiazepines (continued): metaclazepam (**e**), camazepem (**f**), and tofisopam (**g**)

certain strengths and weaknesses; the most convincing studies use most of them in an integrated approach (Table 2.8).

Selective inhibitors are often the easiest reagents to obtain and perform studies with. The results from their use, however, must be interpreted with care, as selectivity is either not complete, or is lost as the concentration of the inhibitor is increased. Recent studies have compared the ability of commonly used selective inhibitors to

Table 2.7 Speculation on putative metabolic pathways for benzodiazepines that have not had metabolites defined

5-Aryl-1,4-benzodiazepines	
Cinolazolam	Conjugation of 3-hydroxyl; N-dealylation
Delorazepam	3-hydroxylation ->conjugation
Ethyl lorazepate	3-ester hydrolysis ->conjugation
Fludiazepam	3-hydroxylation ->conjugation; N-dealylation
Pinazepam	3-hydroxylation ->conjugation; N-dealylation
Tetrazepam	3-hydroxylation ->conjugation; N-dealylation
7-Nitroso-5-aryl-1,4-benzodiazepines	
Nimatazepam	Amine reduction ->N-acetylation 3-hydroxylation ->conjugation; N-dealylation
4,5-Oxazolo-benzodiazepines	
Cloxazolam	Cleavage of 4,5-oxazolo-ring; 3-hydroxylation ->conjugation
Haloxazolam	Cleavage of 4,5-oxazolo-ring; 3-hydroxylation ->conjugation
Mexazolam	Cleavage of 4,5-oxazolo-ring; 3-hydroxylation ->conjugation
1,2-Triazo-benzodiazepine	
Etizolam	Alpha-hydroxylation ->conjugation; 4-hydroxylation

Table 2.8 Tools used to determine involvement of specific enzymes in xenobitotic metabolism

1. Selective inhibitors	• Relatively easy to get and most are relatively inexpensive • Selectivity is concentration dependent • Using titration can help determine % involvement in a pathway • Mechanism-based inhibitors require 10–15 min preincubation before addition of test substrate
2. Selective antibodies	• Either expensive or require collaboration with laboratory that produces them • Selectivity often limited to family of enzyme • Using titration can help determine % involvement in a pathway
3. Correlation	• Requires a phenotyped HLM bank, the higher the number, the better • Requires selective assays for all enzymes monitored • Selectivity is rarely perfect • If marker assay is not evenly distributed, high activity HLMs may bias result
4. cDNA-expressed enzymes	• Excellent to determine if enzymes can carry out metabolism • Activities have improved over time • Newer studies are employing scaling techniques to help estimate % involvement. This requires a phenotyped liver bank

inhibit marker substrate P450 activities in either HLM or cDNA-expressed P450s [22–24]. A summary of their results is presented in Table 2.9. These comparisons can be useful in interpreting results presented in this and other chapters of this book, and when researching the primary literature.

Table 2.9 Selectivity of P450 inhibitors

Inhibitor	μM	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
Fur[a]	5[b]	90				–		–	15	–
	5[d]	20–90	–	–	–	–	–	–	–	–
	100[b]	90				–		–	15	–
	100[d]	30–95	–	20–30	–	15–30	15–30	–	0–15	0–25
	200[c]	90	–	–	45	30		65	30	50
7,8-BF	1[c]	95	–	–	20	–		–	–	–
	10[b]	75				–		+20	+30	–
	100[b]	80				60		–	+90	30
α-NF	1[d]	20–95	–	–	+200	15	25	–	–	0 to +50
	100[d]	90–95	0–65	–	+300	25–35	30–45	–	–	0 to +1000
Orph	100[d]	–	–	0–20	0–25	–	–	0–70	–	0–25
	500[d]	0–70	–	70–75	65–70	25–30	0–65	55–90	30–40	35–70
Tran	1000[c]	60	100	100	80	90		–	60	65
Sulf	10[b]	–				65		–	–	–
	10[c]	–	–	–	100	90		15	–	–
	20[b]	–				75		20	–	–
	20[d]	0–20	–	–	–	90	–	–	–	10–30
	100[b]	–				85		–	–	–
	100[d]	0–30	–	20–35	20–30	90	–	–	15–25	20–25
Quin	0.5[c]	–	–	–	–	45		95	–	–
	0.5[d]	–	–	–	–	–	–	60–70	–	–
	1[b]	–				–		60	–	–
	10[b]	–				–		85	–	–
	10[d]	–	–	–	–	–	–	85–95	–	0–20

(continued)

Table 2.9 (continued)

Inhibitor	μM	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
DDC	10[b]	–				–		–	50	–
	20[d]	–	20–35	–	–	15–35	0–50	–	35	–
	100[b]	20				20		30	75	20
	100[d]	10–30	50–70	10–40	15–45	30–60	35–80	20	70–75	20
	200[c]	–	90	30	35	40		50	90	25
3-MP	50[b]	–				–		65	70	–
	500[b]	35				40		80	75	20
	500[c]	–	20	50	–	60		75	80	35
Keto	1[d]	–	–	–	0–25	–	–	–	–	10–90
	2[b]	–				–		–	–	82
	5[d]	–	–	20–40	50–55	25	–	–	–	90–100
	10[c]	40	35	85	–	60		65	85	100
	50[b]	45				70		60	–	100
TAO	50[b]	–				–		–	–	80
	50[d]	–	–	–	–	–	–	–	–	25–50
	500[d]	–	0–20	0–20	20–30	–	–	–	15–30	75–80
	1000[c]	20	25	30	30	50		40	10	100

Note: "–" means less than 15% inhibition was observed; a blank spot indicates that P450 was not studied

[a]The abbreviations used for inhibitors are listed with the P450 it is commonly believed specific for in parentheses: Fur, furafylline (1A2); 7.8-BF, 7,8-benzoflavone (1A2), α-NF, α-naphthoflavone (1A2), Orph, orphenadrine (2B6), Tran, tranylcypromine (2 C), Sulf, sulfaphenazole (2C9), Quin, quinidine (2D6), DDC, diethyldithiocarbamate (2E1), 3-MP, 3-methylpyrazole (2E1), Keto, ketoconaole (3A4), and TAO, troleandromycin (3A4)

[b]Data from Newton et al. [22] who used 4 HLM with 15 min preincubation for studies with Fur, DDC, and TAO, and no preincubation for all other inhibitors

[c]Data from Ono et al. [23] who used cDNA-expressed P450s with 5 min preincubation for all inhibitors

[d]Data from Sai et al. [24] who used cDNA-expressed P450s with 10 min preincubation for Fur, DDC, and TAO, and 5 min preincubations for all other inhibitors

Selective antibodies are powerful tools, but their selectivity must be carefully determined. The most common limitation is their inability to distinguish P450s of the same family (e.g., 3A4 versus 3A5). A common feature of selective inhibitors and selective antibodies is that they can be used to titrate the activity in liver tissue preparations and provide an estimate of the percent involvement. Selective antibodies can also be used to quantitate the amount of a particular P450 or P450 family in liver tissue.

A common feature of liver tissue preparations is that there is usually large inter-individual variation between preparations. This arises in part from true individual differences and from differences in tissue preparation. When a number of HLM have been phenotyped by immunoquantitation (IQ) and/or by determining P450 selective activities, they can be used for correlational studies. The metabolic pathway in question is measured in the different preparations and plotted as a scatter gram against the marker activities or contents. High and low correlation coefficients provide supportive evidence of the enzyme's positive or negative involvement, respectively. As with any correlation experiments, the distribution of activities should be carefully examined to assure no heterogeneous scatter is creating a biased result [25].

cDNA-expressed P450s provide a means of measuring the pathway in question in a purified and reconstituted system. By themselves, they can only determine the ability of the enzyme to perform the reaction. Comparison of different P450s is complicated by differences in their membrane lipid contents, and the contents of the other enzymes involved in P450-mediated monooxygenations, NADPH cytochrome P450 reductase, and cytochrome b_5 [19]. In more recent experiments, scaling techniques have been employed to estimate the relative contributions of P450s using the results of experiments in cDNA-expressed P450s. The relative contribution of the enzyme (f_i) is calculated from $f_i = (A_i v_i(s)) / \left(\sum A_i v_i(s)\right)$, where A_i is the relative abundance of the P450 and $v_i(s)$ is the concentration velocity function of the P450. Abundance has been alternatively estimated from immunoquantitation (IQ) of P450s in HLM [26] or from relative activity factors (RAFs) calculated from the ratio of activity of enzyme-specific pathways in HLM to that in cDNA-expressed P450s [19]. These methods are well described in the work of Venkatakrishnan et al. [20] and Neff and Moody [27].

Involvement of Specific P450s in the Metabolism of Benzodiazepines

The metabolism of a number of benzodiazepines has been studied using the methods described above. The results of these studies are summarized in Table 2.10. The P450 3A family has been implemented in all of these metabolic pathways that include diazepam 3-hydroxylation and N-demethylation [28–32] and utilization [33], nordiazepam 3-hydroxylation [29, 30], temazepam N-dealkylation [29, 30], midazolam 1′- and 4-hydroxylation [34–46], triazolam 1′- and 4-hydroxylation [35, 44, 47], alprazolam 1′- and 4-hydroxylation [48–51], the first and second N-demethylations of adinozalam [52], flunitrazepam 3-hydroxylation and N-demethylation [53–55],

Table 2.10 Involvement of specific enzymes in the metabolism of benzodiazepines

Drug	Pathway	P450	Level of evidence	References
Diazepam	3-Hydroxylation	3A4, 3A5 >> 2C19	1, 2, 4	[28–32]
	N-Demethylation	2C19, 3A4, 3A5 >> 2B6	1, 2, 4	[28–32]
	Utilization	3A4 >> 2C19, 2B6	1, 4	[33]
Nordiazepam	3-Hydroxylation	3A4 >> 3A5	4	[29, 30]
Temazepam	N-Dealkylation	3A4, 2C19 > 3A5 >> 2B6	4	[29, 30]
Midazolam	1′-Hydroxylation	3A5 > 3A4 >> 2B6	1, 2, 3, 4	[34–46]
	4-Hydroxylation	3A4, 3A5 >> 2B6	1, 2, 3, 4	[35, 36, 38, 40, 41, 44]
Triazolam	1′-Hydroxylation	3A	1, 2, 3	[35, 44, 47]
	4-Hydroxylation	3A	1, 2, 3	[35, 44, 47]
Alprazolam	1′-Hydroxylation	3A5 > 3A4	1, 2, 3, 4	[49–51]
	4-Hydroxylation	3A4, 3A5	1, 2, 3, 4	[48–51]
Adinozalam	N-Demethylation	3A4 > 2C19	1, 4	[52]
	2nd N-Demethylation	3A4 > 2C19	1, 4	[52]
Flunitrazepam	3-Hydroxylation	3A4	1, 2, 4	[53–55]
	N-Demethylation	3A4, 2C19	1, 2, 4	[53–55]
Brotizolam	Utilization	3A4	4	[56]
	1′-Hydroxylation	3A4	1, 2	[56]
	4-Hydroxylation	3A4	1, 2	[56]
Mexazolam	Oxazolo-ring cleavage	3A4	2	[10]
Clobazem	N-Demethylation	3A4 > 2C19 > > 2B6	1, 4	[57]
	4-Hydroxylation	2C19, 2C18	1, 4	[57]
N-Desmethylclobazam	4-Hydroxylation	2C19, 2C18	1, 4	[57]
Quazepam	2-Oxidation	3A4 >> 2C9, 2C19	1, 4	[58]
	N-Desmethylation	3A4 > 2C9	1, 4	[58]
	3-Hydroxylation	3A4 > 2C9	1, 4	[58]
Estazolam	4-Hydroxylation	3A4	1, 4	[59]
Clotiazepam	Utilization	2B6 > 3A4, 2C18, 2C19	1, 4	[33]
Tofisopam	Utilization	3A4 > 2C9, 2C8	1, 4	[33]
Etizolam	Utilization	3A4 > 2C18, 2C19	1, 4	[33]

brotizolam 1′- and 4-hydroxylation [56], the oxazolo-ring cleavage of mexazolam [10], the N-demethylation of clobazam [57], the metabolism of quazepam to 2-oxoquazepam, N-desalkylquazpam, and 3-hydroxyquazepam [58], estazolam 4-hydroxylation [59], and the utilization of clotiazepam, tofisopam, and etizolam [33].

In human liver, there are two members of the 3A family, 3A4 and 3A5. P450 3A4 is the most abundant P450 in most livers, while 3A5 is only detected in approximately 20% of livers [60]. In a few of the studies cited above, 3A4- and 3A5-mediated activities have been compared. Equivalent activities were found for diazepam 3-hydroxylation and N-demethylation [29, 31], and for midazolam 4-hydroxylation [36, 38]. P450 3A4 was more active than 3A5 for nordiazepam 3-hydroxylation and

temazepam N-dealkylation [29, 30]. In contrast, P450 3A5 was more active than 3A4 for midazolam 1′-hydroxylation [36, 38, 45]; however, He et al. [46] studied the distribution of 3A4 and 3A5 genotypes and did not find a correlation. Subsequent studies on the relationship of 3A4 and 3A5 genotypes with midazolam metabolism also found no significant differences [61–64]. There does appear to be a polymorphism at an upstream element of the 3A4 gene that increases midazolam metabolism [63], and a genetic defect in the P450 oxidoreductase does reduce activity [64]. Gorski et al. [49] indirectly suggest that 3A5 is more involved in the 1′-hydroxylation of alprazolam based upon correlation differences between livers that contain both 3A4 and 3A5 versus those containing only 3A4. This has been further supported by the impact of 3A5 genotype on alprazolam metabolism [65]. As some differences have been observed in the response of 3A4 and 3A5 to inhibitors [23], the differential metabolism of benzodiazepines by these two members of the 3A family may play a factor in susceptibility to certain drug interactions.

P450 2C19 appears to play a role in the N-demethylation of diazepam, temazepam, adinazolam, N-desmethyladinazolam, and flurazepam. For diazepam and nordiazepam, this involvement has been confirmed from studies comparing extensive and poor 2C19 metabolizers in Caucasians [66], Koreans [67], Chinese [68], and Japanese [69] populations. An earlier study that suggested lower rates of metabolism of diazepam among phenotyped 2C19 extensive metabolizing Han Chinese [70], appeared to arise from a number of heterozygotes being included in the extensive metabolizer population [68, 71]. These studies are consistent with the in vitro findings that show considerable diazepam N-demethylation activity with cDNA-expressed 2C19, inhibition of diazepam N-demethylation in HLM with omeprazole and with anti-2C family antibodies [28–32]. While the impact of the 2C19 phenotype or genotype on nordiazepam clearance, suggests that 2C19 can also be involved in some 3-hydroxylation reactions, which was not readily apparent from the results of the in vitro studies [29]. A recent report suggests that the 2C19 poor metabolizing genotype was responsible for prolonged excretion of diazepam in a subject undergoing treatment for benzodiazepine abuse [72]. Interpretation of this as new use may have had negative consequences; a concern for this and other cases of interest to forensic toxicologists.

A couple of case studies first suggested the significant involvement of P450 2C19 in clobazam metabolism [73, 74]. Giraud et al. [57] established the involvement of 2C19 in the 4′-hydroxylation of clobazam and N-desmethylclobazam. They also found that subjects heterogeneous for the 2C19*2 allele had a greater plasma N-desmethylcobazam to clobazam ratio, which supported the in vivo involvement of 2C19 in this pathway [57]. This was followed up by a population study confirming 2C19 involvement, primarily in the metabolism of N-desmethylclobazam, and its impact on treatment of epilepsy [75]. Genotyping experiments also suggest that 2C19 plays a significant role in the metabolism of etizolam [76]. While no significant effect was seen for the 2C19 phenotype and/or genotype on metabolism of alprazolam [77], triazolam [78], flunitrazepam [79], and estazolam [80].

P450 2B6 had a major role in clotiazepam utilization [33], and may have a minor role in the N-demethylations of diazepam and temazepam [29–31], as well as the 1′- and 4-hydroxylations of midazolam [42, 44, 45]. Whether this role of 2B6 will

have clinical significance has yet to be determined. In part, this will depend upon the relative content of 2B6 in human livers. Earlier studies on specific P450 content suggested that 2B6 did not exceed 1–2% of total P450 [60], but a more recent one showed 100-fold variation in 2B6 content in 19 HLM from 0.7 to 71.1 pmol/mg protein. Assuming an average P450 content of 500 pmol/mg protein, this is a range of 0.14–14.2% of total P450. If high 2B6 content is coupled with low 3A4 and 3A5 content, then the likelihood of 2B6's contribution to the metabolism of some benzodiazepines may be increased.

In summary, P450 3A4 (and 3A5) are extensively involved in many pathways of oxidative metabolism of benzodiazepines. P450 2C19 is involved in many of the N-demethylation reactions, and may play a role in some other oxidative pathways. P450 2B6 may also have a role in certain oxidative pathways. While a number of metabolic pathways of benzodiazepines have been studied, many have not. Little is known of the role of specific uridine diphosphate glucuronosyl transferases or sulfotransferases in conjugation of benzodiazepines or of the enzymes involved in reduction and subsequent acetylation of the nitroso-benzodiazepines.

Benzodiazepine Drug Interactions

General Considerations

Both pharmacodynamic and pharmacokinetic mechanisms have been observed for drug interactions concerning benzodiazepines. Most pharmacokinetic drug interactions involve either the inhibition or induction of specific P450s involved in the metabolism of benzodiazepines. They are the most common and the better documented of drug interactions with benzodiazepines. Most, however, result in either an increased (inhibitors) or decreased (inducers) activity of the benzodiazepine. When therapeutic doses are used these interactions may have clinical and forensic, if carried into driving or other machine operating environments, but rarely lethal consequences. Pharmacokinetic drug interactions with benzodiazepines are specific for certain benzodiazepines depending upon the enzyme(s) involved in their metabolism. Some of these interactions were reviewed in the mid-1980s [81, 82]. A more recent review was restricted to alprazolam, midazolam, and triazolam [83].

Pharmacodynamic drug interactions with other CNS depressants are more likely to have lethal, as well as clinical and forensic, consequences. These drugs, which include ethanol, opioids, and barbiturates, also cause respiratory depression, and their combined use can have additive, and has been described in some cases, even synergistic effects. The potential for pharmacodynamic interactions exists for all benzodiazepines regardless of route of metabolism; synergistic interactions, however, may involve a combined pharmacodynamic and pharmacokinetic interaction that is specific for certain benzodiazepines. A number of reviews have considered the interactions of benzodiazepines and ethanol [84–87]. None were located addressing interactions with opioids or barbiturates.

Epidemiological Occurrences of Benzodiazepines, Ethanol, and Opioids

The Occurrence of Other Drugs or Ethanol in Benzodiazepine-Associated Deaths

The epidemiologic record presents circumstantial evidence for the importance of drug interactions of benzodiazepines with ethanol and opioids. A number of studies have examined deaths linked to benzodiazepines. Those that investigated the involvement of other drugs and/or ethanol in the deaths are listed in Table 2.11a. In general, deaths linked to benzodiazepine use often, but not always, also have evidence of ethanol and/or other drug use. Some studies investigated only the involvement of ethanol [88, 89], or other drugs [90], in addition to benzodiazepines. It is therefore difficult to get an exact estimate of how often only benzodiazepines were identified. In one study carried out in the USA and Canada that investigated deaths involving diazepam, only 2 of 914 deaths were identified with only diazepam [91]. In another study carried out in Sweden, benzodiazepines were identified in 144 of 702 deaths without other drugs or ethanol [92]. A sufficient dose of benzodiazepines can be lethal, but this appears to be exacerbated when other drugs are involved.

The Occurrence of Benzodiazepines in Opioid-Associated Deaths: the Buprenorphine Story

Benzodiazepines are also apparent in some opioid-related deaths (Table 2.11b). Three studies were identified that investigated heroin-linked deaths. Benzodiazepines were also found in 5–10% of these deaths [93–95]. Opioids are well recognized for their respiratory depressant effects, that a combination with another CNS depressant that also causes respiratory depression may exacerbate the situation is not too surprising.

Buprenorphine has been used for years as an analgesic or for treatment of chronic pain at doses 0.3–0.8 mg. More recently, buprenorphine has been used in substitution therapy for opioid-dependence. For the latter, doses of 8–32 mg are used. Buprenorphine is known as a partial μ agonist that appears to have ceiling effects in regard to its μ-activities such as respiratory depression [96]. Recently in France, however, six cases of deaths involving buprenorphine were also found to involve benzodiazepine use [97] (Table 2.11). That buprenorphine may interact with benzodiazepines was suggested in a series of "letters to the editor" in the journal *Anaesthesia.* Papworth [98] first reported four cases of prolonged somnolence and bradypnoea with combinations of buprenorphine and lorazepam. Forrest [99] then described a case, also with buprenorphine and lorazepam that had prolonged somnolence, bradypnoea, and the need for assisted respiration. This was followed shortly thereafter by a report from Faroqui et al. [100] that found 11 subjects out of 64 that were premedicated with diazepam and had anesthesia induced with buprenorphine required assisted ventilation. This was not observed in 24 patients receiving diazepam and fentanyl.

Table 2.11 The presence of alcohol and other drugs in benzodiazepine poisonings

Year	Population	Location	Reference
(a) The occurrence of other drugs or ethanol in benzodiazepine-associated deaths			
1979	914 diazepam-positive fatalities	USA and Canada	[91]
	912 and other drug or EtOH; 51 EtOH; 295 EtOH and other drug; 566 other drug; propoxyphene > opiates > barbiturates		
1980	2,723 overdoses	Toronto, Canada	[90]
	1,071 benzo positive; 726 other drugs (EtOH apparently not studied)		
1989	3,430 overdoses	Stockholm, Sweden	[92]
	702 benzo positive; 144 benzo; 200 benzo and EtOH; 254 benzo and other drugs; 104 benzo, other drug and EtOH.		
1993	1,576 benzodiazepine-associated deaths	Great Britain	[88]
	891 single benzo; 591 single benzo and EtOH; 94 more than one benzo ± EtOH		
1995	303 benzodiazepine-associated overdoses	Newcastle, Australia	[89]
	303 total; 114 EtOH		
(b) The occurrence of benzodiazepines in opioid-associated deaths			
1976	114 heroin-related deaths	Orange Co., CA	[93]
	9 benzo positives		
1977	268 heroin-related deaths	Wayne Co., MI	[94]
	12 diazepam positive		
1994	21 heroin-related deaths	Baltimore, MD	[95]
	2 benzo positive		
1998	Unknown # of buprenorphine-related deaths	France	[97]
	6 benzo-positive cases		

This combined effect of buprenorphine and a benzodiazepine, midazolam, has now been reproduced in an animal model. Gueye et al. [101] have shown that rats given buprenorphine alone (30 mg/kg, iv) had a mild increase in $PaCO_2$ at 60 min. Rats given midazolam alone (160 mg, ip) had a mild decrease in arterial pH at 90 min and increase in $PaCO_2$ at 60 min. When the doses were combined, there was a prolonged respiratory depression with the changes in blood pH and $PaCO_2$ noted within 20 min, with delayed hypoxia at 120 and 180 min.

This effect is apparently not due to an inhibition of the benzodiazepine metabolism. Kilicarslan and Sellers [102] have shown that metabolism of flunitrazepam to 3-hydroxyflunitrazepam in (HLM) was not inhibited by norbuprenorphine, and while inhibited by buprenorphine, the Ki of 118 μM was suggestive of only 0.1–2.5% inhibition in vivo. We have recently addressed the converse situation, inhibition of buprenorphine metabolism by benzodiazepines; in brief, only a few benzodiazepines showed any tendency to inhibit the metabolism of buprenorphine [103]. This strengthens the argument that any interaction is of the pharmacodynamic nature.

While the percentage of opioid-associated deaths that also show benzodiazepine use are relatively low (Table 2.11b), it is still a concern due to the potential for the

Table 2.12 Benzodiazepine use among opioid users: survey of studies in 1990s

Year	Population	Location	Reference
1990	272 polydrug users (75% heroin) 28% were also using temazepam (use of other benzos not mentioned)	Northwest England	[400]
1990	249 male opiate addicts Greater than 50% used benzos, with flunitrazepam most common	Penang, Malaysia	[401]
1991	323 methadone treatment subjects Daily, few times per week, and a few times per month benzo use was 14, 15, and 39% in those that did not share needles and 25, 18, and 24% in those that did share needles	Philadelphia and New Jersey	[402]
1992	1,245 injecting drug users 36.6% used benzos	Sydney, Australia	[403]
1992	103 methadone treatment subjects All had used heroin and benzodiazepines, relative liking of cocaine > cannabis >> stimulates ≈ benzos. Flunitrazepam and diazepam were the most favored	Innsbruck, Austria	[404]
1993	313 applicants for methadone treatment 42% reported a benzo habit (37% of males; 56% of females).	Kensington, Australia	[405]
1993	973 admittees for inpatient opiate detoxification 80.2% history of benzo use; 68.5% current; 43.1% daily. Flunitrazepam > clorazepate > diazepam	Barcelona, Spain	[406]
1993	222 methadone treatment subjects 36.5% use in the past month; 26.6% daily; and 11.3% 5 or more pills a day	Kensington, Australia	[407]
1994	208 subjects (82.2% for opiate use) 90% had used benzos, 49% by injection	Clinics in 7 cities in Britain	[408]

pharmacodynamic interaction resulting in additive (or synergistic) effects on respiratory depression. Further epidemiological data substantiates the risk. Surveys conducted in the early 1990s in various parts of the world demonstrate that use of benzodiazepines is quite common in opioid-dependent subjects (Table 2.12). Regular benzodiazepine use ranged from 27 to 50%, while most had used benzodiazepines at one time. A great majority reported intravenous use of the benzodiazepines.

The Occurrence of Benzodiazepines, with or Without Ethanol or Other Drugs in Motor Vehicle Investigations

One area in which epidemiological data points to potential interactions between benzodiazepines and ethanol or other drugs is within motor vehicle investigations. Studies that clearly indicated benzodiazepine and ethanol and/or other drug use were reviewed and are listed in Table 2.13. These studies can be divided into three types: (1) studies on fatalities wherein most studies drug use was determined in all

Table 2.13 The occurrence of benzodiazepines with, or without ethanol (or other drugs) in motor vehicle investigations

Year	Population	Location	Reference
(A) Fatalities			
1977	127 driving fatalities 23 drug positive; 13 diazepam, 7 with EtOH	Dallas, Co., TX	[409]
1980	401 motor vehicle fatalities 64 drug positives; 15 benzos; 12 diazepam, 3 with EtOH; 4 & other drugs	Ontario, Canada	[410]
1986	1,518 driving fatalities 32 benzo positive, 25 with EtOH	Alabama	[411]
1987	200 driving fatalities, survivors or blood tested (restricted to with EtOH < 0.05) 34 drug positive; 9 benzo; 7 with EtOH	Tasmania, Australia	[412]
1993	168 trucker fatalities no benzos identified	USA	[104]
1996	318 driving fatalities 61 drug positive; 4 benzo; 2 with EtOH	Washington	[413]
(B) Impaired situations			
1969	180 overt intoxication, but BAC ≤ 0.15% 38 drug positive; 2 chlordiazepoxide (BAC) 1 (0 – < 0.05); 1 (0.10–0.15)	Santa Clara Co, CA	[414]
1979	765 drug positive-impaired driving 171 diazepam, 40 with EtOH; 56 chlordiazepoxide, 9 with EtOH; 14 & phenobarbital	California	[108]
1979	425 under influence (EtOH < 0.08 in 282) Drugs present in 115 cases; benzos in 90 (80 diazepam), 85 with EtOH	Northern Ireland	[415]
1981	71,937 impaired driving, but BAC ≤ 0.10% 684 benzos (571 dizepam), 310 with EtOH	Orange Co., CA	[416]
1984	56 impaired driving (saliva) 10 drug positive; 4 diazepam, 4 with EtOH	Ottawa, Canada	[417]
1987	184 impaired driving, negative with EtOH 30 benzo positive; 10 & barbiturates, 8 & opiates analgesics	St. Louis, MO	[109]
1991	1,398 mandatory railroad post-accident testing 85 drug positives; 2 benzos, 0 with EtOH	USA	[107]
1998	19,386 first road-traffic accidents Based on prescription data, use of benzos had a 1.52 risk factor (8.15 with EtOH) compared to 0.30 (1.0) with tricyclics and 0.51(0.89) with SSRIs.	Tayside region, UK	[418]
2000	486 impaired drivers study restricted to dextropropoxyphene or codeine-positive samples; 346 benzo	Sweden	[110]
2001	29 zolpidem positive-impaired drivers 4 benzo positive; 1 with EtOH	Washington	[111]
(C) Random testing			
1988	317 (88% compliance) random truck drivers 1 benzo positive with prescription	Tennessee	[105]
2002	822 (81% compliant) random track drivers no benzos identified	Oregon/ Washington	[106]

cases, (2) studies on impaired driving where in most studies only cases with ethanol below a certain cutoff were tested for drugs, and (3) random testing where participants volunteered for inclusion in the drug testing part of the study. These different protocols may have an impact on the drug findings.

In studies on driving fatalities, the presence of benzodiazepines ranged from 1.3 to 10.2%. Benzodiazepine positives were found in conjunction with ethanol in 25–78% of the cases. For impaired driving cases, the presence of benzodiazepines ranged from 1% to 30% with the additional finding of ethanol ranging from 22% to 100%. Studies that focused on professional transportation reported very low incidences of benzodiazepine use. In a study on 168 truck driver fatalities, no benzodiazepines were detected [104]. In the two random studies, only commercial truck drivers were included. In one study, only 1 of 317 participants (88% compliance) was benzodiazepine positive and had a prescription for its use [105]. In the other study, none of the 822 (81% compliance) participants were positive for benzodiazepines [106]. In 1,398 mandatory postaccident cases studied for the Federal Railroad Association, only two benzodiazepine-positive cases were detected, one with prescription for its use [107]. Benzodiazepine use in vehicle-related investigations varies widely. This may be due in part to geographic and temporal differences in the studies. In seven of the ten studies that did not include commercial drivers, ethanol was a cofactor in greater than 50% of the cases.

Benzodiazepine positive findings along with other drugs were not always described in these studies. In a study of impaired drivers in California published in 1979, 14 of the 56 cases positive for chlordiazepoxide also had phenobarbital [108]. In a study of ethanol-negative impaired drivers in St. Louis published in 1987, 10 and 8 of the 30 benzodiazepine-positive cases were also positive for barbiturates or opiate analgesics, respectively [109]. Two studies focused on cases positive for a specific drug(s). In a study in Sweden published in 2000 of 486 impaired drivers that had tested positive for codeine or dextropropoxyphene, 346 were also positive for a benzodiazepine [110]. In a study from Washington state published in 2001, 4 of 29 zolpidem-positive cases were also positive for benzodiazepines [111]. As with mixtures of benzodiazepines with ethanol, their mixture with other CNS depressant drugs is common in vehicle-irregularity related studies.

Clinical Studies on Drug Interactions of Benzodiazepines with Other CNS Depressants (See Appendix 2.1)

Pharmacodynamic and Pharmacokinetic Interactions with Analgesics and Anesthetics

Clinical studies on drug interactions between benzodiazepines and opioids, or other CNS depressants, have been mostly limited to interactions between the two benzodiazepines used as anesthetics, diazepam and midazolam, and other anesthetic or analgesic agents (Tables 2.14 and 2.15). One exception is a study on the effect of

Table 2.14 Effect of analgesics and anesthetics on benzodiazepine pharmacodynamics

Benzodiazepine	Dose	Agent dose	Agent time	N	Reference
Methadone					
Diazepam	20 and 40, or	100 and 150% maintenance	0 h	5m	[112]
	40 mg diazepam and 150% maintenance dose induced changes in pupil constriction and subjective opioid effects greater those by either drug alone				
Papaveretum					
Midazolam	0.15–0.5/kg, iv	15–20 mg, im	0 h	37/29	[115]
	Sedative effect of midazolam was potentiated by opiate				
Pethidine					
Midazolam	0.15–0.5/kg, iv	50–75 mg, im	0 h	47/29	[115]
	Sedative effect of midazolam was potentiated by opiate				
Diazepam	10, iv	50–75 mg	0 h	50/50	[116]
	No difference in sedation noted, but patients more comfortable with procedure				
Morphine					
Midazolam	0.01–0.03/kg, iv	0.006–0.12 mg/kg, iv	–10 min	5/dose	[117]
	Dose response: additive effect on visual analog determination of sedation				
Fentanyl					
Diazepam	0–0.5/kg, iv	50 μg/kg	+4 min	5/dose	[119]
	Dose response of diazepam caused significant reduction in arterial pressure and systemic vascular resistance associated with decreases in (nor)epinephrine				
Midazolam	≈0.35/kg, iv	50 μg, iv	–1 min	30/44	[118]
	Combination caused greater respiratory depression than midazolam alone				
Midazolam	0.3/kg, iv	50 or 100 μg, iv	–2 min	52/100	[120]
	Fentanyl decreased onset time for midazolam anesthesia and % asleep at 3 min				
Midazolam	0.05/kg, iv	2 μg/kg, iv	0 h	12m	[121]
	Synergistic increase in apnea and hypoxemia, no further reduction in fentanyl-reduction of ventilatory response to CO_2				
Midazolam	0.02–0.37 /kg, iv	1.9–8.5 μg/kg, iv	+1 min	10f/dose	[122]
	Synergistic increase in inability to open eyes in response to command (anesthesia)				
Alfentanyl					
Diazepam	0.125 /kg, iv	100 or 200 μg/kg, iv	+5 min	10/dose	[123]
	Diazepam reduced the numbers responding to voice at 5 min (10 to 1, 5 to 1), increased heart rate, increased reductions in blood pressure, and increased number (1–5) with inadequate postoperative ventilation.				
Midazolam	0.3/kg, iv	150 or 300 μg, iv	–2 min	40/100	[120]
	Alfentanyl decreased onset time for midazolam anesthesia and % asleep at 3 min				
Midazolam	0.07–0.35/kg, iv	0.02–0.18 mg/kg, iv	+1 min	5/dose	[124]
	Dose response found synergistic response of response to verbal command (sedation)				
Midazolam	0.023–0.2/kg, iv	0.016–0.15 mg/kg, iv	0 h	10/dose	[125]
	Dose response, response to verbal command (hypnosis) and response to tetanic stimulus (anesthesia) are synergistically enhanced				
Naltrexone					
Diazepam	10, or	50 mg	–1.5 h	8f, 18m	[132]
	Negative mood states (sedation, fatigue) were increased and positive mood states (friendliness, feeling high) were decreased by naltrexone				

(continued)

Table 2.14 (continued)

Benzodiazepine	Dose	Agent dose	Agent time	N	Reference
Propofol					
Midazolam	0.1–0.2/kg, iv	0.7–2.5 mg/kg, iv	0 h	10/dose	[135]
	Dose response: response to command was synergistically influenced; midazolam reduced dose of propofol required for response to tetanic stimuli				
Midazolam	0.1–0.4/kg, iv	0.4–2.8 mg/kg, iv	+2 min	10/dose	[136]
	Dose response: response to command was synergistically influenced				
Thiopental					
Midazolam	0.03–0.37/kg, iv	0.7–3.6 mg/kg, iv	+1 min	5/dose	[133]
	Dose response: response to command was synergistically influenced				
Midazolam	0.04–0.2/kg, iv	0.7–4.5 mg/kg, iv	+2.5 min	20/dose	[134]
	Dose response: response to command was synergistically influenced; midazolam reduced dose of thipopental required for response to electrical stimuli				

Table 2.15 Effect of opioids, other analgesics, and anesthetics on the pharmacokinetics of benzodiazepines

Benzodiazepine	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	Reference
Methadone	100% of maintenance dose							
Diazepam	20, or	5m				0.95		[113]
Diazepam	40, or	5m				0.91		[113]
Methadone	150% of maintenance dose							
Diazepam	20, or	5m				1.28		[113]
Diazepam	40, or	5m				1.24		[113]
Propoxyphene	65 mg, or 4/d, multidose							
Alprazolam	1, or	6f, 2m	3.46	0.94	1.58*		0.62*	[114]
Diazepam	10, iv	2f, 4m			1.14		0.87	[114]
Lorazepam	2, iv	1f, 4m			0.99		1.10	[114]
Fentanyl	Patients undergoing orthopedic surgery ± 200 μg, iv							
Midazolam	0.2/kg, iv	15/15			1.49*	1.54*	0.70*	[126]
Naltrexone	50 mg at –1.5 h							
Diazepam	10, or	8f, 18m	1.80*	0.93	1.05*	0.95		[132]
Propofol	Patients undergoing elective surgery ± 2 mg/kg bolus, 9 mg/kg/h infusion							
Midazolam	0.2/kg, iv	12/12			1.61*	1.58*	0.63*	[137]

diazepam on methadone maintenance. In an initial paper, Preston et al. demonstrated that a combination of diazepam and methadone produced subjective opioid effects greater than either drug alone [112] (Table 2.14). In a follow-up report, these investigators studied the effect of methadone on the pharmacokinetics of diazepam. Although not significant, a combination of 150% of the maintenance dose of methadone with either 20 or 40 mg oral diazepam resulted in a approximately 25% increase in the area under the curve (AUC) of diazepam [113] (Table 2.15).

Propoxyphene is an extensively used analgesic; its coadministration with benzodiazepines would not be uncommon. In a single study, subjects took three different benzodiazepines, oral alprazolam and intravenous diazepam and lorazepam, each one twice. In one setting no other drug was taken, in the other, propoxyphene was

administered every 6 h from 12 h prior to the benzodiazepine for the duration of the study [114]. Coadministration of propoxyphene significantly inhibited the elimination of propoxyphene, there was a slight, but nonsignificant inhibition of diazepam, and no effect on the pharmacokinetics of lorazepam (Table 2.15). No information was found on the in vitro inhibition of P450s by propoxyphene, but these data would support an inhibitory effect of propoxyphene on P450 3A4 that spares P450 2C19. No data were presented on the effect of propoxyphene on the pharmacodynamics of benzodiazepines.

When midazolam or diazepam is combined with the opioids papaveretum, pethidine, or morphine during anesthesia, potentiation of the sedative or subjective effects is consistently found [115–117] (Table 2.14). Pharmacokinetic interactions between these drugs were not studied.

The combination of midazolam or diazepam with fentanyl has also been consistently found to result in potentiation of the sedative and in some cases respiratory depressant effects of the drugs [118–122]. In the latter two studies, which used midazolam, statistic evaluation of dose-responses suggested that the drugs interacted in a synergistic manner [121, 122]. A similar finding was found for combined use of diazepam or midazolam with alfentanil, including the synergistic response with midazolam [120, 123–125] (Table 2.14). With fentanyl it has been shown its combination with midazolam results in a significant increases in the terminal elimination half-life ($t_{1/2}$) and AUC and significant decrease in the clearance of midazolam [126] (Table 2.15). A similar pharmacokinetic study has not been done with alfentanil, but both are P450 3A4 substrates [127–130] and may have similar potential to inhibit midazolam metabolism, as has been found in vitro for fentanyl [131].

The interaction between naltrexone, an opioid μ receptor antagonist, and diazepam is another exception to the studies between anesthetics. Naltrexone was found to increase the negative mood states such as sedation, and decrease the positive mood effects such as friendliness of diazepam (Table 2.14), with no effect on its pharmacokinetics (Table 2.15) [132].

The interaction of the structurally unique anesthetic propofol or the barbiturate thiopental with midazolam has also been reported to have synergistic effects on the sedative effects of the drugs (Table 2.14) [133–136]. A pharmacokinetic study has been performed on the interaction of midazolam and propofol, and propofol was found to significantly increase the $t_{1/2}$ and AUC of midazolam (Table 2.15) [137]. This is consistent with the in vitro inhibition of midazolam metabolism by propofol [138].

Clinical studies confirm that additive interactions occur between the opioids and other anesthetic agents. These have sometimes been found to be synergistic in their response. The synergistic response appears to occur when there is also a pharmacokinetic interaction resulting in the inhibition of the benzodiazepines' clearance.

Pharmacodynamic and Pharmacokinetic Interactions with Ethanol

The effect of combined use of ethanol on pharmacodynamic endpoints has been studied with a large number of benzodiazepines (Table 2.16). In general, ethanol has a potentiating effect on some of the psychomotor and subjective measures, but rarely

Table 2.16 Effect of ethanol on benzodiazepine pharmacodynamics

Benzodiazepine	Dose (mg)	Ethanol dose	Ethanol time	N	Reference
Alprazolam	0.5, or	0.8 g/kg	+3 h	10m	[145]
	No effect on measures of side effects, tracking skills, angle recognition, or free recall; diminished choice reaction time				
Alprazolam	2, or	0.8 g/kg	+3 h	10m	[145]
	No effect on measures of side effects, tracking skills, angle recognition, or free recall; diminished choice reaction time				
Alprazolam	1, or	0.5 g/kg,	+ 0.75 h	12/12	[139]
	Produced predictive additive effects on sedation, unsteadiness, dizziness, tiredness, and psychomotor performance				
Bromazepam	6, or 3/d × 14d	0.5 g/kg	0 h	20m	[419]
	Enhanced impairment of learning skills, but not short-term memory				
Bromazepam	6, or 3/d ×14d	0.5 g/kg	0 h	1f, 16m	[142]
	No effect on reaction time or mistakes; enhanced effects on coordination skills, attention, and proprioception				
Brotizolam	0.25, or	24 mL	0 h	13m	[150]
	Subjective perceptions of sedation were enhanced, but psychomotor performance was not				
Chlordiazepoxide	5, or 3/d ×2d	45 mL		6f, 12m	[420]
	Subjects were tested on mental and then psychomotor performance starting at +1 h. No significant difference ± ethanol				
Chlordiazepoxide lactam	10, or 3/d × 14d	0.5 g/kg	0 h	20	[144]
	No effect on reaction time; enhanced coordination mistakes at fixed and free speed and impairment of attention and proprioception				
Clobazam	20, or	77 g	0–1.5 h	8m	[140]
	Enhanced impairment of reaction errors and time, deviations of two-hand coordination and body sway				
Clorazepate	20, or	1 g/kg		14m	[421]
	Enhance alcohol acute euphoric effects and decreased dysphoric effects in the following morning				
Diazepam	5, or 3/d × 3d	42 mL	0 h	20	[422]
	Measured ability for cancellation of letters, digit substitution, addition, and pegboard placement beginning at +75 min. Performance under diazepam, ± EtOH, was slightly poorer than with placebo tablet				
Diazepam	2, or 3/d ×2d	45 mL		6f, 12m	[420]
	Subjects were tested on mental and then psychomotor performance starting at +1 h. Ethanol enhanced the effects on two of nine mental tests; no effect on psychomotor tests				
Diazepam	10, or/70 kg	0.75 mL/70 kg	0 h	8m	[159]
	Starting at +90 min, no effect on mirror tracing; slight enhancement of attention and time evaluation; significant with attempted letter cancellations, sorting, flicker fusion, complex coordination, and clinical symptoms				
Diazepam	10, or	0.5 g/kg		10/10	[146]
	Simulated driving by professional drivers from +30–70 min. Enhanced number of collisions and driving off the road instances				
Diazepam	10, 20 or 40, or	0.5 g/kg	0 h	6m	[423]
	Markedly enhanced the effects on coordination and mood				

(continued)

Table 2.16 (continued)

Benzodiazepine	Dose (mg)	Ethanol dose	Ethanol time	N	Reference
Diazepam	10, or	0.8 g/kg	–0.5 h	10	[157]
	Enhanced impairment of tracking skills and oculomotor coordination; enhanced nystagmus				
Diazepam	10, iv	at 0.8–1.0 g/L	−1 to 8 h	6m	[158]
	Enhanced impairment of pursuit rotor performance and intoxication indices and visual analog scale				
Diazepam	10, or/d × 2d	0.8 g/kg		12m	[141]
	Enhanced impairment on coordination, reaction, flicker fusion, Maddox wing and attention tests				
Diazepam	10, or	at 0.5 g/L	−1.5–+2.5 h	12m	[424]
	Produced additive effects on subjective alertness and measures of performance; synergistic effect on smooth pursuit eye movements				
Diazepam	5, or	at 0.5 g/L	−1.5 to +4 h	8m	[425]
	Produced additive effects on adaptive tracking, smooth pursuit, DSST, and body sway; did see supra-additive effects in two subjects				
Diazepam	10, or	0.8 g/kg	+3 h	10m	[145]
	No effect on measures of side effects, tracking skills, choice reaction time, angle recognition, or free recall				
Flunitrazepam	2, or	0.8 g/kg	–0.5 h	12m	[154]
	Alcohol did not effect impairment of tracking skills at =1 h, but did enhance impairment the following morning				
Flurazepam	30, or/d × 14d	0.5 g/kg	+10 h	7f, 33m	[426]
	No effect on reaction time or mistakes or attention; enhanced effects on coordination skills				
Loprazolam	1, or	0.7 g/kg	0 h	8m	[143]
	No effects on simple reaction time; alleviated lop-impairment of manual dexterity; both alone impaired tracking, but not together; memory impaired by lop, improved by EtOH, not effected together				
Oxazepam	10, 20 or 40, or	0.5 g/kg	0 h	6m	[423]
	Slightly enhanced the effects on coordination and mood				
Oxazepam	15, or 3/d × 14d	0.5 g/kg	0 h	20	[144]
	No effect on reaction time, attention or proprioception; enhanced coordination mistakes at fixed and free speed				
Midazolam	0.1/kg, iv	0.7 g/kg	+4 h	16m	[427]
	Midazolam did not add to the +5 h or +7 h effects of EtOH				
Nitrazepam	10, or/d × 14d	0.5 g/kg	+10 h	3f, 17m	[428]
	No effect on reaction times; enhanced choice reaction and coordination mistakes and impaired attention				
Nordiazepam	5, or 3/d × 14d	0.5 g/kg	0 h	20	[144]
	No effect on reaction time, attention, or proprioception; enhanced coordination mistakes at fixed speed, no effect at free speed				
Prazepam	20, or	05 g/kg	0 h	12m	[155]
	Enhanced impairment in auditory reaction and DSST; reduced reaction to auditory stimuli and cancellation test and enhanced drowsiness				
Temazepam	20, or 3/d × 14d	0.5 g/kg	0 h	20	[144]
	No effect on reaction time or attention; enhanced coordination mistakes at fixed speed, but not at free speed; enhanced impairment of proprioception				

(continued)

Table 2.16 (continued)

Benzodiazepine	Dose (mg)	Ethanol dose	Ethanol time	N	Reference
Tofisopam	100, or×3	0.8 g/kg		12m	[141]
	Enhanced impairment on coordination, reaction, flicker fusion, Maddox wing and attention tests				
Triazolam	0.25, or	at 0.8–0.95 g/L	–0.5 to 7.5 h	1f, 6m	[152]
	Enhanced impairment of free recall, postural stability, and hand–eye coordination				

affects all such measures in any one study. In part because the studies were not designed to detect it, synergistic effects were not noted. Because of the diverse endpoints in the studies there was no apparent general set of pharmacodynamic endpoints that ethanol consistently had an effect upon. For example, reaction time was a common endpoint. Ethanol was reported as enhancing impairment of reaction time for alprazolam [139], clobazam [140], diazepam [141], and tofisopam [141], while it had no effect on reaction time with bromazepam [142], loprazolam [143], oxazepam [144], nordiazepam [144], and temazepam [144]. Few of the studies compared benzodiazepines under the same conditions. It is therefore difficult to draw conclusions about some benzodiazepines being more susceptible to the interactive effects with ethanol.

The timing of the administration of ethanol was an important factor. When ethanol was given 3 h after alprazolam, only minimal effects were found [145]. When ethanol was given only 45 min after alprazolam, however, it had additive effects on most of the endpoints measured [139]. Similarly, combining ethanol with diazepam at the same time leads to enhanced impairment of reaction time [141], while giving the ethanol 3 h after diazepam did not [145].

Ethanol therefore does appear to enhance the impairing effects of benzodiazepines in an additive fashion. In the one study that measured driving skills, diazepam and ethanol were taken together and the stimulated driving of professional drivers was studied. The combined use of ethanol and diazepam resulted in increased numbers of collisions and driving off the road instances [146].

Ethanol is known to affect the metabolism of many drugs. In general, acute use of ethanol is associated with the inhibition of drug metabolism; chronic use induces metabolism [147, 148]. While induction appears to be predominantly for compounds metabolized by P450 2E1, studies in primary cultured hepatocytes show ethanol can also induce P4540 3A4 [149]. Therefore, examination of the effect of ethanol on benzodiazepine pharmacokinetics should differentiate between studies on acute exposure in nonalcoholics (Table 2.17) and studies in alcoholics (Table 2.18).

Acute exposure to ethanol was found to inhibit the clearance of a number of benzodiazepines as seen from increased C_{max}s, $t_{1/2}$s, AUCs, and/or decreased clearance. Thus is the case for brotizolam [150], chlordiazepoxide [151], clobazam [140], and triazolam [152]. With some benzodiazepines, however, ethanol did not have any effect on their pharmacokinetics; these include alprazolam [145],

Table 2.17 Effect of ethanol on the pharmacokinetics of benzodiazepines in nonalcoholics

Benzodiazepine	Dose	EtOH dose	EtOH time	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	Reference
Alprazolam	0.5, or	0.8 g/kg	+3 h	10m			No change			[145]
Alprazolam	2, or	0.8 g/kg,	+3 h	10m			No change			[145]
Brotizolam	0.25, or	24 mL	0 h	13m	0.95	1.23*	1.18*		0.84*	[150]
Chlordiazepoxide	25, or	0.8 g/kg	0 h	5m	1.67	1.48*				[151]
Clobazam	20, or	39 g		8m	1.00	1.59*		1.55*		[140]
Clotiazepam	5, or	24 mL	0 h	11			1.21		0.93	[153]
Diazepam	10, or	0.8 g/kg	0 h	5m	1.25	1.03				[151]
Diazepam	0.14/kg, or	0.75 mL/kg	0 h	8m	3.0	1.19				[159]
Diazepam	0.07/kg, iv	15 mL	0 h	1f, 6m	1.42	1.58*				[156]
Diazepam	5, or	17 mL	0 h	2f, 4m	2.27	0.94		1.00		[160]
Diazepam	10, or	0.8 g/kg (b)	–0.5 h	10	0.38	1.58*		1.15		[157]
Diazepam	10, or	0.8 g/kg (wh)	–0.5 h	10	0.50	1.16		1.07		[157]
Diazepam	10, or	0.8 g/kg (wi)	–0.5 h	10	1.00	1.57*		1.21*		[157]
Diazepam	10, iv	at 0.8–1.0 g/L	−1–8 h	6m				1.31		[158]
Diazepam	5, or	24 mL	–0.5 h	2f, 4m	3.94	0.84	1.23	1.04		[161]
N-desmethyl					1.00	1.10		1.00		
Diazepam	5, or	24 mL	0 h	2f, 4m	2.11	0.87	1.21	1.07		[161]
N-desmethyl					1.12	1.00		0.94		
Diazepam	10, or	0.8 g/kg	+3 h	10m		≈ 35% higher				[145]
Diazepam	10, or	at 0.5 g/L	−1.5–+2.5 h	12m	1.23	1.15		1.12		[424]
Flunitrazepam	2, or	0.8 g/kg	–0.5 h	12m	0.98	1.02	0.81	1.05		[154]
Prazepam	20, or	05.g/kg	0 h	12m	0.83	1.09		0.92		[155]
Triazolam	0.25, or	at 0.8–0.95 g/L	–0.5–7.5 h	1f, 6m		1.08	1.22*	0.84*		[152]

Table 2.18 Effect of ethanol on the pharmacokinetics of benzodiazepines in chronic alcoholics

Benzodiazepine	Dose	Condition	N	T_{max}	C_{max}	$t_{1/2}$	AUC Cl	Reference
Chlordiazepoxide	50, or	Acute vs. 7d abst	5	1.87	1.01	1.52	2.35	[163]
N-desmethyl					2.60	0.71		
Chlordiazepoxide	50, im	Acute vs. 7d abst	5	2.41	1.94	1.85	3.35	[163]
N-desmethyl					1.70	1.02		
Chlordiazepoxide	25, or (md)	2 vs. 6d abst	6		2.1ss*			[164]
N-desmethyl						1.91ss*		
Demoxepam						0.15ss*		
Diazepam	10, or	1–11d abst	11/14	1.00	0.43*			[165]
Diazepam	10, iv	1–3d abst	14/13				0.71*	[166]
N-desmethyl							0.65*	
Diazepam	6	1d vs 6d abst	7			0.83	0.67	[167]

clotiazepam [153], flunitrazepam [154], and prazepam [155] (Table 2.17). For the latter studies, either the 3-h interval between alprazolam and ethanol administration, or the ability of non-P450-dependent pathways to metabolize flunitrazepam may explain the negative findings. Such is not the case, however, for clotiazepam and prazepam, which requires P450 for either hydroxylation or N-dealkylation reactions. For these two benzodiazepines the effect was not significant, but could be considered suggestive of impaired elimination. Diazepam interactions with ethanol were the subject of numerous studies that showed varying results. An inhibition of clearance was reported in some studies [156–158], while only a prolongation of the C_{max} was found in some studies [151, 159–161]. In general, the former studies administered ethanol 30–60 min prior to diazepam, while the latter administered the two drugs at the same time.

The results from these clinical studies indicate that acute ethanol, taking either with or shortly before, may interfere with the elimination of many, but not all benzodiazepines. While this would appear to arise from the inhibition of P450-dependent metabolism of the benzodiazepines, some inconsistencies exist. A single study was found on the in vitro inhibition of different forms of human liver P450s [162]. At concentrations close to 0.10 g/100 mL, only P450s 2C19 and 2D6 were partially inhibited. Cytochrome P450 3A4, which is associated with the metabolism of many benzodiazepines, was fairly resistant to the inhibitory effects of ethanol for the marker substrate studied (Fig. 2.10) [162]. Due to the complex nature of the P450 3A4 substrate binding site(s), however, it has become apparent that some substrates may show different responses to inhibitors.

The study of benzodiazepine pharmacokinetics in chronic alcoholics entering treatment programs has been used to support the theory that chronic ethanol induces the metabolism of benzodiazepines [84]. The studies were designed in two ways (Table 2.18). Either a comparison within the subjects at 1–2 days after initiation of treatment versus 6–7 days later, or comparison of the subjects to control subjects. With the former design, administration of oral, intramuscular, or intravenous chlordiazepoxide had longer $t_{1/2}$s of higher steady-state concentrations at the beginning of the

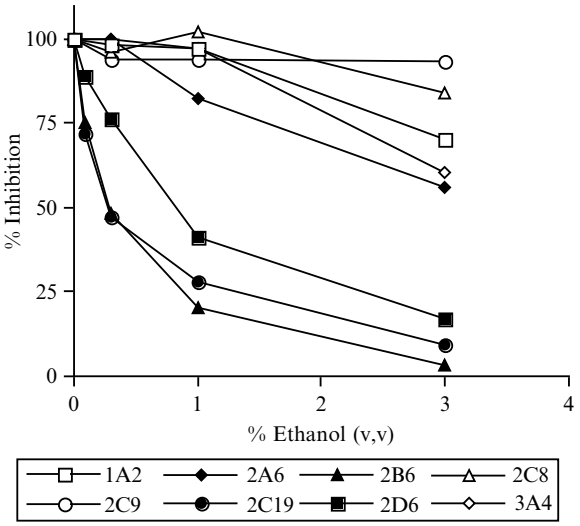

Fig. 2.10 The effect of ethanol on the in vitro metabolism of cDNA-expressed P450s. Adapted from data presented by Busby et al. [162]. Note experiments were designed to test ethanol as a solvent for addition of substrates. The two lower concentrations, 0.1 and 0.3% (v,v), would equate to 0.0789 and 0.237 g/100 mL, respectively

study [163, 164]. It was suggested that these results arose from an initial inhibition of chlordiazepoxide from residual ethanol in the first session with unmasking of an induced state in the later session [84]. This is supported by studies on diazepam where abstinent alcoholics were compared to nonalcoholic controls (Table 2.17). With oral or intravenous administration of diazepam, elimination was greater in the alcoholics [165, 166]. One study was contradictory. When seven subjects entering a detoxification ward were given intravenous diazepam on day one and again 4–20 days later, the $t_{1/2}$ and clearance were higher in the latter session, but not significantly due to large intra-subject variations [167]. An inductive effect of ethanol pretreatment on the metabolism of diazepam was also found in rats [166]. A rationale for this inductive effect was found from a report that ethanol induces P450 3A, as well as 2E, in cultured human hepatocytes [149].

The Interaction Between Benzodiazepines and Other Drugs

With most of the other drugs for which interactions have been described with the benzodiazepines they are dependent upon whether the benzodiazepine is metabolized by P450. For this reason, in the applicable subsections some time has been spent to summarize the P450 inhibitory or inductive activity of the class of drugs being discussed. This will generally take the course of examining the in vitro potency of the drugs as inhibitors.

Benzodiazepines and Gastrointestinal Agents

Benzodiazepines, Antacids, and Miscellaneous Gastrointestinal Agents

Benzodiazepines have an acidic pKa, and changes in the pH of the gastrointestinal tract may influence their rate of absorption. Some of the earliest drug interactions studies focused on the effect of antacids on the pharmacokinetics of benzodiazepines (Table 2.19). In 1976, Nair et al. [168] gave 10 mg oral diazepam alone or in combination with aluminum hydroxide, magnesium trisilicate, or sodium citrate to 200 woman undergoing minor gynecological procedures. Aluminum hydroxide and sodium citrate were reported to hasten the onset of the soporific effect of diazepam, with no apparent effect on its pharmacokinetics. Magnesium trisilicate was found to delay the effect; it also prolonged the T_{max} and decreased the C_{max} (Table 2.19). In contrast to Nair et al. [168] findings with magnesium trisilicate and diazepam, Elliot et al. [169] found no effect on the pharmacokinetics of temazepam or midazolam (Table 2.19).

The mixture of aluminum and magnesium hydroxides (Maalox) were found to prolong the T_{max} and decrease the C_{max} for chlordiazepoxide [170], clorazepate [171, 172], and diazepam [173]. The mixture of aluminum hydroxide and magnesium trisilicate (Gelusil) had a similar effect on diazepam [173]. In one of the studies on clorazepate and Maalox, this was found associated with reduced pharmacodynamic effects [172]. For clorazepate, not only is the absorption of the drug dependent upon pH, but so is its conversion to nordiazepam. Abruzzo et al. [174] showed that maintenance of the stomach pH at 6 with sodium bicarbonate greatly prolonged and reduced the peak of plasma nordiazepam from clorazepate. After multidose treatment with both clorazepate and Maalox, however, steady-state concentrations of the metabolite nordiazepam were not affected [175], which suggests that antacids will have no effect under multidosing schemes.

Aluminum hydroxides are also taken by patients on dialysis to bind dietary phosphates. Kroboth et al. [176] found this treatment had no effect on the absorption of temazepam. In another study, however, they found the elimination of triazolam was reduced in dialysis patients taking aluminum hydroxide [177]. The renal disease enhanced elimination of triazolam, so the net effect of aluminum hydroxide was to return the pharmacokinetic parameters toward those noted in matched controls [177] (Table 2.19).

Misoprostol is a novel synthetic prostaglandin E1 analog with antisecretory properties. When misoprostol was given in combination with oral diazepam it did not have any effect on diazepam pharmacokinetics [178]. Cisapride increases gastric motility. Intravenous cisapride was found to enhance the absorption of oral diazepam with consequent increased impairment in early (45 min) tests on reaction time [179].

Table 2.19 Drug interactions with antacids and miscellaneous gastrointestinal agents

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Antacids									
AlOH	40 mL								
Diazepam	10, or	20/17	1.00	0.94				+	[168]
MgOH/AlOH	30 mL×2, 100 mL (chlor)								
Chlordiazepoxide	25, or	10m	2.13	0.93	1.03	0.97			[170]
Clorazepate	15, or	15m	2.00	0.80*	0.96	0.94			[171]
Clorazepate*	15, or	5f, 5m	1.56*	0.69*		0.90*		+	[172]
Diazepam	5, or	9	1.40	0.66*		0.98			[173]
MgOH/AlOH	30 mL, multidose								
Clorazepate	7.5, or (md)	4f, 6m		0.95ss					[175]
Mg trisilicate/AlOH	30 mL×2								
Diazepam	5, or	9	1.30	0.74*		0.96			[173]
Mg trisilicate	30 mL								
Diazepam	10, or	15/17	1.50	0.78				+	[168]
Midazolam	15, or	5m	0.86	1.13	1.23	1.37	0.86		[169]
Temazepam	20, or	1f, 4m	0.95	1.04	0.93	1.00	1.00		[169]
Sodium citrate	9 µmol at 0 h								
Diazepam	10, or	15/17	1.00	0.91				+	[168]
Sodium bicarbonate	enough to maintain pH 6 for 2 h								
Clorazepate	15, or	4m	1.11	0.81					[174]
N-desmethyl			14.0*	0.28*		0.55*			
AlOH gel	3,600 mg pretreatment in dialysis patients								
Temazepam	30, or	11	1.30	1.00	1.13	1.08*		0	[176]
Triazolam	0.5, or	11	0.93	1.58*	0.99	1.28*	0.74*		[177]
Other Gastrointestinal agents									
Misoprostol	200 µg, 4/d, oral multidose								
Diazepam	10, or/d (md)	6m		1.02	1.01	1.03		0	[178]
N-desmethyl				1.00	0.89	1.00			
Cisapride	8 mg, iv at -8 min								
Diazepam	10, or	8	0.72*	1.18*		0.92		++ (early)	[179]

Interactions with H_2-Receptor Antagonists

The H_2-receptor antagonists are widely used for treatment of gastrointestinal ulcers. Cimetidine was the first H_2-receptor antagonist and was followed by ranitidine, famotidine, oxmetidine, nizatidine, and ebrotidine. Among these drugs, cimetidine is well known to cause drug–drug interactions with a number of drugs due to its inhibitory effects on several P450s [180, 181]. The other H_2-receptor antagonists are relatively mild inhibitors. Knodell et al. [182] studied the effect of cimetidine on a number of P450-selective activities and found inhibition was greatest for 2D6>2C19>3A4, 2E1>2C9, 1A2 (Fig. 2.11). Martinez et al. [183] directly compared the in vitro effects of cimetidine, ranitidine, and ebrotidine on a number of P450-selective activities (Fig. 2.11). In brief, cimetidine was found to have significant

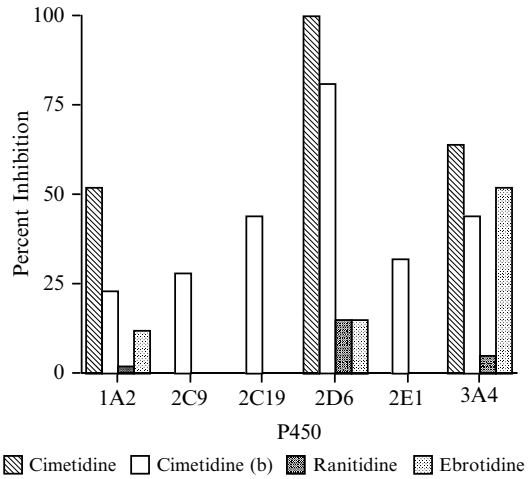

Fig. 2.11 A summary of in vitro experiments on the inhibition of P450-selective substrates in (HLM) with H_2-receptor antagonists. The data on cimetidine (b) is from Knodell et al. [182], where the markers reactions were: *1A2* ethoxyresorufine deethylase, *2C9* tobultamide hydroxylase, *2C19* hexobarbital hydroxylase, *2D6* bufuralol hydroxylase, *2E1* aniline hydroxylase, *3A4* an average of responses of nifedipine oxidase and erythromycin demethylase. The other data are from Martinez et al. [183], where the marker reactions are: *1A2* caffeine N-demethylation to paraxanthine, *2D6* dextromethorphan O-demethylation, and *3A4* dextromethorphan N-demethylation

inhibitory effects on P450 2D6 > 1A2 and 3A4. Ranitidine and ebrotidine had some, but relatively less inhibitory effects on these P450s.

Klotz et al. [184] compared the spectral dissociation constants of the H_2-receptor antagonists with (HLM) and determined the following K_s values: oxmetidine, 0.2 mM; cimetidine, 0.87 mM; ranitidine, 5.1 mM; famotidine and nizatidine, no effect up to 4 mM. In another in vitro comparison of the effect of cimetidine and nizatidine on the 1′-hydroxylation of midazolam in (HLM), Wrighton and Ring [39] determined K_is of 268 and 2,860 μM, respectively. For comparative purposes, the K_is of ketoconazole and nifidipine were 0.11 and 22 μM. With the exception of oxmetidine, for which only a single clinical study was performed, these in vitro findings will favorably describe the interactions seen between the H_2-receptor antagonists and benzodiazepines that rely upon P450-mediated metabolism for their elimination.

Coadministration of multiple doses of cimetidine has been found to diminish the elimination of a number of benzodiazepines (Table 2.20), that include: adinazolam [185], alprazolam [186, 187], bromazepam [188], chlordiazepoxide [189], clobazam [190], clorazepate [191], diazepam [178, 192–197], flurazepam [198], midazolam [169, 199], nitrazepam [200], nordiazepam [201], and triazolam [186, 187, 202]. Single doses of cimetidine seem to have milder effect, but have been found to diminish the elimination of diazepam [203] and midazolam [183, 204, 205] in a dose-dependent fashion (Table 2.20). In all studies, but one,

Table 2.20 Drug interactions with H_2-receptor antagonists

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Cimetidine	800–1,000 mg/d in divided doses, multidose								
Adinazolam	20/d, or (md)	6f, 6m	1.33	1.39*	1.08	1.45*	0.67*	++	[185]
N-desmethyl			1.44	1.19	1.08	1.43*			
Adinazolam	40/d, or (md)	6f, 6m	1.09	1.21*	1.18	1.44*	0.73*	++	[185]
N-desmethyl			1.00	1.25*	0.95	1.27*			
Adinazolam	60/d, or (md)	6f, 6m	1.06	1.26*	1.35*	1.36*	0.75*	++	[185]
N-desmethyl			1.25	1.25*	1.00	1.32*			
Alprazolam	1, or	9	1.00	1.03	1.34*		0.63*		[186]
Alprazolam	0.5, 3/d (md)	4f, 4m	0.90	1.85*	1.16	1.73*	0.59*		[187]
Bromazepam	6, or	26f, 6m	1.91	1.22	1.26*		0.50*		[188]
Chlordiazepoxide	0.6/kg, iv	4f, 4m			2.36*		0.37*		[189]
Clobazam	30, or	9m	1.12	0.91	1.11*	1.17*			[429]
N-desmethyl			0.98	1.03		1.11			
Clobazam	30, or	6	0.59	1.16	1.39*	1.59			[190]
N-desmethyl			1.54	1.29*	1.90*	1.57*			
N-Desmethylclobazam	30, or	5	1.68	1.04	1.24*	1.37*			[190]
Clorazepate	15, or	3 young			1.62*		0.67*		[191]
Clorazepate	15, or	5 elderly			1.71*		0.53*		[191]
Clotiazepam	5, or	11			0.97		0.95		[153]
Diazepam	0.1/kg	2f, 4m			1.53*		0.57*	++	[192]
Diazepam	5, or (md)	6		1.38ss*	2.56*		0.67*		[193]
Diazepam	10, or	3f, 4m			1.33*	1.76*	0.50*	0	[194]
Diazepam	10, iv	8			1.47*		0.76*		[195]
Diazepam	5–30, or (md)	3f, 7m		1.39ss*				++	[196]
N-desmethyl				1.38ss*					
Diazepam	10, iv	11m			1.32*	1.20*	0.73*		[215]
N-desmethyl						1.19*			
Diazepam	0.1/kg, iv	12m			1.39*	1.53*	0.58*		[197]
N-desmethyl						0.81*			
Diazepam	10, or (md)	6m		1.57*	1.81*	1.83*			[178]
N-desmethyl				1.59*	1.49*	1.59*			
Flurazepam	30, or	6m	1.43	1.10	1.50*	1.46			[198]
Lorazepam	2, iv	4f, 4m			0.90		1.21		[206]
Lorazepam	2, iv	8			1.10		0.96		[195]
Lorazepam	2, or	6m	0.81	0.88	1.00	0.97			[198]
Midazolam	15, or	5m	0.72	2.38*	1.20	2.02*	0.52*		[169]
Midazolam	15, or	1f, 7m			1.07	1.35*			[199]
Midazolam	0.07/kg, iv	10m						+++	[430]
Nitrazepam	5–10, or	6m	0.81	1.00	1.25*		0.83*		[200]
Nordiazepam	20, or	2f, 3m			1.40*		0.72*	++	[201]
Oxazepam	50, or	2f, 3m			0.90		0.87	0	[201]
Oxazepam	45, or	2f, 2m			0.78		1.37		[206]
Oxazepam	30, or	4f, 4m	1.41	0.95	1.04	1.11*			[198]
Temazepam	20, or	1f, 4m	0.74	0.87	0.84	0.99	0.85		[169]

(continued)

Table 2.20 (continued)

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Temazepam	30, or	9	0.95	0.89	1.15		1.01		[207]
Triazolam	0.5, or	9	1.06	1.20	0.97	1.54*	0.66*		[186]
Triazolam	0.5, or (md)	2f, 6m	1.40	1.51*	1.68*	2.22*	0.45*		[187]
Triazolam	0.5, or	4m	1.06	1.51*	1.01	1.54*			[202]
Cimetidine	400 (mid b) 800 mg (mid a,c) oral, 200 (dia a, lor a) 400 iv (dia b, lor b) single dose								
Diazepam a	10, or	5/5	1.00	1.26					[203]
Diazepam b	10, or	5/5	0.50	1.34*					[203]
Lorazepam a	2.5, or	7/7	1.00	1.12					[203]
Lorazepam b	2.5, or	6/7	1.00	1.24					[203]
Midazolam a	0.025/kg/h	8m		1.26ss*				0	[204]
Midazolam b	15, or	6	0.81	1.37*	1.61	1.36*		+++	[205]
Midazolam c	7.5, or	8m			1.46*	1.50*	0.68*		[183]
Ranitidine	150 mg 2/d, oral multidose								
Diazepam	5, or (md)	6		0.74*	1.06		1.33*		[208]
Diazepam	0.1/kg, iv	4			1.04		1.04		[208]
Diazepam	10, iv	10m			0.89		0.93		[211]
Diazepam	10, iv	9			1.04		1.04		[212]
Lorazepam	2, iv	10m			0.97		1.09		[211]
Midazolam	15, or	5m		1.53*		1.66*		+	[209]
Midazolam	15, or	5m	0.93	1.52*	1.00	1.66*	0.59		[169]
Midazolam	10, or	32f/32f						++	[431]
Midazolam	15, or	1f, 7m			1.21*	1.23*			[199]
Midazolam	0.07/kg, iv	8/10						0	[430]
Temazepam	20, or	1f, 4m	1.10	0.95	1.20	1.15	0.85		[169]
Temazepam	20, or	20/20						0	[431]
Triazolam	0.25, or	12m	1.00	1.30	0.97	1.27*			[210]
Triazolam	0.25, iv	12m		0.79	1.01	0.99	1.01		[210]
Ranitidine	300 mg, oral, single dose								
Adinazolam	30, or	12m	0.86	1.03	1.00	0.99	1.01	0	[213]
N-desmethyl			0.75	1.01	1.07	1.02			
Midazolam	0.05/kg inf	8m		1.08ss					[204]
Midazolam	7.5, or	8m			1.29	1.32	0.82		[183]
Famotidine	40 mg 2/d, oral multidose								
Diazepam	0.1/kg, iv	8m			0.86		1.11	0	[214]
Diazepam	10, iv	11m			0.96	0.97	1.01		[215]
N-desmethyl						1.02			
Diazepam	10, iv	8			0.86		1.14		[212]
Oxmetidine	800 mg/d, oral multidose								
Diazepam	10, iv	8			1.12		0.94		[212]
Nizatidine	300 mg/d, oral multidose								
Diazepam	10, or	9			1.07		0.95		[212]
Ebrotidine	400 mg, oral								
Midazolam	7.5, or	8m			0.79	1.07	0.85		[183]

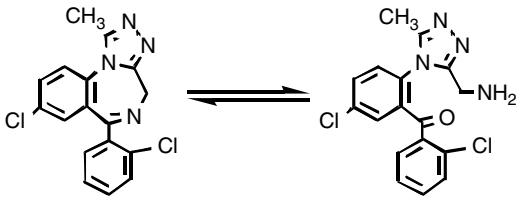

Fig. 2.12 The equilibrium reaction between triazolam and its benzophenone. Formation of the benzophenone is favored at pH < 4. As the benzophenone would not be absorbed as effectively as triazolam, it was postulated that agents that increase stomach pH would decrease the amount of the benzophenone and thereby increase the absorption of the benzodiazepine. While this conversion is useful for the gas chromatographic detection of many benzodiazepines, as explained in the text, it does not appear to impact drug interactions involving agents that change stomach pH

that monitored pharmacodynamic effects these were mildly diminished also (Table 2.20). Gough et al. [194] found inhibition of diazepam pharmacokinetics without any change in the monitored pharmacodynamic measures. Lorazepam [195, 198, 203, 206], and oxazepam [198, 201, 206], which are exclusively glucuronidated, and temazepam [169, 207], which can be glucuronidated without further metabolism, were resistant to the effects of cimetidine (Table 2.20). The outlier in this scheme is clotiazepam, which appears to require P450-dependent metabolism, but was unaffected by cimetidine. It was also resistant to inhibitory effects by ethanol [153].

Multidose ranitidine inhibited the elimination of oral diazepam [208], midazolam [169, 199, 209], and triazolam [210], but was ineffective against intravenous doses of these benzodiazepines [208, 210–212], intravenous lorazepam [211], and oral temazepam [169]. A single dose of ranitidine had no effect on oral adinazolam [213], oral midazolam [183], or infused midazolam [204]. Multidose famotidine [184, 214, 215], oxmetidine [184], and nizatidine [184] had no effect on the pharmacokinetics of intravenous diazepam. A single dose of ebrotidine had no effect on oral midazolam [183] (Table 2.20).

Vanderveen et al. [210] found that ranitidine diminished the elimination of oral, but not intravenous triazolam. They hypothesized that the increase in pH after ranitidine was responsible for the diminished elimination of oral triazolam. The basis of their hypothesis was that at acidic pH triazolam is in equilibrium with its more poorly absorbed benzophenone (Fig. 2.12). With increased pH, less benzophenone is formed, and more triazolam is absorbed [210]. The prior findings of Cox et al. [202], however, seem to dispute this hypothesis. They administered intraduodenal infusions of triazolam in solutions at pH 2.3, where 47% was the benzophenone, and pH 6.0, with negligible benzophenone, and found no difference in the pharmacokinetics. Ranitidine does appear to inhibit the metabolism of some benzodiazepines. This appears to be limited to first-pass metabolism within either the gastrointestinal tract or the liver.

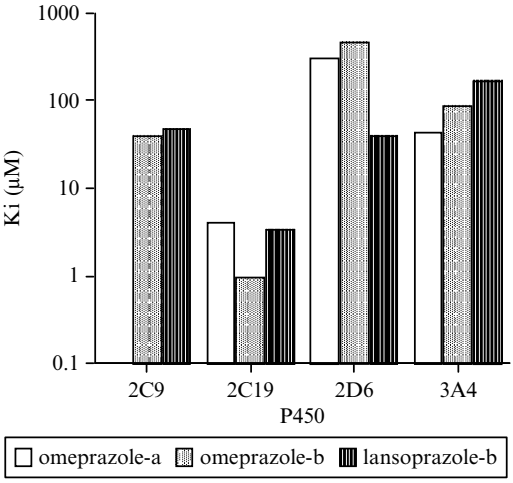

Fig. 2.13 Inhibition of P450-selective pathways in (HLM) by omeprazole and lansoprazole. Omeprazole-a is from [216], where the pathways for were: *2D6* bufuralol 1′-hydroxylation, *2C19*, 2C19, S-mephenytoin 4′-hydroxylation, and *3A4* midazolam 1′-hydroxylation. Omeprazone-b and lansoprazole-b are from [217], where the pathways were: *2D6* dextromethorphan O-demethylation, *2C9* tolbutamide 4-methylhydroxylation, *2C19* 2C19, S-mephenytoin 4′-hydroxylation, and *3A4* dextromethorphan N-demethylation

Interactions with H^+-K^+ ATPase Inhibitors (Proton Pump Inhibitors)

The H^+-K^+ ATPase, or proton pump, inhibitors suppress gastric acid secretion and are used to treat gastric ulcer, duodenal ulcer, gastroesophageal reflux, and other hypersecretory states. Omeprazole has been best characterized as an inhibitor of P450 2C19, and can cause drug interactions with drugs that are 2C19 substrates. In vitro, both omeprazole and lansoprazole inhibit 2C19 with K_is tenfold lower than those for inhibition of other P450s (Fig. 2.13) [216, 217]. Data on the in vitro inhibition of P450s by pantoprazole was not found. In vivo, only omeprazole is the only consistent inhibitor of P450 2C19 [218, 219]. This is seen with their effects on diazepam pharmacokinetics (Table 2.21). In four different studies, omeprazole was found to inhibit elimination of either intravenous or oral diazepam [197, 220–222]. Andersson et al. further demonstrated that omeprazole did not effect diazepam pharmacokinetics in 2C19 poor metabolizers [221]. Lansoprazole [223] and pantoprazole [224] had no effect on the pharmacokinetics of diazepam (Table 2.21).

Interactions with Imidazole Antifungal Agents

The imidazole antifungal agents are well known for their ability to inhibit P450-mediated drug metabolism [225]. Ketoconazole is the prototype, and is an often used 3A4-selective inhibitor. Most studies comparing the effects of the imidazole

Table 2.21 Drug interactions with H^+-K^+ ATPase inhibitor antisecretory agents

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Omeprazole	20 mg/d (dia b, c), 40 mg/d (dia a, d), oral multidose								
Diazepam a	0.1/kg, iv	8m			2.30*		0.45*		[220]
Diazepam b	0.1/kg, iv	12m			1.36*	1.39*	0.73*		[197]
Diazepam c	0.1/kg, iv	6 2C19em			1.20*	2.34*	0.74*		[221]
Diazepam c	0.1/kg, iv	4 2C19pm			0.95	1.10	0.90		[221]
Diazepam d	10, or	8m Chi, em			0.95		0.76*		[222]
N-desmethyl					1.03	1.24*			
Diazepam d	10, or	7m Cau, em			1.34*		0.61*		[222]
N-desmethyl					1.58*	1.41*			
Lansoprazole	60 mg, oral/d, multidose								
Diazepam	0.1/kg, iv	12m			1.11	1.12	0.91		[223]
Pantoprazole	240 mg, iv/d, multidose								
Diazepam	0.1/kg, iv	7f, 5m			0.91	0.99	1.01		[224]

antifungal agents on different P450s have utilized ketoconazole [22–24, 226]. These demonstrate that ketoconazole can inhibit many P450s, but that its ability to inhibit 3A4 at concentrations of ≈ 1 μM makes it 10–100 times more specific for this P450 gene product (Fig. 2.14a). Studies comparing the inhibitory ability of the other imidazole antifungal agents are limited. That by Maurice et al. [226], who studied inhibition of cyclosporin oxidase, suggests a ranking of: clotrimazole, ketoconazole > miconazole >> fluconazole > secnidazole > metronidazole (Fig. 2.14b). von Moltke et al. [41, 227] found a similar ranking, ketoconazole > itraconazole > fluconazole for the inhibition of midazolam α- and 4-hydroxylation and for triazolam α- and 4-hydroxylation (not shown). Jurima-Romet at al. studied another 3A4 substrate, terfenadine, and found ketoconazole, itraconazole, and fluconazole had almost equivalent K_is [228]. When studying the inhibition of 2C9 using tolbutamide as the substrate, Back et al. found miconazole, with an IC_{50} of 0.85 μM, was the most potent inhibitor of 2C9, with a relative ranking of miconazole > clotrimazole > ketoconazole, fluconazole > terconazole > metronidazole (Fig. 2.14b). Tassaneeyakul et al. [229] studied the effect of the azoles on 2E1-mediated 4-nitrophenol hydroxylation. While fluconazole, itraconazole, and ketoconazole were without effect, miconazole, bifonazole, clotrimazole, and econazole inhibited the activity with K_is of 4, 7, 12, and 25 μM (not shown).

In clinical studies on drug interactions between benzodiazepines and the imidazole antifungal agents, the responses appear to follow inhibition of P450 3A4 potencies (Table 2.22). Ketoconazole has been found to inhibit the elimination of alprazolam [230, 231], chlordiazepoxide [232], midazolam [233], and triazolam [47, 230, 234] (Table 2.22). Fluconazole has been found to inhibit the elimination of midazolam [235, 236], and triazolam [237], but not bromazepam [238] (Table 2.2). Itraconazole has been found to inhibit the elimination of alprazolam [239], diazepam [240], midazolam [233, 235, 241], and triazolam [234, 242]. Metronidazole and had no effect on the elimination of alprazolam [243], diazepam [244], lorazepam [243], or midazolam [245]. The same was true for the non-imidazole antifungal

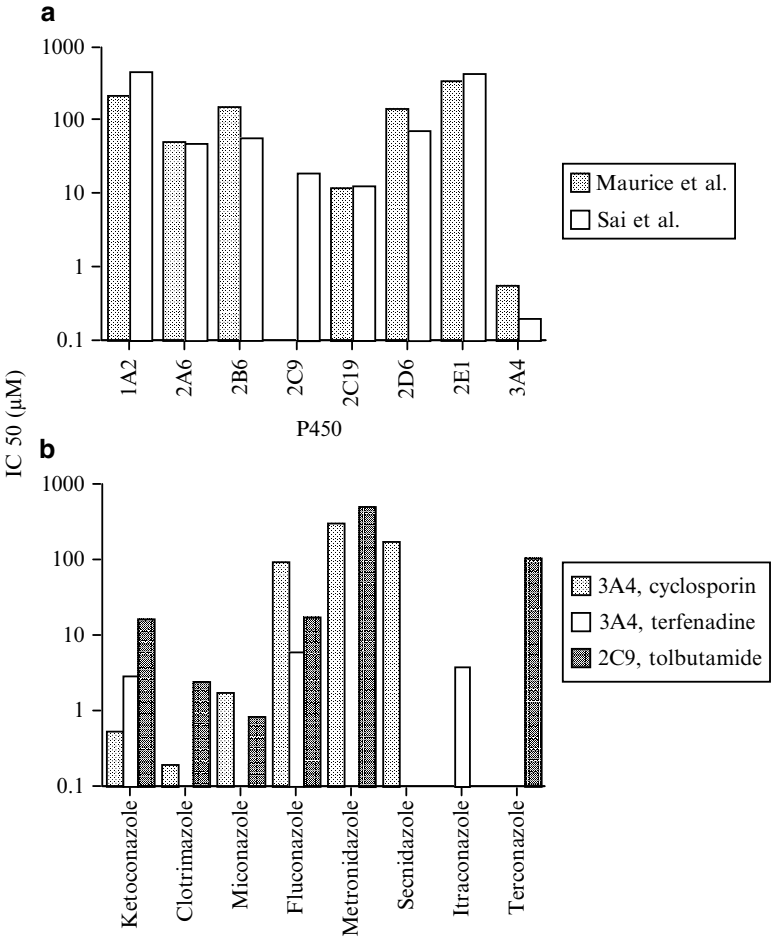

Fig. 2.14 Inhibition of human liver P450s by imidazole antifungal agents. (**a**) The inhibition of different P450s by ketoconazole in (HLM) from Maurice et al. [226] where the marker activities are: *1A2* phenacetin O-deethylase, *2A6*, coumarin 7α-hydroxylase, *2B6* benzphetamine demethylase, *2C19*, mephenytoin 4-hydroxylase, *2D6* debrisoquine 4-hydroxylase, *2E1* aniline hydroxylase, and *3A4* cyclosporin oxidase, and in cDNA-expressed P450s from Sai et al. [24]. (**b**) Inhibition of P450 3A4 and 2C9 in (HLM) by different imidazoles. The cyclosporin data are from Maurice et al. [226]; the terfenadine data are from Jurima-Romet et al. [228]; and the tolbutamide data are from Back et al. [434]

agent, terbinafine, on midazolam [241] and triazolam [246] (Table 2.22). The increases in AUC for midazolam were 15.9, 10.8, and 3.59 following ketoconazole, itraconazole, and fluconazole, respectively (Table 2.22). A similar potency was seen with triazolam of 13.7, 8.15, and 3.65 (Table 2.22).

For studies that followed the pharmacodynamic effects of benzodiazepines, the imidazole antifungal agents were found to diminish these in all cases (Table 2.22).

Table 2.22 Drug interactions with antifungal agents

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Ketoconazole	200 mg 2/d, 400 mg 1/d (chlor, mid, tri a), oral multidose								
Alprazolam	1, or	7m	1.07	1.10	3.88*	3.98*	0.31*	+++	[230]
Alprazolam	1, or	9	0.83	1.08	1.45*	1.76*	0.54*		[231]
Chlordiazepoxide	0.6/kg, iv	6m			1.82*	1.54*	0.62*		[232]
N-desmethyl							0.64*		
Demoxepam							0.70*		
Midazolam	7.5, or	7f, 2m	1.84*	4.09*	3.11*	15.9*		+++	[233]
Triazolam a	0.25, or	6f, 3m	1.67*	3.07*	6.45*	8.15*		+++	[234]
Triazolam b	0.125, or	2f, 7m	1.45	2.27*	3.97*	9.16*	0.12*	+++	[47]
Triazolam c	0.25, or	7m	1.58	2.08*	6.10*	13.7*	0.09	+++	[230]
Fluconazole	50 mg/d (tri b), 100 mg/d (bro, tri a,c), 200 mg/d (tri d, mid a) oral multidose single 400 mg oral (mid c) versus iv (mid b)								
Bromazepam	3, or	12m	1.60	0.99	1.00	1.09	0.89	0	[238]
Bromazepam	3, rectal	12m	0.92	0.98	1.00	1.09	0.86	0	[238]
Midazolam a	0.05/kg, iv	5f, 7m			1.52*		0.49*	++	[235]
Midazolam a	7.5, or	5f, 7m	1.70	1.74*	2.14*	3.59*		++	[235]
Midazolam b	7.5, or	4f, 5m	2.00	1.79*	2.23*	3.08*		++	[236]
1-hydroxy				1.24	2.42*	1.50*			
Midazolam c	7.5, or	4f, 5m	2.00	2.30*	2.23*	3.41*		++	[236]
1-hydroxy				1.11	2.57*	1.56*			
Triazolam a	0.25, or	10f, 2m	1.11*	1.25*	1.84*	2.46*		+++	[246]
Triazolam b	0.25, or	5f, 3m	1.15	1.47*	1.29*	1.59*		0	[237]
Triazolam c	0.25, or	5f, 3m	1.92*	1.40*	1.77*	1.99*		++	[237]
Triazolam d	0.25, or	5f, 3m	1.54*	2.33*	2.26*	3.65*		++++	[237]
Itraconazole	200 mg/d,100 mg/d (mid b) oral multidose, 200 mg once at –3 h (tri b)								
Alprazolam	0.8, or	10m	1.94	1.29	2.57*	1.62*	0.39*	++	[239]
Diazepam	5, or	5f, 5m	0.81	1.06	1.34*	1.34*		0	[240]
N-desmethyl				0.99		0.97			
Midazolam a	7.5, or	7f, 2m	1.54	3.41*	2.82*	10.8*		+++	[233]
Midazolam b	7.5, or	8f, 4m	0.80	2.56*	2.08*	5.74*		+++	[241]
Midazolam c	7.5, or	5f, 7m	1.80	2.51*	3.59*	6.64*		+	[235]
Midazolam d	0.05/kg (md)	5f, 7m			2.41*		0.31*	+	[235]
Triazolam a	0.25, or	4f, 3m	2.67*	2.80*	6.76*	8.15*		++++	[234]
Triazolam b	0.25, or	4f, 6m	1.94*	1.76*	3.11*	2.83*		++	[242]
Metronidazole	400 mg, or 2/d								
Alprazolam	1, or	4f, 6m	0.79	1.05	0.94		1.18		[243]
Diazepam	0.1/kg, iv	3f, 3m			1.00		1.23		[244]
Lorazepam	2, iv	4f, 4m			0.85		1.15		[243]
Midazolam	15, or	6f, 4m	1.25	0.94	1.10	0.91		0	[245]
1-hydroxy			1.00	1.00	0.76	0.88			
Terbinafine	250 mg/d, multidose								
Midazolam	7.5, or	8f, 4m	0.8	0.82	0.92	0.75		0	[241]
Triazolam	0.25, or	10f, 2m	0.83*	0.85	0.86	0.81		0	[246]

Their ability to do this followed the same potency ranking as was their effects on the pharmacokinetics, ketoconazole > itraconazole > fluconazole. Indeed, multiple doses of ketoconazole strongly enhanced the pharmacodynamic effects of triazolam and midazolam; triazolam was also strongly enhanced by itraconazole and fluconazole. These imidazole antifungals were some of the most potent inhibitors found during the research for this chapter.

Interactions with Serotonin Selective Reuptake Inhibitors

The serotonin selective reuptake inhibitors (SSRIs) are fairly potent inhibitors of human liver P450s (Fig. 2.15). They are most active against P450 2D6, where they have relative potency of paroxetine > flouxetine > sertraline, fluvoxamine > citalopram > venalafaxine, nefazodone, with K_is ranging from 0.07 to 33 μM (Fig. 2.15a) [247–250]. Their inhibitory action, however, is not limited to P450 2D6. P450 3A4-dependent metabolism of alprazolam is inhibited with K_is ranging from 10 to 83 μM (fluvoxamine > nefazodone, sertraline > paroxetine > fluoxetine); 2C19 metabolism of mephenytoin with K_is ranging from 1.1 to 87; and 2C9 metabolism of phenytoin with K_is ranging from 6 to 66 μM (Fig. 2.15b) [249–251]. Of particular importance for this class of drugs is that the initial metabolite often has equal inhibitory potency to the parent drug (Fig. 2.15). This is seen with midazolam where the substrate inhibition constant for α-hydroxylation was 1.4 and 11.5 μM for norfluoxetine and fluoxetine; those for 4-hydroxylation were 17 and 67 μM [41].

Since benzodiazepines that undergo oxidative metabolism are primarily P450 3A4 (or 2C19) substrates, they are not affected by SSRI comedication to the extent of some P450 2D6 substrates. Pharmacokinetically significant drug interactions have, however, been identified (Table 2.23). Fluoxetine was found to inhibit the elimination of alprazolam [252, 253], and diazepam [254], but was reported as without effect on clonazepam [253] and triazolam [255].

During one of the studies on alprazolam, Greenblatt et al. [253] demonstrated the clinical relevance of the inhibition by the metabolite, norfluoxetine. Subjects were randomly allocated to either the placebo-fluoxetine or fluoxetine-placebo order of study, with a 14-day washout period between sessions. For subjects that took placebo first, the inhibition of alprazolam elimination was significant; for those that took fluoxetine first, it was not. The reason for this was that in subjects that took fluoxetine first, norfluoxetine plasma concentrations were still quite high [253]. During the 8 days of active treatment with fluoxetine, mean norfluoxetine concentrations rose from 25 to 80 ng/mL. During the 14–31 days after cessation of treatment they went from 55 to 45 ng/mL [253]. Further discussion on the effect of long half-life of SSRI metabolites can be found in the chapter by M. Mozayani in this monograph.

Fluvoxamine was found to inhibit the elimination of diazepam [256] and midazolam [257]. Nefazodone was found to inhibit the elimination of alprazolam and triazolam [258–260], but not lorazepam [258, 261]. Sertraline had no effect on clonazepam [262] or diazepam [263]. While venlafaxine actually enhanced the elimination of alprazolam [264] and diazepam [265] (Table 2.23).

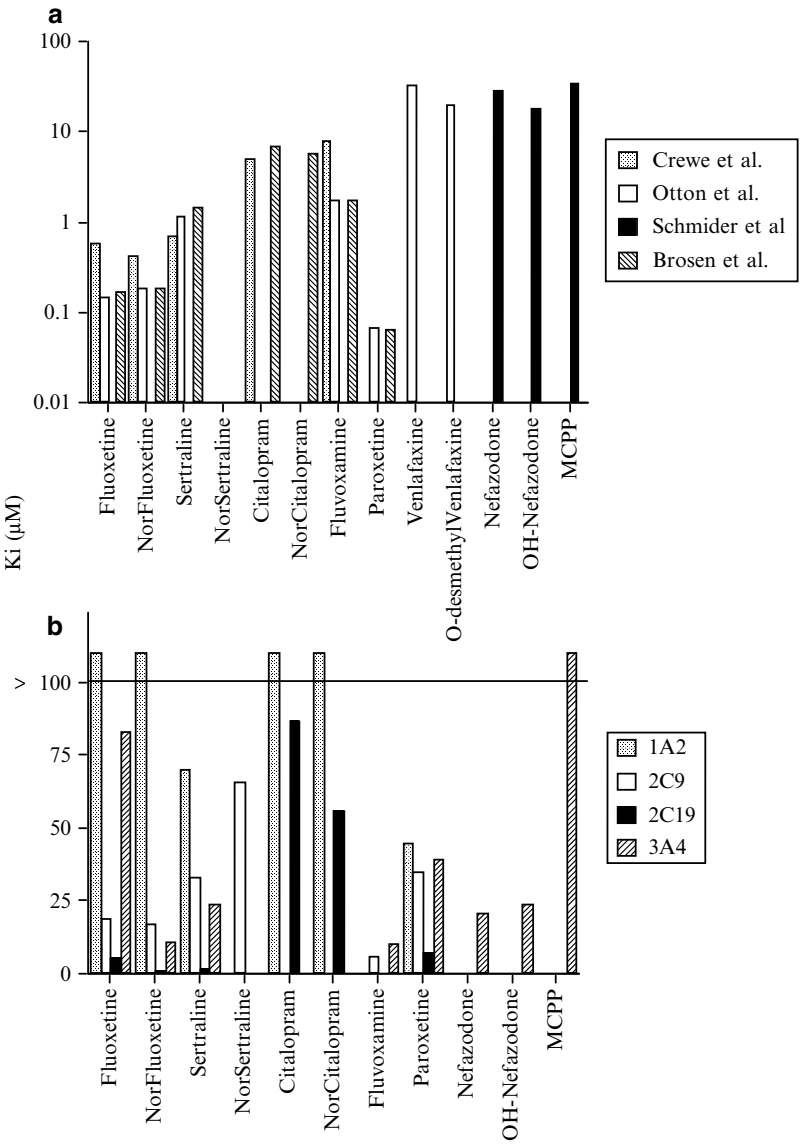

Fig. 2.15 Inhibition of human liver P450s by the selective serotonin reuptake inhibitors. (**a**) Inhibition of P450 2D6 activities. The data are from Crewe et al. [247] using sparteine 2-dehydrogenation, and Otton et al. [248], Schmider at al. [249], and Brosen et al. [250] using dextromethorphan O-demethylation. (**b**) Inhibition of other P450s. The 1A2, 2C19, and 3A4 (except Nefazodone and metabolites) data are from Brosen et al. [250] using paracetamol, S-mephenytoin, and alprazolam as the respective substrates. The 3A4 inhibition by Nefazodone and metabolites is from Schmider et al. [249] using dextromethorphan N-demethylation, and the 2C9 data are from Schmider at al. [251] using phenytoin p-hydroxylation

Table 2.23 Drug interactions with antidepressants

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Fluoxetine	60 mg/d (tria, alp a) or 20 mg 2/d (clon, alp b)								
Alprazolam a	1, or (md)	20/20		1.33ss*	1.27*			++	[252]
Alprazolam b	1, or	6m	0.71	1.46	1.17*	1.26*	0.79*		[253]
Clonazepam	1, or	6m	0.46*	1.22*	0.93	0.99	1.01		[253]
Diazepam	10, or	6m			1.50*	1.48*	0.62*	0	[254]
N-desmethyl						0.65*			
Triazolam	0.25, or	19	0.71	1.10	1.01	1.02	0.93		[255]
Fluvoxamine	Titrated up to 150 mg/d, multidose								
Diazepam	10, or	4f, 4m	1.33	1.32	2.31*	2.80*	0.35*		[256]
N-desmethyl				3.32*	1.15		1.41*		
Midazolam	0.025/kg, iv	10f, 10m					0.67*		[257]
Nefazodone	200 mg oral 2/d, multidose								
Alprazolam	1, or (md)	12/12	1.14	1.60*	2.05*	1.98*		+++	[258, 259]
1-hydroxy				2.00	1.00				
4-hydroxy				2.00	0.64*		0.72*		
Lorazepam	2, or (md)	12/12	0.88	0.99	0.91	1.02		0	[258, 261]
Triazolam	0.25, or	12m	2.20	1.66*	4.59*	3.90*		+++	[258, 260]
Sertraline	100 mg 1/d (clon), 50 increased to 200 mg 1/d (dia), or multidose								
Clonazepam	1, or (md)	8f, 8m			0.96		1.10	0	[262]
7-amino					0.78*	1.05			
Diazepam	10, iv	10/10			0.88		0.92		[263]
N-desmethyl			1.23	1.26		1.13			
Venlafaxine	37.5 mg 2/d (alp), or 50 mg 3/d (dia), oral multidose								
Alprazolam	2, or	1f, 15m	0.80	0.94	0.79*	0.71*	1.37*	–	[264]
Diazepam	10, or	18m	0.86	1.07		0.84*	1.08*	–	[265]
N-desmethyl			0.88	0.93		0.91	1.02		

Where studied, the effects of the SSRIs on the pharmacodynamics of the benzodiazepine reflected their effect on its pharmacokinetics (Table 2.23). Nefazodone had greater inhibitory effect on alprazolam than did fluoxetine, and in turn enhanced the pharmacokinetics of alprazolam to a greater extent [252, 258, 259]. The pharmacodynamics of lorazepam and clonazepam were not affected by nefazodone or sertraline, respectively, as was not their pharmacokinetics [258, 261, 262]. The enhanced elimination of alprazolam and diazepam caused by venlafaxine was associated with diminished pharmacodynamics. An exception was the study on diazepam and fluoxetine, where a pharmacokinetic interaction was found, but there was no effect on the pharmacodynamic measures in the study [254] (Table 2.23).

Interactions with Oral Contraceptives

The oral contraceptives are known to interfere with the elimination of a number of drugs [266]. Oral contraceptives vary in their composition, but in general they contain an estrogen and a progestin. These can be given in combination or in sequence.

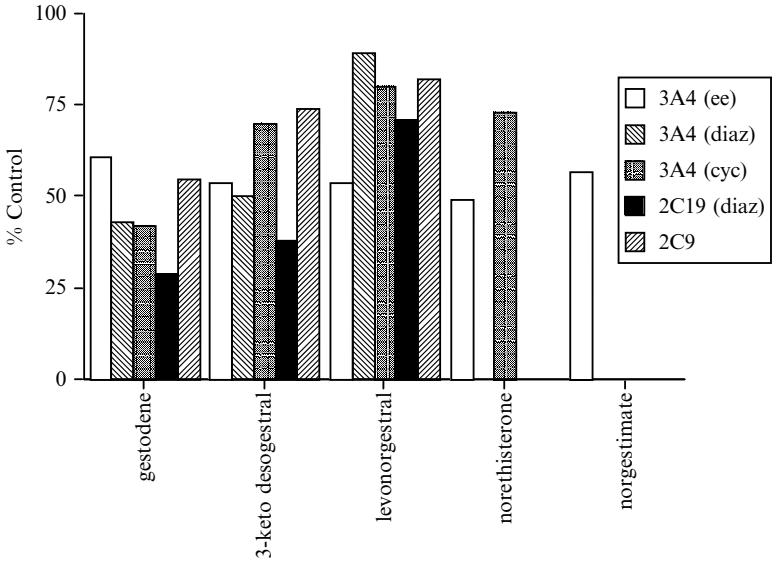

Fig. 2.16 Inhibition of human liver P450s by progestogens. Data are taken from Back et al. [268] where marker assays were performed in (HLM) after coincubation with the progestogens. The values shown are the percentage of control after use of the highest concentration of the progestogen. The substrates and concentration of progestogens were: *3A4 (ee)* ethinylestradiol, 100 μM; *3A4 (diaz)* diazepam hydroxylation, 100 μM; *3A4 (cyc)* cyclosporin hydroxylation, 50 μM; *2C19 (diaz)* diazepam N-demethylation, 100 μM; and *2C9 (tol)* tolbutamide, 25 μM

In most oral contraceptives the estrogen is ethinylestradiol. Ethinylestradiol is a mechanism-based inhibitor of P450 3A4 [267]. A number of progesterones are used including, norethindrone, norgestrel, levonorgestrel, ethynodiol diacetate, norethisterone, desogestrel, 3-keto-desogestrel, gestodene, and norgestmate. In a study by Back et al. [268] the progestins studied were found to inhibit a number of P450s (3A4, 2C19, and 2C9), but with IC_{50}s in the 25 to > 100 μM range (Fig. 2.16). In combination with the inhibition of P450-mediated reactions, oral contraceptives are also inducers of glucuronidation.

A number of studies compared the pharmacokinetics of benzodiazepines in woman who did not use oral contraceptives (Table 2.24). Inhibition of the elimination of benzodiazepines primarily metabolized by P450 has been found for alprazolam [269], chlordiazepoxide [270, 271], clotiazepam [153], diazepam [272, 273], midazolam [274], nitrazepam [275], and triazolam [269]. No effect was found in another study on alprazolam [276], for bromazepam [188], with intramuscular midazolam [277] or in a study that compared unlabeled intravenous midazolam to $_{13}N^3$-labeled oral midazolam [278]. In contrast, the elimination of benzodiazepines depending primarily on glucuronidation was enhanced as found for lorazepam [269, 271, 279], oxazepam [271, 279] and temazeapm [269].

Table 2.24 Drug interactions with oral contraceptives

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Regular therapeutic doses of low-dose estrogen									
Alprazolam	1, or	10/10	0.71	1.18	1.29*	1.35*	0.79*	+	[269, 281]
Alprazolam	1, or	16/23			1.03	1.07	1.02		[276]
Bromazepam	6, or	11/7	0.91	1.14	1.06		0.99		[188]
Chlordiazepoxide	0.6/kg, iv	7/11			1.64		0.66		[270]
Chlordiazepoxide	0.6/kg, iv	6/6			1.77*		0.40*		[271]
Clotiazepam	5, or	6/8			2.27		1.01		[153]
Diazepam	10, iv	5/10			1.83*		0.51*		[272]
Diazepam	10, iv	8/8			1.47*		0.60*		[273]
Lorazepam	2, iv	15/15			0.93		1.20		[279]
Lorazepam	2, iv	7/8			0.43*		3.73*		[271]
Glucuronide			6.00*	1.50*					
Lorazepam	2, or	11/9	0.86	1.06	0.78*	0.94	1.12	+	[269, 281]
Midazolam	7.5, im	8/7	1.17	0.78	1.61	0.84	1.11		[277]
1-hydroxy			0.94	0.88	0.94	0.89			
Midazolam	7.5, or	9f	1.00	1.16	1.10	1.20*		0	[274]
1-hydroxy			1.00	1.25	1.30	1.43*			
Midazolam	0.05/kg, iv	9f			1.09	0.93	1.08	0	[278]
$^{13}N_3$-Midazolam	3, or	9f	0.78	1.06	0.89	1.10	0.92	0	[278]
Nitrazepam	5, or	6/6	1.19	1.17	1.00		0.82		[275]
Oxazepam	30, or	17/14			0.94		1.27		[279]
Oxazepam	45, or	5/6			0.64		2.57*		[271]
Temazepam	30, or	10/10	0.89	0.82	0.60*	0.61*	1.62*	0	[269, 281]
Triazolam	0.5, or	10/10	1.50	1.06	1.16	1.44	1.47	+	[269, 281]
Conjugated estrogens (0.625 mg) ± medroxyprogesterone (5 mg)									
Midazolam	3, or	10/10			1.20	1.18	0.89		[280]

In a study on conjugated estrogens and medroxyprogesterone at doses used for estrogen replacement therapy, no or minimal effect was found on the pharmacokinetics of midazolam [280] (Table 2.24).

The changes in woman taking oral contraceptives were not dramatic. In studies on the pharmacodynamic responses no effect was found for midazolam [274, 278] or temazepam [281]. Interestingly, Kroboth et al. [281] found minimal stimulation to the benzodiazepine effect in woman taking oral contraceptives along with alprazolam, triazolam, and lorazepam. The finding for lorazepam was contrary to the pharmacokinetic response. In a subsequent study, Kroboth and McAuley [282] discuss these findings in light of the ability of a progesterone metabolite3α-, 5α-tetrahydroprogesterone to bind to the GABA receptor and enhance binding of benzodiazepines. Pretreatment with progesterone was found to enhance the pharmacodynamic effects of triazolam. These findings suggest that the progesterones used in oral contraceptives and estrogen replacement therapy may stimulate the action of benzodiazepines despite their actions on the pharmacokinetics of the benzodiazepine.

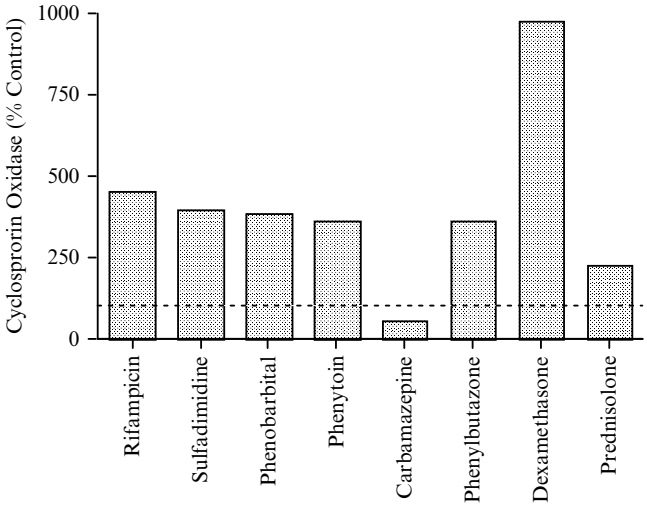

Fig. 2.17 The induction of cyclosporin oxidase activity, a marker for P450 3A4, in primary cultures of human hepatocytes. The data are from Pichard et al. [283], the *dashed line* shows 100% control activity

Interactions with Anticonvulsants

The anticonvulsants include many medications that are known to induce P450s, including P450 3A4. In an in vitro study using primary cultures of human hepatocytes, Pichard et al. [283] were able to produce this induction of both P450 3A4 content measured immunochemically and the 3A4-mediated activity, cyclosporin oxidase, with the anticonvulsants phenobarbital and phenytoin (Fig. 2.17). Carbamazepine induced 3A4 content, but reduced its activity. This reduction was not found in (HLM), and was attributed by the authors to cellular toxicity at the doses used in the induction study [283].

Clinical studies following epileptic patients who use a mixture of anticonvulsants that include carbamazepine and/or phenytoin when compared to non-medicated controls have shown that anticonvulsant treatment enhances the elimination of clobazam [284], diazepam [285], and midazolam [286] (Table 2.25). In a study comparing patients taking non-inducing anticonvulsants, inducing anticonvulsants, and inducing anticonvulsants that included felbamate, the ratio of N-desmethylclobazam to clobazam were greatest in the latter group, suggesting that inductive properties of felbamate [287]. The clearance of clorazepate was greater in epileptic patients taking phenytoin and/or phenobarbital than for literature values for non-medicated subjects [288].

Controlled studies in healthy volunteers with carbamazepine alone have demonstrated its ability to enhance the elimination of alprazolam [289], clobazepam [290], and clonazepam [291] (Table 2.25). The effect of carbamazepine on alprazolam is consistent with a case report on decreased alprazolam plasma concentrations and effectiveness in a patient with atypical bipolar disorder once he was started on carbamazepine treatment [292].

Table 2.25 Drug interactions with anticonvulsants

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Anticonvulsants several, but including carbamazepine and/or phenytoin									
Clobazam	30, or	6/6				0.43*			[284]
N-desmethyl						2.90*			
Diazepam	10, iv	9/6			0.39*		2.58*		[285]
N-desmethyl			0.71*	1.50*					
Midazolam	15, or	6/7	1.00	0.07*	0.42*	0.06*		–	[286]
Carbamazepine	100 mg 3/d (alp), 200 mg 2/d (clob), 200 mg 1/d (clon), oral multidose								
Alprazolam	0.8, or	7m	0.62	1.11	0.45*		2.22*	–	[289]
Clobazam	20, or (md)	2f, 4m		0.38ss*	0.37*		2.58*		[290]
N-desmethyl				1.44*	0.59*				
Clonazepam	1, or (md)	2f, 5m		0.29ss*	0.70*				[291]
Valproic acid	250 or 500 mg 2/d (lor), 500 mg 3/d (diaz), or multidose								
Diazepam	10, iv	6m			0.99	0.69*	1.45*		[294]
Lorazepam	2, iv	8m	(Effect in 6 of 8)				0.60*		[295]
Glucuronide							0.42*		
Lorazepam	1, or	16m	1.05	1.08*	1.35*	1.20	0.69*	±	[296]

Valproic acid was found to increase the clearance of diazepam without any effect on its $t_{1/2}$, this was attributed to the ability of valproic acid to displace diazepam from it plasma protein binding sites [293, 294]. Valproic acid also decreases the elimination of lorazepam, with decreases in clearance and increased $t_{1/2}$ [295, 296]. This was shown to be due to inhibition of lorazepam glucuronide formation [295] (Table 2.25).

In the study on carbamazepine and/or phenytoin on midazolam, the AUC and C_{max} of midazolam were greatly reduced, to 5.7 and 7.4% of non-treated controls, and the pharmacodynamic measures were significantly reduced [286]. When alprazolam was given along with carbamazepine, only minimal diminution of the pharmacodynamic effects was observed. The authors attributed this to the sedative nature of carbamazepine [289], which would be greater in these non-tolerant volunteer subjects than in the epileptic patients used for the midazolam study. Sedation scales were only minimally affected during the study on the interaction between valproic acid and lorazepam [296].

Interactions with Cardiovascular Agents

Drug interactions of benzodiazepines have been found with a number of cardiovascular agents, particularly the ß-adrenoreceptor antagonists and the calcium channel blockers. Information on the in vitro interactions of these drugs with P450s is essentially limited to the calcium channel blockers (Fig. 2.18). Early studies found only moderate to weak inhibitory action on P450 3A4 metabolism by calcium channel

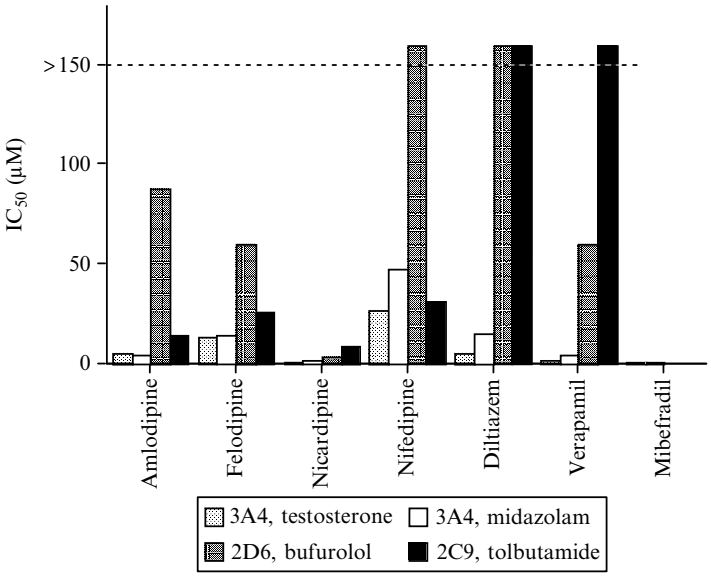

Fig. 2.18 Inhibition of P450s by calcium channel blockers. Data are from Ma et al. [299] using the results after preincubation of the inhibitor with (HLM) and NADPH prior to addition of substrate. Preincubation decreased the IC_{50}s for all 3A4 inhibition except for mibefradil and nifedipine. Preincubation had no effect on inhibition of 2D6 or 2C9. Bars extending above the *dashed line* had IC_{50}s greater than 150 μM (100 μM for verapamil and 2C9)

blockers; the percent inhibition of cyclosporin oxidation using 50 μM nicardipine, nifedipine, verapamil, and diltiazem was 81, 17, 29, and 20, respectively, when the inhibitor was added at the start of the reaction [297]. More recently, Sutton et al. [298] found that the N-desmethyl- and N,N-didesmethyl- metabolites of diltiazem were much more potent inhibitors of 3A4 activity (respective IC_{50}s of 11 and 0.6 μM) than the parent compound (IC_{50} of 120 μM). When diltiazem was preincubated with microsomes and NADPH prior to addition of substrate its effective inhibitory potential greatly increased due to metabolite formation. In a subsequent study, Ma et al. [299] tested the ability of a number of calcium channel blockers to inhibit 3A4, 2D6, and 2C9 activities (Fig. 2.18). For all, except mibefradil and nifedipine, inhibition of 3A4 was enhanced with preincubation in the presence of NADPH; this did not have any effect on inhibition of 2C9 or 2D6 activities. Whether the preincubation effect was due to generation of more active metabolites, or some other mechanism-based or metabolite intermediary complex formation route of inhibition has not been determined except for diltiazem. Although metabolites of propranolol are known to bind to microsomes [300] no studies were found on P450 selective inhibition by this or other ß-adrenoreceptor antagonists, even though (as seen below) they have been found to cause drug interactions.

Propranolol has mixed effects on benzodiazepines in clinical studies (Table 2.26). It enhanced the elimination of alprazolam [301], it inhibited the elimination of bromazepam [188] and diazepam [301, 302], and it had no effect on the elimination

Table 2.26 Drug interactions with cardiovascular agents

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Propranolol	80 mg, or 2–3/d, multidose								
Alprazolam	1, or	6	1.50	0.79*	0.86		1.38		[301]
Bromazepam	6, or	2f, 5m	0.97	1.19	1.20*		0.79		[188]
Diazepam	5, or (md)	12m	1.31	1.16		1.19		+	[302]
Diazepam	5, iv	8			1.20		0.83*		[301]
Lorazepam	2, iv	9			1.04		0.98		[301]
Propranolol	80 mg, or at 0 h								
Oxazepam	15, or	2f, 4m	0.91	0.84	0.93		1.09	±	[303]
Metoprolol	100 mg, or 2/d, multidose								
Bromazepam	6, or	12m	0.98	1.17	0.92	1.35	0.87	0	[304]
Diazepam	5, or (md)	12m	1.15	1.21*		1.25*		+	[302]
Diazepam	0.1/kg, iv	6m			1.27		0.81	+	[305]
Lorazepam	2, or	12m	1.14	0.93	0.92	1.01	0.97	0	[304]
Atenolol	25 mg, oral 2/d, multidose								
Diazepam	5, or (md)	12m	1.23	1.08		1.06		0	[302]
N-desmethyl						1.00			
Labetalol	200 mg, or at 0 h								
Oxazepam	15 mg, or	2f, 4m	1.00	0.91	0.95		0.90	0	[303]
Diltiazem	60 mg, or plus 0.1 mg/kg/h infusion during anesthesia								
Midazolam	0.1/kg, iv	15/15			1.43	1.15*			[306]
Diltiazem	60 mg, or, 3/d, multidose								
Midazolam	15, or	9f	1.09	2.05*	1.49*	3.75*		++	[307]
Triazolam	0.25, or	7f, 3m	1.50*	1.86*	2.35*	2.83*		++	[308]
Triazolam	0.25, or	7m	1.19	1.71*	1.85*	2.28*		++	[309]
Verapamil	80 mg, or 3/d, multidose								
Midazolam	15, or	9f	0.64	1.97*	1.41*	2.92*		++	[307]
Mibefradil	50 mg, or 1/d, multidose								
Triazolam	0.25, or	5f, 2m	2.00*	1.89*	4.62*	8.36*		+++	[310]
Isradipine	5 mg, or, multidose								
Triazolam	0.25, or	5f, 2m	1.00	0.94	0.78*	0.77*		0	[310]

of lorazepam [301] or oxazepam [303]. Metoprolol also inhibited the elimination of bromazepam [304] and diazepam [302, 305] with no effect on lorazepam [304]. Atenolol and labetalol had no effect on the pharmacokinetics of diazepam [302] and oxazepam [303], respectively. In the above studies, the inhibition of elimination was only slight to mild, and where studied [302, 303, 305] there were only slight or no effects on the pharmacodynamics of the benzodiazepines (Table 2.26).

Diltiazem has been shown to inhibit the elimination of intravenous [306] and oral [307] midazolam and oral triazolam [308, 309]. Verapamil inhibits the elimination of midazolam [307], and mibefradil the elimination of triazolam [310]. Isradipine was without effect on triazolam [310]. The inhibitory calcium channel blockers had significant enhancing effects on the pharmacodynamics of the benzodiazepines [307–310] (Table 2.26).

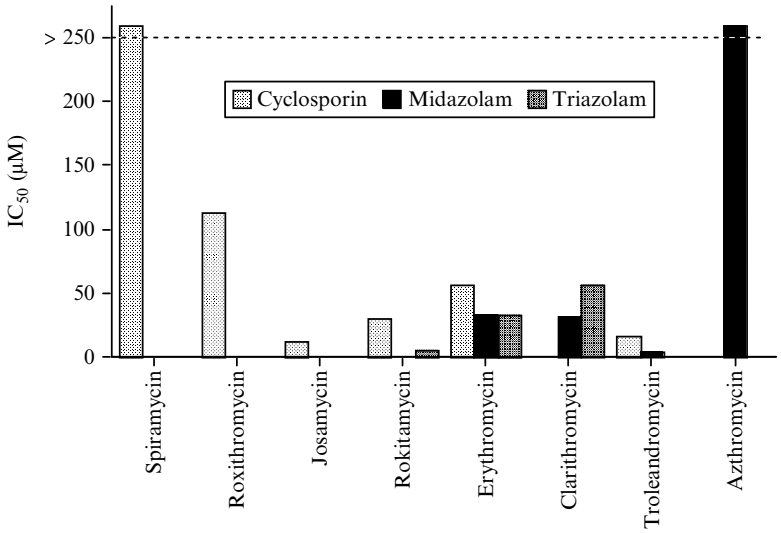

Fig. 2.19 The relative inhibitory potency of macrolide antibiotics toward P450 3A4 activities in (HLM). The data for cyclosporin (oxidase) are from Marre et al. [316]. These incubations were performed without preincubation of the inhibitors, which generally results in higher IC_{50}s. The data for midazolam (α-hydroxylation) and triazolam (α-hydroxylation) are from Greenblatt et al. [317] and Zhao et al. [314], respectively. Both of these studies preincubated the microsomes with the macrolide antibiotics prior to addition of substrate

Interactions with Antibiotics

Among the antibiotics, the antitubucular agent rifampin (rifampicin) is well known for its ability to induce drug metabolism [311], as can also be seen in in vitro systems (Fig. 2.17). The macrolide antibiotics are well-known inhibitors of P450 3A4 [312]. The specificity of the macrolide antibiotics is exemplified by troleandomycin, which is commonly used as a selective inhibitor of 3A4 (Table 2.9). Yamazaki and Shimada [313] have also demonstrated that erythromycin, roxithromycin, and the M1, M2, and M3 metabolites of roxithromycin inhibit P450 3A4 with no effect on activities selective for 1A2 or 2C9. In a similar study Zhao et al. [314] demonstrated that erythromycin, clarithromycin, rokitamycin, and the rokitamycin metabolite, LMA7, inhibit 3A4 selective activity with no effect on 1A2, 2C9, or 2D6 activities. The macrolide antibiotics form metabolite intermediate complexes with human liver microsomal P450 [313, 315]. This should be taken into consideration when comparing studies on the in vitro inhibition with these compounds, as lower IC_{50} or K_i values will be obtained when the inhibitor is preincubated with the microsomes and a source of NADPH prior to addition of substrate (Fig. 2.19). A number of studies have compared the ability of the macrolide antibiotics to inhibit P450 3A4 selective activities [314, 316, 317].

From these studies the relative inhibitory potency of the macrolide antibiotics can be ranked as josamycin, troleandomycin > rokitamycin > erythromycin, clarithromycin > roxithromycin >> azithromycin, spiramycin, the latter two having no inhibitory effect at concentrations up to 250 μM (Fig. 2.19). The clinical studies discussed below also address drug interactions with isoniazid. A recent study found isoniazid was a mechanism-based inhibitor of P450 1A2, 2A6, 2C19, and 3A4 (respective K_is of 56, 60, 10, and 36 μM), with little or no effect on 2D6 and 2E1 [318]. The fluoroquinolone antibiotics that include ciprofloxacin are also addressed and are known to inhibit P450 1A2 activities both in vivo [319] and in vitro [320, 321]. Their selectivity for that P450, however, has not been established.

Generalized antitubercular treatment that included a combination of rifampin, ethambutol, and isoniazid was found to result in significantly enhanced elimination of diazepam [322] (Table 2.27). In the same study, ethambutol was found to have no significant effect on diazepam elimination, while isoniazid actually inhibited the elimination of diazepam [322]. This strongly suggested that the induction of diazepam elimination was due to rifampin, which was subsequently confirmed by Ohnhaus et al. [323]. Isoniazid has also been found to inhibit the elimination of triazolam [324], while having no effect on oxazepam [324] or clotiazepam [153]. Rifampin has also been shown to induce the elimination of alprazolam [231], midazolam [325, 326], nitrazepam [327], and triazolam [328]; it had no or only a slight inductive effect on temazepam [327] (Table 2.27). In the studies on midazolam [325, 326] and triazolam [328], the induction of drug elimination almost negated any pharmacodynamic effect of the benzodiazepine (Table 2.27).

Erythromycin has been found to inhibit the elimination of alprazolam [329], diazepam [330], flunitrazepam [330], midazolam [331–333], and triazolam [317, 334]. It had little or no effect on the pharmacokinetics of temazepam [335]. Olkkola et al. demonstrated that the effect of erythromycin was more potent for oral than intravenous midazolam [332]. For oral midazolam, the erythromycin interaction produced significantly enhanced pharmacodynamic reactions [331–333], while the interaction of erythromycin with alprazolam [329], diazepam [330], flunitrazepam [330], and intravenous midazolam [332] had little or no effect on the pharmacodynamics of the drugs (Table 2.27). Troleandomycin [336] and clarithromycin [317] inhibit the elimination of triazolam; the interaction with troleandomycin being associated with a significant effect on its pharmacodynamics. Roxithromycin had a small but significant effect on the pharmacokinetics and pharmacodynamics of midazolam [337]. Azithromycin had no effect on the pharmacokinetics and pharmacodynamics of midazolam [317, 333] (Table 2.27).

The fluoroquinolone antibiotic ciprofloxacin was found to inhibit the elimination of 5 mg intravenous diazepam in one study [338], with little or no pharmacodynamic effect. In another study, ciprofloxacin had little or no effect on the elimination of 10 mg intravenous diazepam [339] (Table 2.27). Possibly higher doses of diazepam overcome a weak inhibitory action of ciprofloxacin.

Table 2.27 Drug interactions with antibiotics

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Generalized antitubucular treatment (isoniazid, rifampin, and ethambutol) for at least 2 weeks									
Diazepam	5–7.5, iv	7/7			0.25*		4.05*		[322]
Ethambutol	25 mg/kg, iv, 1/d, multidose in newly diagnosed tubucular patients								
Diazepam	5–7.5, iv	6/6			1.15		0.78		[322]
Isoniazid	90 mg, or 2/d, multidose								
Clotiazepam	5, or	11			1.27		1.17		[153]
Diazepam	5–7.5, iv	6f, 3m			1.33*		0.74*		[322]
Oxazepam	30, or	5f, 4m	0.74	1.03	1.11	0.98	1.09		[324]
Triazolam	0.5, or	2f, 4m	1.16	1.20	1.31*	1.46*	0.58*		[324]
Rifampin	1,200 mg, or 1/d, multidose								
Diazepam	10, or	7m	0.76	0.69*	0.28*	0.27*	3.72*		[323]
N-desmethyl						0.42*	3.18r*		
3-hydroxy						0.52*	2.68r*		
Oxazepam						0.77*	1.29r*		
Rifampin	600 mg, or 1/d, multidose								
Alprazolam	1, or	4	0.75	0.64*	0.18*	0.12*	7.54*		[231]
Diazepam	10, or	7m	1.18	0.80	0.30*	0.23*	4.27*		[323]
N-desmethyl						0.51*	1.48r*		
3-hydroxy						0.57*	1.88r*		
Oxazepam						0.87	1.20r*		
Midazolam	15, or	5f, 5m	1.25	0.06*	0.42*	0.04*		–-	[325]
Midazolam	15, or	5f, 4m	0.67	0.05*	0.20*	0.02*		–-	[326]
Nitrazepam	5, or	8	0.75	0.96	0.61*		1.83*		[327]
Temazepam	10, or	8	0.86	0.90	0.86		1.11		[327]
Triazolam	0.5, or	4f,6m	1.00	0.12*	0.46*	0.06*		–-	[328]
Erythromycin	750 mg, or at -1 h								
Midazolam	10, or	5m	0.50*	1.20*				++	[331]
Erythromycin	500 mg (diaz, flun, tem, mid, triaz b) 400 mg (alp), 333 mg (triaz a), or 3/d, multidose								
Alprazolam	0.8, or	12m	2.63*	1.18	2.52*	1.61*	0.40*	0	[329]
Diazepam	5, or	5f, 1m	0.62	1.21	1.72	1.07*		0	[330]
N-desmethyl						0.81			
Flunitrazepam	1, or	3f, 12m	2.00	1.17	1.56*	1.28*		0	[330]
Midazolam	0.05/kg, iv	4f, 2m			1.77*		0.46*	+	[332]
Midazolam	15, or	9f, 3m	0.66	2.79*	2.38*	4.42*		+++	[332]
Midazolam	15, or	8f, 4m	1.00	2.71*	2.19*	3.81*		+++	[333]
Temazepam	20, or	6f, 4m	0.87	1.13	1.00			0	[335]
Oxazepam			1.05	0.96	1.07				
Triazolam a	0.5, or	16m	0.90	1.46*	1.54*	2.06*	0.48*		[334]
Triazolam b	0.125, or	6f, 6m	1.00	1.77*	2.25*	3.80*	0.35*	+++	[317]
Troleandomycin	1 g, oral 2/d, multidose								
Triazolam	0.25, or	7m	1.57*	2.08*	3.58*	3.76*	0.26*	+++	[336]
Roxithromycin	300 mg, or 1/d, multidose								
Midazolam	15, or	5f, 5m	0.94	1.37	1.29*	1.47*		+	[337]

(continued)

Table 2.27 (continued)

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Azithromycin	500 mg, or 3/d (mid), 2/d (triaz), multidose								
Midazolam	15, or	8f, 4m	1.00	1.29	1.09	1.26		0	[333]
Triazolam	0.125, or	6f, 6m	1.00	1.14	0.94	1.02	1.01	±	[317]
Clarithromycin	500 mg, or 2/d, multidose								
Triazolam	0.125, or	6f, 6m	1.22	1.97*	3.07*	5.25*	0.23*	++++	[317]
Ciprofloxacin	500 mg, or 2/d, multidose								
Diazepam	10, iv	10m			1.18	1.16	0.91		[339]
Diazepam	5, iv	6f, 6m			1.94*	1.50*	0.63*	0	[338]

Interactions with Antiretroviral Agents

The antiretroviral agents, particularly the protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are an emerging group of potent inhibitors, and, in some cases, inducers of drug-metabolizing enzymes [340–342]. In vitro, the protease inhibitors are particularly potent inhibitors of P450 3A4; with 2C9 and 2C19 also inhibited by some (Fig. 2.20a). The relative potency for inhibition of 3A4 is ritonavir > indinavir > saquinavir [343–348] (Fig. 2.20a). Saquinavir has variously been found equipotent to nelfinavir [345], less potent than nelfinavir [346, 347], and more potent than nelfinavir [348]. In a single study on amphenavir, it was found to inhibit 3A4 with a potency similar to ritonavir [347]. A single study comparing the inhibitory potency of the non-nucleoside reverse transcriptase inhibitors suggests that their relative ability to inhibit P450 3A4 is delaviridine > efanvirenz >> nevirapine [349]. P450s 2C9 and 2C19 are also susceptible to inhibition by delaviridine and efanvirenz (Fig. 2.20b) [349].

The antiretroviral agents are given in combination. Much of what is currently known about their ability to induce drug metabolism comes from clinical studies on the combination of two or more of these drugs. From these studies the protease inhibitors, ritonivar, nelfinavir, amprenavir, and the non-nucleoside reverse transcriptase inhibitors, efavirenz and nevirapine, have all shown the potential to induce drug metabolism [340, 342]. They also inhibit the metabolism of some of the other antiretroviral agents.

Studies on the interactions of antiretroviral agents with benzodiazepines are currently limited to interactions with midazolam, which was used to phenotype P450 3A4 activity. Triazolam and alprazolam have each been studied once; ritonavir, after 2 or 3 days of treatment, has been found to inhibit the elimination of triazolam [350] and alprazolam [351] (Table 2.28). The inhibition of triazolam is quite significant with major effects on the pharmacokinetics of this benzodiazepine. The effects on alprazolam are also significant, but did not have as great an impact on its pharmacodynamics. The interaction of midazolam with saquinavir has also been studied. Three- or 5-day treatment with saquinavir causes a significant inhibition of the elimination of oral midazolam associated with a significant enhancement of its pharmacokinetics. Saquinavir also inhibited the elimination of intravenous midazolam, but to a lesser extent [352] (Table 2.28). Many antiretrovirals are given in combination

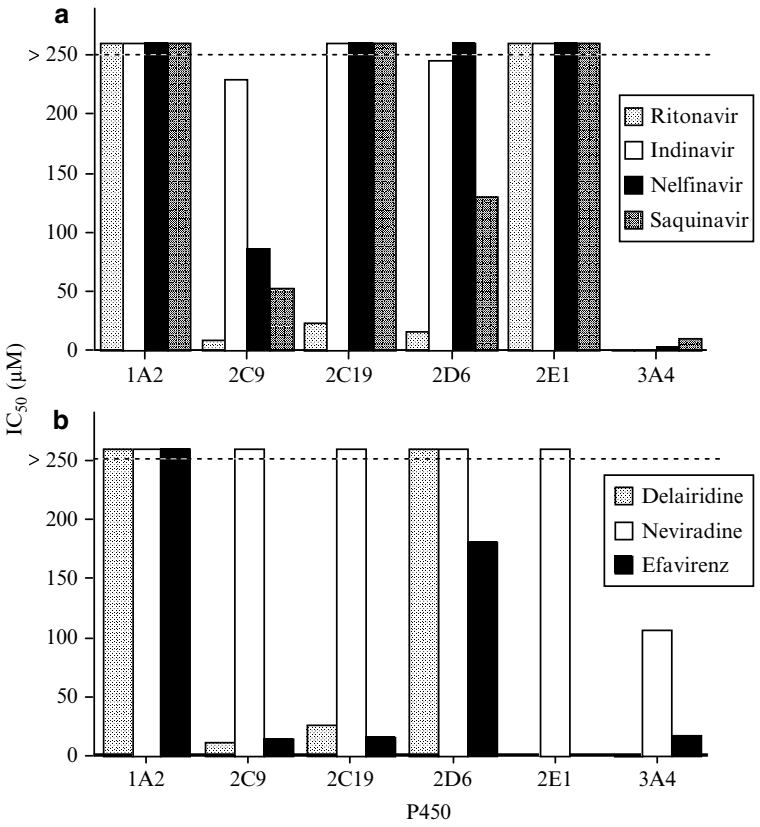

Fig. 2.20 The relative inhibitory potency of (**a**) protease inhibitor and (**b**) non-nucleoside reverse transcriptase inhibitor antiretroviral agents toward selective P450 activities in (HLM). The data for the protease inhibitors is from von Moltke et al. [346], except for the effect of saquinavir on P450 2C9, which is from Eagling et al. [343]. The data for the non-nucleoside reverse transcriptase inhibitors is from von Moltke et al. [349], except for the effect of nevirapine on P450 2E1, which is from Erickson et al. [435]

with ritonavir; ritonavir inhibition of P450 3A4 enhancing bioavailability of the other antiretroviral. Such is the case for lopinavir. When given in combination with ritonavir both intravenous (hepatic) and oral (combination of hepatic and intestinal) midazolam clearance was significantly reduced [353] (Table 2.28). The study by Fellay et al. [354] demonstrates some of the classic effects of antiretrovirals. Here subjects were grouped based on the main antiretroviral they were taking and phenotyped for midazaolam metabolism using a single blood collection and determination of metabolic ratio (1-hydroxymidazolam/midazolam) before starting treatment and then after at least 30 days. The inductive effect of efavirenz is evident as are the inhibitory effects of nelfinavir and ritonavir. The inhibitory effect of ritonavir is such as to negate induction when given together with efavirenz (Table 2.28).

Table 2.28 Drug interactions with antiretroviral agents

Inhibitor/ Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Ritonavir	200 mg, or 2/d, 4 doses (triaz at +1 h after 3rd dose; alpraz at +1 h after 2nd dose)								
Triazolam	0.125, or	6m	1.80*	1.87*	13.6*	20.4*	0.04*	++++	[350]
Alprazolam	1.0, or	8	1.50	1.04	2.23*	2.48*	0.41*	++	[351]
Saquinavir	1,200 mg, 3/d, 5d (midaz on d3 and d5)								
Midazolam	7.5, or	6f, 6m	1.33	2.35*	2.53*	5.18*		+++	[352]
α-hydroxy-			1.33	0.62*		0.19*			
Midazolam	0.05/kg, iv	6f, 6m		0.90ss	2.31*	2.49*	0.44	+	[352]
α-hydroxy-			1.00	0.57*		0.42*			
Lopinavir/Ritonavir 400/100 mg or 2/d, 14 d									
Midazolam	0.025 mg/kg, iv	8f, 6m					0.23		[353]
	7.5 mg or	8f, 6m					0.08		
Maraviroc	300 mg or 2/d, 10 d								
Midazolam	7.5 mg or	12	1.02	1.21	1.02	1.18*			[355]
AMD070	200 mg or 2/d, 8d								
Midazolam	5 mg or	3f, 9m	1.20	1.09	1.22	1.21*	0.75*		[356]
Elvitegravir	125 mg or 1/d, 10d	given with escalating doses of ritonavir, 20–200 mg							
Midazolam	1 mg iv	12							[357]
and 20 mg ritonavir					1.76*	3.19*	0.30*		
and 50 mg ritonavir					3.29*	4.52*	0.22*		
and 100 mg ritonavir					4.31*	6.81*	0.15*		
and 200 mg ritonavir					4.23*	4.90*	0.20*		

Midazolam	0.075 mg or and primary antiretroviral	1-OH-mid/midazolam	Reference
Efaviranz, 600 mg or 4/d, at least 30d		4.56*	[354]
Nelfinavir 2,500 mg or 2/d, at least 30d		0.08*	
Ritonavir 200 mg or 2/d, at least 30d		0.02*	
Efaviranz/Ritonavir 600/200 mg 4/d, at least 30d		0.06*	

As newer types of antiretrovirals are introduced, their effect on P450 3A4 has also been determined. The CCR5 antagonist maraviroc [355] and the CXCR4 antagonist [356] have very modest inductive effects (Table 2.28). When studying the HIV-1 integrase inhibitor, elvitegravir, Mathias et al. [357] determined the proper titration of ritonavir to give optimal effect. They show that inhibition saturates at 100 mg with no further effect from increasing the dose to 200 mg (Table 2.28).

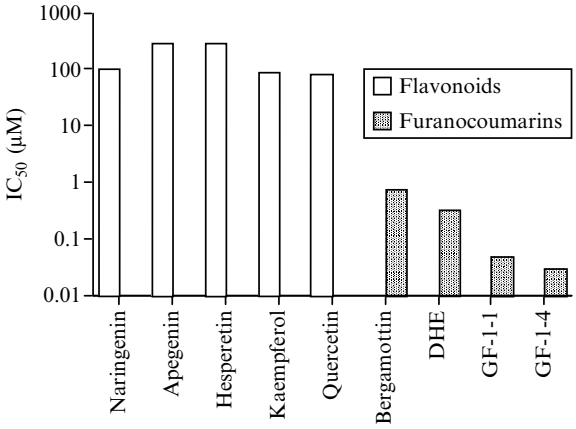

Fig. 2.21 The relative potency of components of grapefruit juice to inhibit P450 3A4 activities. The data for the flavonoids is for nifedipine oxidation and is from Guengerich and Kim [365]. Data for the furocoumarins, bergamottin, and 6′,7′-dihydroxybergamottin (DHB) are for saquinavir metabolism and are from Eagling et al. [369], the data for the HPLC fractions containing furocoumarins designated GF-1-1 and GF-1-4 are K_is for inhibition of testosterone 6ß-hydroxylation and are from Fukuda et al. [374]

Interactions with Grapefruit Juice

In a seminal study reported in 1991, Baily et al. [358] demonstrated that grapefruit juice, but not orange juice, significantly increased the bioavailability of oral felodipine and nifedipine, both P450 3A4 substrates. In combination with studies demonstrating grapefruit juice had no effect on intravenously administered drugs, and since the AUCs and C_{max}s were often increased but not $t_{1/2}$s, it was concluded that grapefruit juice had its main impact on bioavailability at the level of the gastrointestinal system. P450 3A4 is also the major P450 in the gastrointestinal system [359, 360], and the drugs affected by grapefruit juice are 3A4 substrates [361, 362]. This connection was highlighted when it was shown that ingestion of grapefruit juice in human volunteers was associated with a loss of 3A4 content, but not mRNA [363, 364]. Efforts to determine the components of grapefruit juice responsible for its inhibitory effects therefore centered on P450 3A4 inhibitors.

A major unique component of grapefruit juice is the flavonoid, naringen. It can make up to 10% of the dry weight of the juice and is responsible for the bitter taste. The initial study on inhibition of P450 3A4 found that naringen was essentially ineffective; the aglycone of naringen, narinengen, however, did inhibit nifedipine oxidation with an IC_{50} of 100 μM [365]. In the same study, it was shown that other aglycone flavonoids unique to grapefruit, quercetin, kaempferol, apegenin, and hesperetin, also inhibited nifedipine oxidation with respective approximate IC_{50}s of 80, 90, 300, and 300 μM (Fig. 2.21). Additional studies confirmed the ability of these flavonoids to inhibit 3A4 specific activities, including nifedipine oxidation [366], midazolam α-hydroxylation [40, 367], quinidine 3-hydroxylation [367],

17ß-estradiol metabolism [368], and saquinavir metabolism [369]. Two clinical studies examined the relative inhibitory action of quercetin versus grapefruit juice on nifedipine pharmacokinetics [370] and naringen versus grapefruit juice on felodipine pharmacokinetics [371]. Neither flavoniods when administered at doses comparable to those in the grapefruit juice caused any effect on the bioavailability of the drug [370, 371].

Examination of the inhibitory capacity of HPLC fractions of extracts of grapefruit juice pointed to the furanocoumarin components of grapefruit juice as other inhibitors of P450 3A4 [369, 372–374]. Their inhibitory capacity for 3A4-related substrates was 1- to 2-orders of magnitude greater than the flavonoids (Fig. 2.21). Subsequent studies demonstrated that the furanocoumarins were mechanism-based inhibitors of P450 3A4 [364, 375], which was consistent with the loss of 3A4 content in enterocytes. With only limited amounts of the furanocoumarins available, there has not yet been a clinical study to indicate they can substitute for grapefruit juice in causing drug interactions. Their role in grapefruit juice drug interactions therefore has not yet been established.

The effect of grapefruit juice may not be limited to 3A4 substrates, one of the furanocoumarins, bergamottin, was shown to inhibit activities selective for P450s 2A6, 2C9, 2D6, 2E1, and 3A4 all with IC_{50}s in the 2–6 μM range [376]. In addition, Fuhr et al. found that grapefruit juice decreases the oral clearance of caffeine, a P450 1A2 substrate [377]. Grapefruit juice also effects P-glycoprotein-mediated transport; increasing the basolateral to apical flux [369, 378, 379]. The relative role the transporter and P450 3A4 have on a drug's bioavailability may also be important in determining the active component in the effect of grapefruit juice. For benzodiazepines undergoing oxidative metabolism, P450 3A4 appears to be more important.

Coadministration of grapefruit juice was found to increase the AUC of oral, but not intravenous, midazolam [380, 381], oral triazolam [382], and oral alprazolam [383] (Table 2.29). In normal subjects, the effect was modest, and accompanied with no or only minor effects on the pharmacodynamics of the benzodiazepines [380, 382–384]. In a study performed on subjects with cirrhosis of the liver, the effect of grapefruit juice was much greater, and a related decrease in the C_{max} and AUC of the 1-hydroxy-metabolite was found that was not seen in normal subjects [381]. This suggests that cirrhotics are more dependent upon intestinal metabolism of midazolam. In a study on other juices, tangerine juice was found to delay the absorption of midazolam and slightly delay its pharmacodynamic effects [385] (Table 2.29).

Interactions with Miscellaneous Agents

Clinical studies concerning potential drug interactions with benzodiazepines have been performed with a number of drugs for which either only a single drug in its class was studied, or there was no explicit connection with an aspect of drug metabolism. These studies will be considered in this section.

Table 2.29 Drug interactions with juices

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Grapefruit juice	250–400 mL								
Midazolam	10, or	13/12						+	[384]
Midazolam	5, iv	8 m			1.00	1.04	0.95	0	[380]
1-hydroxy			0.89	1.19	1.00	1.06			
Midazolam	15, or	8m			0.98	1.52*	0.96	++	[380]
1-hydroxy			2.05*	1.00	1.00	1.30*			
Midazolam	15, or	3f, 7m[a]	1.24	1.16	1.00	2.31*			[381]
1-hydroxy			1.73	0.27*	1.06	0.38*			
Triazolam	0.25, or	13/12						0	[384]
Triazolam	0.25, or	4f, 6m	1.67	1.25*	1.18	1.47*		+	[382]
Grapefruit juice	200 mL 3/d, multidose								
Alprazolam	0.8, or	6m	0.83	1.08	1.38*	1.18*		+	[383]
Tangerine juice	100 mL at -0.25 h and 100 mL at 0 h								
Midazolam	15, or	4f, 4m	2.00*	0.82	1.00	0.86		Delay	[385]
1-hydroxy			1.25*	0.70*	0.95	0.87			

[a]Subjects had liver cirrhosis

Interactions with Methylxanthines

Intravenous aminophylline, a prodrug of theophylline, was tested as a potential antagonist of diazepam. It produces a slight, but insignificant decrease in the T_{max} and C_{max} of diazepam, with no effect on the AUC. It did produce a significant decrease in the pharmacodynamic measures of diazepam [386] (Table 2.30). The effect of chronic theophylline on alprazolam was compared in subjects with chronic obstructive pulmonary disease that were or were not taking theophylline. Following 7 days of 1/d alprazolam the pharmacokinetics were compared in the two groups; in the group taking theophylline a significant decrease in the steady-state level and AUC of alprazolam was observed [387] (Table 2.30). Caffeine was found to have no effect on the pharmacokinetics of diazepam [388] or alprazolam [231]; but caffeine did slightly diminish the pharmacodynamic measures for diazepam [388] (Table 2.30).

Interactions with Antipyrine

Antipyrine has long been known to be an inducer of drug metabolism in humans. In an initial study, Ohnhaus et al. [389] demonstrated that a 7-day treatment with antipyrine significantly decreased the AUC and $t_{1/2}$ of oral diazepam. In this study, the AUC and $t_{1/2}$ of N-desmethyldiazepam were also significantly decreased. In a follow-up study comparing the effects of antipyrine and rifampin on the elimination of diazepam, 7-day pretreatment with antipyrine had similar effects on the parent drug, the AUCs of the N-desmethyl-, 3-hydroxy-, and oxazepam metabolites were not suppressed as much suggesting relative induction of these pathways [323] (Table 2.30).

Table 2.30 Drug interactions with miscellaneous agents

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Aminophylline	5.6 mg/kg, iv								
Diazepam	0.25/kg, or	8m	0.75	0.86		1.00		–	[386]
Theophylline	Chronic for obstructive pulmonary disease								
Alprazolam	0.5, or, 7d	6/5		0.25ss*		0.32*			[387]
Caffeine	6 mg/kg (diaz) or 100 mg (alpr) at 0 h								
Diazepam	0.3/kg, or	3f, 3m	1.00	1.00				-	[388]
Alprazolam	1, or	9	1.08	1.03	1.22	1.07	0.82		[231]
Antipyrine	600 mg, oral 2/d, multidose								
Diazepam	10, or	2f, 5m	1.09	0.95	0.49*		1.93*		[389]
N-desmethyl					0.42*	0.46*			
Diazepam	10, or	7	0.82	1.01	0.59*	0.51	2.02*		[323]
N-desmethyl						0.84	1.40r		
3-hydroxy						0.82	1.28r		
Oxazepam						1.06	0.87r		
Disulfiram	500 mg, or 1/d, multidose								
Chlordiazepoxide	50, iv	6			1.84*		0.46*		[390]
Diazepam	0.143/kg, or	6	0.85	0.97	1.37*		0.59*		[390]
Oxazepam	0.429/kg, or	5	1.00	0.83	1.17		1.02		[390]
Disulfiram	Chronic treatment of alcoholics								
Alprazolam	2, or	5f, 6m	1.19	0.88	0.92	0.94			[391]
Diflunisal	500 mg, or 2/d, multidose								
Oxazepam	30, or	6m	0.96	0.62*	1.13	0.84	1.48*		[432]
Glucuronide			1.20	1.34	1.30*	1.70*	0.62r*		
Glucocorticoid	Chronic treatment								
Midazolam	0.2/kg, iv	8/10			0.96	0.64	1.27		[392]
1-hydroxy					0.60*	0.67			
Dexamethasone	1.5 mg, or 1/d, multidose								
Triazolam	0.5, or	8f, 2m	1.00	1.15	1.05	0.82		0	[393]
Paracetamol	1 g/d from –1d to +3d								
Diazepam	10, or	1f, 2m	1.00	1.01	1.12		0.94		[394]
Probenecid	2 g, or at –2 h (adin) or 500 mg, oral 4/d (lor) or 500 mg 1/d (tem, nit) multidose								
Adinazolam	60, or	16m	0.67	1.37*	1.06	1.13*	0.84*	++	[396]
N-desmethyl			1.92*	1.49*	0.90	1.77*			
Lorazepam	2, iv	9			2.31*		0.55*		[395]
Nitrazepam	5, or	8	1.20	1.08	1.21*		0.75*		[327]
Temazepam	10, or	8	1.09	0.93	1.06		0.90		[327]
Modafinil	200 mg/d, 7d; 400 mg/d, 21d								
Triazolam	0.125, or	16f	1.43*	0.56*	0.65*	0.38*			[398]
Herbal dietary supplements									
Garlic oil	*500 mg, 3/d, 28d*								
Midazolam	8, or	6f, 6m		1.00	(1-h 1′-OH/midazolam)				[399]

(continued)

Table 2.30 (continued)

Inhibitor/Benzo	Dose	N	T_{max}	C_{max}	$t_{1/2}$	AUC	Cl	PhDyn	Reference
Panax ginseng 500 mg, 3/d, 28d (5% ginseosides)									
Midazolam	8, or	6f, 6m		1.00		(1-h 1′-OH/midazolam)			[399]
Ginkgo biloba 60 mg, 4/d, 28d (24% flavone glycosides; 6 terpene lactones)*									
Midazolam	8, or	6f, 6m		1.00		(1-h 1′-OH/midazolam)			[399]
Hypericum perforatum (St. John's wort) 300 mg, 3/d, 28d (0.3% hypericin)									
Midazolam	8, or	6f, 6m		1.98*		(1-h 1′-OH/midazolam)			[399]

Interactions with Disulfiram

Both disulfiram and certain benzodiazepines are used to treat alcoholism. Chronic disulfiram treatment was found to diminish the elimination of chlordiazepoxide and diazepam, but not that of oxazepam in normal subjects (Table 2.30). The clearance and $t_{1/2}$ of the three benzodiazepines in chronic alcoholics who had received chronic disulfiram treatment were similar to those in the disulfiram treated normal subjects [390]. In a study with 11 chronic alcoholics, alprazolam was given prior to initiation of disulfiram treatment and again after 2 weeks of disulfiram; no change in the pharmacokinetics of alprazolam was noted [391] (Table 2.30).

Interaction with Diflunisal

Diflunisal is a salicyclic derived non-steroidal anti-inflammatory agent. Like oxazepam it is primarily eliminated after glucuronidation, and both are highly protein bound. When oxazepam was given before and after 7 days of 2/d treatment with diflunisal, the C_{max} of oxazepam was decreased and its oral clearance increased. Significant increases were also found in the $t_{1/2}$ and AUC, and decrease in the clearance of the oxazepam glucuronide (Table 2.30). The authors conclude the interaction resulted from the displacement of oxazepam from its protein binding sites and by inhibition of the tubular secretion of the oxazepam glucuronide.

Interactions with Glucocorticoids

The effect of glucocorticoids (primarily predonisolone) on the pharmacokinetics of midazolam was studied by comparing surgery patients receiving intravenous midazolam who were on chronic glucocorticoid therapy to those who were not [392]. There was a decrease in the AUC of midazolam and 1′-hydroxymidazolam and increase in the clearance of midazolam in the glucocorticoid group, but the changes did not reach significance (Table 2.30). The $t_{1/2}$ of 1′-hydroxymidazolam was significantly decreased and the renal clearance of its glucuronide significantly increased. The authors concluded that these findings were consistent with the induction

of P450 and/or glucuronidation [392]. Five daily "small" doses of dexamethasone were found to have no significant effect on the pharmacokinetics or pharmacodynamics of triazolam in normal volunteers [393] (Table 2.30).

Interaction with Paracetamol

When paracetamol was taken 1 day before and 3 days following a single oral dose of diazepam, there was no effect on the plasma pharmacokinetics of diazepam (Table 2.30). The authors did detect a significant decrease in the percentage of diazepam plus metabolites excreted in urine over a 96-h period [394]. The findings suggest that paracetamol may decrease the glucuronidation of diazepam metabolites.

Interactions with Probenecid

Probenecid is well known for its ability to inhibit renal tubular secretion of organic acids. The effect of probenecid on the elimination of benzodiazepines was first studied with lorazepam. Abernethy et al. [395] gave probenecid 4/d from 12 h before a single intravenous dose of lorazepam. The $t_{1/2}$ of lorazepam was significantly increased and its clearance significantly decreased (Table 2.30). This result suggested not just inhibition of excretion, but also inhibition of glucuronide formation [395]. Brockmeyer et al. [327] studied the pharmacokinetics of nitrazepam and temazepam both before and after 7 days treatment with probenecid. With nitrazepam, there was a moderate increase in $t_{1/2}$ and decrease in clearance (Table 2.30). With temazepam there was no significant effect on plasma pharmacokinetics (Table 2.30), but there was reduced urinary content of the temazepam glucuronide [327]. When adinazolam was given with probenecid [396], there were increases in the C_{max} and AUC for both adinazolam and its N-desmethyl metabolite, more so for the metabolite. This was associated with potentiation of the psychomotor effects of the benzodiazepine (Table 2.30). The authors suggest that the major effect is on the elimination of the metabolite [396]. Probenecid does effect the renal elimination of many benzodiazepines; it may also have an effect on glucuronidation and possibly P450-mediated reactions.

Interaction with Modafinil

Modafinil is a novel wake-promoting agent used to treat excessive daytime sleepiness. In (HLM), modafinal inhibited P450 2C19, with no significant effect on the other P450 activities studied. In cultured human hepatocytes, it induced P450s 1A2, 2B6, and 3A4/5 [397]. The effect of modafinal on the pharmacokinetics of triazolam (and ethinyl estradiol) was studied in females taking daily birth control medication containing ethinyl estradiol [398]. In a group of woman given triazolam before and after

28 days of treatment with modafinal, there was a significant induction of the elimination of triazolam (Table 2.30).

Interactions with Herbal Dietary Supplements

Gurley and coworkers [399] studied the effect on 28-day use of various herbal supplements (St. John's wort, garlic oil, *Panax ginseng*, *Ginkgo biloba*) on a P450 phenotyping "cocktail" designed to measure 1A2, 2D6, 2E1, and 3A4 activities. The ratio of 1′-OH-midazolam to midazolam in 1-h serum samples was used to monitor P450 3A4. Individuals had the phenotyping cocktail before and after a 28-day period of use of the supplement, each supplement use was separated by a 30-day washout period. St. John's wort (*Hypericum perforatum*) was found to increase the 1′-OH/midazolam almost 98% indicating induction of its metabolism. None of the other supplements affected the P450 3A4 phenotype ratio (Table 2.30). St. John's wort also induced P450 2E1; while garlic oil decreased 2E1 [399].

Conclusions

A number of drugs and some dietary substances are known to interact with the benzodiazepines. Other CNS depressants including ethanol, opioids, and anesthetics have an additive effect on the pharmacodynamics of the benzodiazepine that is unrelated to the route of benzodiazepine metabolism. When an inhibition of metabolism is also encountered, the effect may be synergistic. Interactions with other drugs and dietary substances are generally based upon an interaction at the site of metabolism. Most often this reflects the involvement of P450 3A4, but in some instances the involvement of 2C19 in diazepam metabolism, and glucuronidation are also sites of interaction. A few examples of displacement from protein binding and inhibition of renal tubular secretion also exist. These metabolic interactions can vary from having little or no effect on the pharmacodynamics to inhibitions that produce toxic side effects and inductions that essentially negate the pharmacodynamics of the benzodiazepine. These studies, however, have been conducted at "normal" therapeutic doses. A misadventure with either or both interactant is likely to magnify the end result.

Appendix

Appendix 2.1 Key to drug interaction tables

Interacting drug	The route is oral, unless stated otherwise. An indication of the duration of treatment is given, and when different the benzodiazepines considered are noted separately in parentheses (e.g., triaz a, triaz b)
Benzodiazepines	The benzodiazepine of interest is indented 1/4 in., if a metabolite was also studied, it is listed directly below with a 1/2-inch indentation

Dose	All doses are in mg. The abbreviations for route of administration are: or, oral; iv, intravenous; im, intramuscular
N	For cross-over studies, only one group of subject numbers is provided; if gender was specified, females are noted with a "f"; males with a "m" (e.g., 8 or 4f, 4m). For comparisons between groups, a "/" separates the groups; the one receiving the interactant is listed first (50/40, refers to a study where 50 subjects received the interactant and 40 did not)
Pharmacokinetics	Are presented as the ratio of the interactant to the control group. Findings presented as significant by the authors are noted with an asterisk "*"
T_{max}	Time to maximal plasma (serum or blood) concentration
C_{max}	Maximum plasma (serum or blood) concentration. If ratio is followed by "ss," this was a steady-state measurement
$t_{1/2}$	Terminal elimination half-life
AUC	Area under the time versus concentration curve. If the AUC for both the actual time of measurement and one extrapolated to infinity were presented, the former was used
Cl	Clearance for iv administration; apparent oral clearance for oral administration. If followed by an "r," this refers to renal clearance
PhDyn	A qualitative assessment of the results of pharmacodynamic measures recorded in the study. This was both an assessment of the degree of change and the number of measures that changed: 0 – no effect; – to – – – –, a diminution in the pharmacodynamics ranging from slight to loss al all effect; + to ++++, an enhancement of the pharmacodynamics ranging from slight to toxic

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References

1. Greenblatt DJ, Shader RI, and Abernethy DR. Drug Therapy. Current status of benzodiazepines. First of two parts. N Engl J Med, 309: 354–358 (1983).
2. Greenblatt DJ, Shader RI, and Abernethy DR. Drug Therapy. Current status of benzodiazepines. Second of two parts. N Eng J of Med, 309: 410–416 (1983).
3. Jones GR, and Singer PP. The newer benzodiazepines. In *Analytical Toxicology*, 2., Baselt RC, Ed. Year Book Medical Publishers, Chicago, 1989, pp. 1–69.
4. Hobbs WR, Rall TW, and Verdoorn TA. Hypnotics and sedatives: ethanol. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, and Gilman AG, Ed. McGraw-Hill, New York, 1996, pp. 361–396.
5. Benet LZ, Oie S, and Schwartz JB. Design and optimization of dosage regimes: pharmacokinetic data. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, Hardman JG,

Limbird LE, Molinoff PB, Ruddon RW, and Gilman AG, Ed. McGraw-Hill, New York, 1996, pp. 1707–1792.
6. Baselt RC, and Cravey RH. *Disposition of toxic drugs and chemicals in man*. Chemical Toxicology Institute, Foster City, CA, 1995.
7. Parfitt K. Martindale The Complete Drug Reference. (1999).
8. Murray L. Physicians' Desk Reference. (2002).
9. ® TM. Healthcare Series. (2009).
10. Ishigami M, Honda T, Takasaki W, Ikeda T, Komai T, Ito K, and Sugiyama Y. A comparison of the effects of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-COA) reductase inhibitors on the CYP3A4-dependent oxidation of mexazolam in vitro. Drug Metab Dispos, 29: 282–288 (2001).
11. Sethy VH, Collins RJ, and Daniels EG. Determination of biological activity of adinazolam and its metabolites. J Pharm Pharmacol, 36: 546–548 (1984).
12. Fleishaker JC, and Phillips JP. Adinazolam pharmacokinetics and behavioral effects following administration of 20–60 mg doses of its mesylate salt in volunteers. Psychopharmacology, 99: 34–39 (1989).
13. Borchers F, Achtert G, Hausleiter HJ, and Zeugner H. Metabolism and pharmacokinetics of metaclazepam (Talis®), Part III: Determination of the chemical structure of metabolites in dogs, rabbits and men. Eur J Drug Metab Pharmacokinet, 9: 325–346 (1984).
14. Lu X-L, and Yang SK. Enantiomer resolution of camazepam and its derivatives and enantioselective metabolism of camazepam by (HLM). J Chromatogr A, 666: 249–257 (1994).
15. Tomori E, Horvath G, Elekes I, Lang T, and Korosi J. Investigation of the metabolites of tofizopam in man and animals by gas-liquid chromatography-mass spectrometry. J Chromatogr A, 241: 89–99 (1982).
16. Wrighton SA, Vandenbranden M, Stevens JC, Shipley LA, Ring BJ, Rettie AE, and Cashman JR. In vitro methods for assessing human drug metabolism: their use in drug development. Drug Metab Rev, 25: 453–484 (1993).
17. Rodrigues AD. Use of in vivo human metabolism studies in drug development: an industrial perspective. Biochem Pharmacol, 48: 2147–2156 (1994).
18. Guengerich FP. In vitro techniques for studying drug metabolism. J Pharmacokin Biopharm, 24: 521–533 (1996).
19. Crespi CL, and Miller VP. The use of heterologously expressed drug metabolizing enzymes – state of the art and prospects for the future. Pharmacol Ther, 84: 121–131 (1999).
20. Venkatakrishnan K, Von Moltke LL, Court MH, Harmatz JS, Crespi CL, and Greenblatt DJ. Comparison between cytochrome P450 (CYP) content and relative activity approaches to scaling from cDNA-expressed CYPs to (HLM): ratios of accessory proteins as sources of discrepancies between approaches. Drug Metab Dispos, 28: 1493–1504 (2000).
21. Nelson AC, Huang W, and Moody DE. Variables in human liver microsome preparation: impact on the kinetics of *l*-α-acetylmethadol (LAAM) N-demethylation and dextromethorphan O-demethylation. Drug Metab Dispos, 29: 319–325 (2001).
22. Newton DJ, Wang RW, and Lu AYH. Cytochrome P450 inhibitors: evaluation of specificities in the in vitro metabolism of therapeutic agents by (HLM). Drug Metab Dispos, 23: 154–158 (1995).
23. Ono S, Hatanaka T, Hotta H, Satoh T, Gonzalez FJ, and Tsutsui M. Specificity of substrate and inhibitor probes for cytochrome P450s: evaluation of in vitro metabolism using cDNA-expressed human P450s and (HLM). Xenobiotica, 26: 681–693 (1996).
24. Sai Y, Dai R, Yang TJ, Krausz KW, Gonzalez FJ, Gelboin HV, and Shou M. Assessment of specificity of eight chemical inhibitors using cDNA-expressed cytochromes P450. Xenobiotica, 30: 327–343 (2000).
25. Moody DE, James JL, Clawson GA, and Smuckler EA. Correlations among changes in hepatic microsomal components after intoxication with alkyl halides. Mol Pharmacol, 20: 685–693 (1981).
26. Shimada T, Tsumura F, and Yamazaki H. Prediction of human liver microsomal oxidations of 7-ethoxycoumarin and chlorzoxazone with kinetic parameters of recombinant cytochrome P-450 enzymes. Drug Metab Dispos, 27: 1274–1280 (1999).

27. Neff JA, and Moody DE. Differential N-demethylation of l-α-acetylmethadol (LAAM) and norLAAM by cytochrome P450s 2B6, 2C18, and 3A4. Biochem Biophys Res Commun, 284: 751–756 (2001).
28. Andersson T, Miners JO, Veronese ME, and Birkett DJ. Diazepam metabolism by (HLM) is mediated by both S-mephenytoin hydroxylase and CYP3A isoforms. Br J Clin Pharmacol, 38: 131–137 (1994).
29. Ono S, Hatanaka T, Miyazawa S, Tsutsui M, Aoyama T, Gonzalez FJ, and Satoh H. Human liver microsomal diazepam metabolism using cDNA-expressed cytochrome P450s: role of CYP2B6, 2C19 and the 3A subfamily. Xenobiotica, 26: 1155–1166 (1996).
30. Yang TJ, Shou M, Korzekwa KR, Gonzalez FJ, Gelboin HV, and Yang SK. Role of cDNA-expressed human cytochromes P450 in the metabolism of diazepam. Biochem Pharmacol, 55: 889–896 (1998).
31. Yang TJ, Krausz KW, Sai Y, Gonzalez FJ, and Gelboin HV. Eight inhibitory monoclonal antibodies define the role of individual P-450 s in human liver microsomal diazepam, 7-ethoxycoumarin, and imipramine metabolism. Drug Metab Dispos, 27: 102–109 (1999).
32. Shou MG, Lu T, Krausz KW, Sai Y, Yang TJ, Korzekwa KR, Gonzalez FJ, and Gelboin HV. Use of inhibitory monoclonal antibodies to assess the contribution of cytochromes P450 to human drug metabolism. Eur J Pharmacol, 394: 199–209 (2000).
33. Niwa T, Shiraga T, Ishii I, Kagayama A, and Takagi A. Contribution of human hepatic cytochrome P450 isoforms to the metabolism of psychotropic drugs. Biol Pharm Bull, 28: 1711–1716 (2005).
34. Fabre G, Rahmani R, Placidi M, Combalbert J, Covo J, Cano J-P, Coulange C, Ducros M, and Rampal M. Characterization of midazolam metabolism using hepatic microsomal fractions and hepatocytes in suspension obtained by perfusing whole human livers. Biochem Pharmacol, 37: 4389–4397 (1988).
35. Kronbach T, Mathys D, Umeno M, Gonzalez FJ, and Meyer UA. Oxidation of midazolam and triazolam by human liver cytochrome P450IIIA4. Mol Pharmacol, 36: 89–96 (1989).
36. Gorski JC, Hall SD, Vandenbranden M, Wrighton SA, and Jones DR. Regioselective biotransformation of midazolam by members of the human cytochrome p450 3A (CYP3A) subfamily. Biochem Pharmacol, 47: 1643–1653 (1994).
37. Thummel KE, Shen DD, Podoll TD, Kunze KL, Trager WF, Hartwell PS, Raisys VA, Marsh CL, McVicar JP, Barr DM, Perkins JD, and Carithers J, R.L. Use of midazolam as a human cytochrome P450 3 probe: In vitro-in vivo correlations in liver transplant patients. J Pharmacol Exp Ther, 271: 54956 (1994).
38. Wandel C, Bocker R, Bohrer H, Browne A, Rugheimer E, and Martin E. Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaesth, 73: 658–661 (1994).
39. Wrighton SA, and Ring BJ. Inhibition of human CYP3A catalyzed 1′-hydroxy midazolam formation by ketoconazole, nifedipine, erythromycin, cimetidine, and nizatidine. Pharm Res, 11: 921–924 (1994).
40. Ghosal A, Satoh H, Thomas PE, Bush E, and Moore D. Inhibition and kinetics of cytochrome P4503A activity in microsomes from rat, human, and cDNA-expressed human cytochrome P450. Drug Metab Dispos, 24: 940–947 (1996).
41. von Moltke LL, Greenblatt DJ, Schmider J, Duan SX, Wright CE, Harmatz JS, and Shader RI. Midazolam hydroxylation by (HLM) in vitro: Inhibition by fluoxetine, norfluoxetine, and by azole antifungal agents. J Clin Pharmacol, 36: 783–791 (1996).
42. Ekins S, Vandenbranden M, Ring BJ, Gillespie JS, Yang TJ, Gelboin HV, and Wrighton SA. Further characterization of the expression in liver and catalytic activity of CYP2B6. J Pharmacol Exp Ther, 286: 1253–1259 (1998).
43. Wandel C, Bocker RH, Bohrer H, deVries JX, Hofman W, Walter K, Kleingeist B, Neff S, Ding R, Walter-Sack I, and Martin E. Relationship between hepatic cytochrome P450 3A content and activity and the disposition of midazolam administered orally. Drug Metab Dispos, 26: 110–114 (1998).
44. Perloff MD, von Moltke LL, Court MH, Kotegawa T, Shader RI, and Greenblatt DJ. Midazolam and triazolam biotransformation in mouse and (HLM): Relative contribution of CYP3A and CYP2C isoforms. J Pharmacol Exp Ther, 292: 618–628 (2000).

45. Hamaoka N, Oda Y, Hase I, and Asada A. Cytochrome P4502B6 and 2C9 do not metabolize midazolam: kinetic analysis and inhibition study with monoclonal antibodies. Brit J Anaesth, 86: 540–544 (2001).
46. He P, Court MH, Greenblatt DJ, and von Moltke LL. Factors influencing midazolam hydroxylation activity in (HLM). Drug Metab Dispos, 34: 1198–1207 (2006).
47. von Moltke LL, Greenblatt DJ, Harmatz JS, Duan SX, Harrel LM, Cotreau-Bibbo MM, Pritchard GA, Wright CE, and Shader RI. Triazolam biotransformation by (HLM) in vitro: Effects of metabolic inhibitors and clinical confirmation of a predicted interaction with ketoconazole. J Pharmacol Exp Ther, 276: 370–379 (1996).
48. Schmider J, Greenblatt DJ, von Moltke LL, Harmatz JS, Duan SX, Karsov D, and Shader RI. Characterization of six in vitro reactions mediated by human cytochrome P450: application to the testing of cytochrome P450-directed antibodies. Pharmacology, 52: 125–134 (1996).
49. Gorski JC, Jones DR, Hamman MA, Wrighton SA, and Hall SD. Biotransformation of alprazolam by members of the human cytochrome P4503A subfamily. Xenobiotica, 29: 931–944 (1999).
50. Hirota N, Ito K, Iwatsubo T, Green CE, Tyson CA, Shimada N, Suzuki H, and Sugiyama Y. In vitro/in vivo scaling of alprazolam metabolism by CYP3A4 and CYP3A5 in humans. Biopharm Drug Dispos, 22: 53–71 (2001).
51. Allqvist A, Miura J, Bertilsson L, and Mirghani RA. Inhibition of CYP3A4 and CYP3A5 catalyzed metabolism of alprazolam and quinine by ketoconazole as racemate and four different enantiomers. Eur J Clin Pharmacol, 63: 173–179 (2007).
52. Venkatakrishnan K, von Moltke LL, Duan SX, Fleishaker JC, Shader RI, and Greenblatt DJ. Kinetic characterization and identification of the enzymes responsible for hepatic biotransformation of adinazolam and N-desmethyladinazolam in man. J Pharm Pharmacol, 50: 265–274 (1997).
53. Coller JK, Somogyi AA, and Bochner F. Flunitrazepam oxidative metabolism in (HLM): involvement of CYP2C19 and CYP3A4. Xenobiotica, 29: 973–986 (1999).
54. Hesse LM, Venkatakrishnan K, von Moltke LL, Shader RI, and Greenblatt DJ. CYP3A4 is the major CYP isoform mediating the in vitro hydroxylation and demethylation of flunitrazepam. Drug Metab Dispos, 29: 133–140 (2001).
55. Kilicarslan T, Haining RL, Rettie AE, Busto U, Tyndale RF, and Sellers EM. Flunitrazepam metabolism by cytochrome P450s 2C19 and 3A4. Drug Metab Dispos, 29: 460–465 (2001).
56. Senda C, Kishimoto W, Sakai K, Nagakura A, and Igarashi T. Identification of human cytochrome P450 isoforms involved in the metabolism of brotizolam. Xenobiotica, 27: 913–922 (1997).
57. Giraud C, Tran A, Rey E, Vincent J, Treluyer JM, and Pons G. In vitro characterization of clobazam metabolism by recombinant cytochrome P450 enzymes: Importance of CYP2C19. Drug Metab Dispos, 32: 1279–1286 (2004).
58. Miura M, and Ohkubo T. In vitro metabolism of quazepam in human liver and intestine and assessment of drug interactions. Xenobiotica, 34: 1001–1011 (2004).
59. Miura M, Otani K, and Ohkubo T. Identification of human cytochrome P450 enzymes involved in the formation of 4-hydroxyestazolam from estazolam. Xenobiotica, 35: 455–465 (2005).
60. Shimada T, Yamazaki H, Mimura M, Inui Y, and Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther, 270: 414–423 (1994).
61. Floyd MD, Gervasini G, Masica AL, Mayo G, George AL, Bhat K, Kim RB, and Wilkinson GR. Genotype-phenotype associations for common CYP3A4 and CYP3A5 variants in the basal and induced metabolism of midazolam in European- and African-American men and women. Pharmacogenetics, 13: 595–606 (2003).
62. He P, Court MH, Greenblatt DJ, and von Moltke LL. Genotype-phenotype associations of cytochrome P450 3A4 and 3A5 polymorphism with midazolam clearance in vivo. Clin Pharmacol Ther, 77: 373–387 (2005).

63. Perera MA, Thirumaran RK, Cox NJ, Hanauer S, Das S, Brimer-Cline C, Lamba V, Schuetz EG, Ratain MJ, and Di Rienzo A. Prediction of CYP3A4 enzyme activity using haplotype tag SNPs in African Americans. Pharmacogenomics J, 9: 49–60 (2009).
64. Oneda B, S. C, Sirot EJ, Bochud M, Ansermot N, and Eap CB. The P450 oxidoreductase genotype is associated with CYP3A4 activity as measured by the midazolam phenotyping test. Pharmacogenet Genom, 19: 877–883 (2009).
65. Park JY, Kim KA, Park PW, Lee OJ, Kang DK, Shon JH, Liu KH, and Shin JG. Effect of CYP3A5*3 genotype on the pharmacokinetics and pharmacodynamics of alprazolam in healthy subjects. Clin Pharmacol Ther, 79: 590–599 (2006).
66. Bertilsson L, Henthorn TK, Sanz E, Tybring G, Sawe J, and Villen T. Importance of genetic factors in the regulation of diazepam metabolism: Relationship to S-mephenytoin, but not debrisoquin, hydroxylation phenotype. Clin Pharmacol Ther, 45: 348–355 (1989).
67. Sohn D-R, Kusaka T, Shin SG, Jang I-J, Shin JG, and Chiba K. Incidence of S-mephenytoin hydroxylation deficiency in a Korean population and the interphenotypic differences in diazepam pharmacokinetics. Clin Pharmacol Ther, 52: 160–169 (1992).
68. Qin Y-P, Xie H-G, Wang W, He N, Huang S-L, Xu Z-H, Ou-Yang D-S, Wang Y-J, and Zhou H-H. Effect of the gene dosage of CYP2C19 on diazepam metabolism in Chinese subjects. Clin Pharmacol Ther, 66: 642–646 (1999).
69. Inomata S, Nagashima A, Itagaki F, Homma M, Nishimura M, Osaka Y, Okuyama KA, Tanaka E, Nakamura T, Kohda Y, Naito S, Miyabe M, and Toyooka H. CYP2C19 genotype affects diazepam pharmacokinetics and emergence from general anesthesia. Clin Pharmacol Ther, 78: 647–655 (2005).
70. Zhang Y, Reviriego J, Lou Y, Sjoqvist F, and Bertilsson L. Diazepam metabolism in native Chinese poor and extensive hydroxylators of S-mephenytoin: interethnic differences in comparison with white subjects. Clin Pharmacol Ther, 48: 496–502 (1990).
71. Bertilsson L, and Kalow W. Why are diazepam metabolism and polymorphic S-mephenytoin hydroxylation associated with each other in white and Korean populations but not in Chinese populations. Clin Pharmacol Ther, 53: 608–610 (1993).
72. Lennestal R, Lakso HA, Nilsson M, and Mjorndal T. Urine monitoring of diazepam abuse – new intake or not? J Anal Toxicol, 32: 402–407 (2008).
73. Contin M, Sangiorgi S, Riva R, Parmeggiani A, Albani F, and Baruzzi A. Evidence of polymorphic CYP2C19 involvement in the human metabolism of N-desmethylclobazam. Ther Drug Monit, 24: 737–741 (2002).
74. Parmeggiani A, Posar A, Sangiorgi S, and Giovanardi-Rossi P. Unuasual side-effects due to clobazam: a case report with genetic study of CYP2C19. Brain Dev, 26: 63–66 (2003).
75. Seo T, Nagata R, Ishitsu T, Murata T, Takaishi C, Hori M, and Nakagawa K. Impact of CYP2C19 polymorphisms on the efficacy of clobazam therapy. Pharmacogenomics, 9: 527–537 (2008).
76. Fukasawa T, Yasui-Furukori N, Suzuki A, Inoue Y, Tateishi T, and Otani K. Pharmacokinetics and pharmacodynamics of etizolam are influenced by polymorphic CYP2C19 activity. Eur J Clin Pharmacol, 61: 791–795 (2005).
77. Otani K, Yasui N, Kaneko S, Ohkubo T, Osanai T, Sugawara K, Hayashi K, Chiba K, and Ishizaki T. Effects of genetically determined S-mephenytoin 4-hydroxylation status and cigarette smoking on the single-dose pharmacokinetics of oral alprazolam. Neuropsychopharmacology, 16: 8–14 (1997).
78. Yasui N, Otani K, Ohkubo T, Osanai T, Sugawara K, Chiba K, Ishizaki T, and Kaneko S. Single-dose pharmacokinetics and pharmacodynamics of oral triazolam in relation to cytochrome P4502C19 (CYP2C19) activity. Ther Drug Monit, 19: 371–374 (1997).
79. Gafni I, Busto UE, Tyndale RF, Kaplan HL, and Sellers EM. The role of cytochrome P450 2C19 activity in flunitrazepam metabolism in vivo. J Clin Psychopharmacol, 23: 169–175 (2003).
80. Aoshima T, Fukasawa T, Otsuji Y, Okuyama N, Gerstenberg G, Miura M, Ohkubo T, Sugawara K, and Otani K. Effects of the CYP2C19 genotype and cigarette smoking on the single oral dose pharmacokinetics and pharmacodynamics of estazolam. Prog Neuro-Psych Biol Psych, 27: 535–538 (2003).

81. Abernethy DR, Greenblatt DJ, Ochs HR, and Shader RI. Benzodiazepine drug-drug interactions commonly occurring in clinical practice. Curr Med Res Opin, 8: (Suppl 4) 80–93 (1984).
82. Abernethy DR, Greenblatt DJ, and Shader RI. Benzodiazepine hypnotic metabolism: drug interactions and clinical implications. Acta Psychiatr Scand Suppl 332, 74: 32–38 (1986).
83. Yuan R, Flockhart DA, and Balian JD. Pharmacokinetic and pharmacodynamic consequences of metabolism-based drug interactions with alprazolam, midazolam, and triazolam. J Clin Pharmacol, 39: 1109–1125 (1999).
84. Sellers EM, and Busto U. Benzodiazepines and ethanol: assessment of the effects and consequences of psychotropic drug interactions. J Clin Psychopharmacol, 2: 249–262 (1982).
85. Chan AWK. Effects of combined alcohol and benzodiazepine: a review. Drug Alcohol Depend, 13: 315–341 (1984).
86. Linnoila MI. Benzodiazepines and alcohol. J Psychiat Res, 24: (Suppl 2) 121–127 (1990).
87. Tanaka E. Toxicological interactions between alcohol and benzodiazepines. Clin Toxicol, 40: 69–75 (2002).
88. Serfaty M, and Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980 s. Br J Psychiatry, 163: 386–393 (1993).
89. Buckley NA, Dawson AH, Whyte IM, and O'Connell DL. Relative toxicity of benzodiazepines in overdose. Br Med J, 310: 219–221 (1995).
90. Busto U, Kaplan HL, and Sellers EM. Benzodiazepine-associated emergencies in Toronto. Am J Psychiatry, 137: 224–227 (1980).
91. Finkle BS, McCloskey KL, and Goodman LS. Diazepam and drug-associated deaths: a survey in the United States and Canada. J Am Med Assoc, 242: 429–434 (1979).
92. Hojer J, Baehrendtz S, and Gustafsson L. Benzodiazepine poisoning: experience of 702 admissions to an intensive care unit during a 14-year period. J Int Med, 226: 117–122 (1989).
93. Richards RG, Reed D, and Cravey RH. Death from intravenously administered narcotics: a study of 114 cases. J Forensic Sci, 21: 467–482 (1976).
94. Monforte JR. Some observations concerning blood morphine concentrations in narcotic addicts. J Forensic Sci, 22: 718–724 (1977).
95. Goldberger BA, Cone EJ, Grant TM, Caplan YH, Levine BS, and Smialek JE. Disposition of heroin and its metabolites in heroin-related deaths. J Anal Toxicol, 18: 22–28 (1994).
96. Walsh SL, Preston KL, Stitzer ML, Cone EJ, and Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther, 55: 569–580 (1994).
97. Reynaud M, Tracqui A, Petit G, Potard D, and Courty P. Six deaths linked to misuse of buprenorphine-benzodiazepine combinations. Am J Psychiatry, 155: 448–449 (1998).
98. Papworth DP. High dose buprenorphine for postoperative analgesia. Anaesthesia, 38: 163 (1983).
99. Forrest AL. Buprenorphine and lorazepam. Anaesthesia, 38: 598 (1983).
100. Faroqui MH, Cole M, and Curran J. Buprenorphine, benzodiazepines and respiratory depression. Anaesthesia, 38: 1002–1003 (1983).
101. Gueye PN, Borron SW, Risede P, Monier C, Buneaux F, Debray M, and Baud FJ. Buprenorphine and midazolam act in combination to depress respiration in rats. Toxicol Sci, 65: 107–114 (2002).
102. Kilicarslan T, and Sellers EM. Lack of interaction of buprenorphine with flunitrazepam metabolism. Am J Psychiatry, 157: 1164–1166 (2000).
103. Chang Y, and Moody DE. Effect of benzodiazepines on the metabolism of buprenorphine in (HLM). Eur J Clin Pharmacol, 60: 875–881 (2005).
104. Crouch DJ, Birky MM, Gust SW, Rollins DE, Walsh JM, Moulden JV, Quinlan KE, and Beckel RW. The prevalence of drugs and alcohol in fatally injured truck drivers. J Forensic Sci, 38: 1342–1353 (1993).
105. Lund AK, Preusser DF, Blomberg RD, and Williams AF. Drug use by tractor-trailer drivers. J Forensic Sci, 33: 648–661 (1988).
106. Couper FJ, Pemberton M, Jarvis A, Hughes M, and Logan BK. Prevalence of drug use in commercial tractor-trailer drivers. J Forensic Sci, 47: 562–567 (2002).

107. Moody DE, Crouch DJ, Andrenyak DM, Smith RP, Wilkins DG, Hoffman AM, and Rollins DE. Mandatory post-accident drug and alcohol testing for the Federal Railroad Administration: A comparison of results for two consecutive years. NIDA Res Mono, 100: 79–96 (1991).
108. Lundberg GD, White JM, and Hoffman KI. Drugs (other than or in addition to ethyl alcohol) and driving behavior: a collaborative study of the California Association of Toxicologists. J Forensic Sci, 24: 207–215 (1979).
109. Poklis A, MaGinn D, and Barr JL. Drug findings in "driving under the influence of drugs" cases: a problem of illicit drug use. Drug Alcohol Depend, 20: 57–62 (1987).
110. Jonasson U, Jonasson B, Saldeen T, and Thuen F. The prevalence of analgesics containing dextropropoxyphene or codeine in individuals suspected of driving under the influence of drugs. Forensic Sci Int, 112: 163–169 (2000).
111. Logan BK, and Couper FJ. Zolpidem and driving impairment. J Forensic Sci, 46: 105–110 (2001).
112. Preston KL, Griffiths RR, Stitzer ML, Bigelow GE, and Liebson IA. Diazepam and methadone interactions in methadone maintenance. Clin Pharmacol Ther, 36: 534–541 (1984).
113. Preston KL, Griffiths RR, Cone EJ, Darwin WD, and Gorodetzky CW. Diazepam and methadone blood levels following concurrent administration of diazepam and methadone. Drug Alcohol Depend, 18: 195–202 (1986).
114. Abernethy DR, Greenblatt DJ, Morse DS, and Shader RI. Interaction of propoxyphene with diazepam, alprazolam and lorazepam. Br J Clin Pharmacol, 19: 51–57 (1985).
115. Gamble JAS, Kawar P, Dundee JW, Moore J, and Briggs LP. Evaluation of midazolam as an intravenous induction agent. Anaesthesia, 36: 868–873 (1981).
116. Boldy DAR, English JSC, Lang GS, and Hoare AM. Sedation for endoscopy: a comparison between diazepam, and diazepam plus pethidine with naloxone reversal. Br J Anaesth, 56: 1109–1111 (1984).
117. Tverskoy M, Fleyshman G, Ezry J, Bradley EL, and Kissin I. Midazolam-morphine sedative interaction in patients. Anesth Analges, 68: 282–285 (1989).
118. Kanto J, Sjovall S, and Vuori A. Effect of different kinds of premedication on the induction properties of midazolam. Br J Anaesth, 54: 507–511 (1982).
119. Tomicheck RC, Rosow CE, Philbin DM, Moss J, Teplick RS, and Scheider RC. Diazepam-fentanyl interaction-hemodynamic and hormonal effects in coronary artery surgery. Anesth Analg, 62: 881–884 (1983).
120. Dundee JW, Halliday NJ, McMurray TJ, and Harper KW. Pretreatment with opioids: the effect on thiopentone induction requirements and on the onset of action of midazolam. Anaesthesia, 41: 159–161 (1986).
121. Bailey PL, Pace NL, Ashburn MA, Moll JWB, East KA, and Stanley TH. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology, 73: 826–830 (1990).
122. Ben-Shlomo I, Abd-El-Khalim H, Ezry J, Zohar S, and Tverskoy M. Midazolam acts synergistically with fentanyl for induction of anaesthesia. Br J Anaesth, 64: 45–47 (1990).
123. Silbert BS, Rosow CE, Keegan CR, Latta WB, Murphy AL, Moss J, and Philbin DM. The effect of diazepam on induction of anesthesia with alfentanyl. Anesth Analg, 65: 71–77 (1986).
124. Vinik HR, Bradley EL, and Kissin I. Midazolam-alfentanyl synergism for anesthetic induction in patients. Anesth Analg, 69: 213–217 (1989).
125. Short TG, Plummer JL, and Chui PT. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanyl. Br J Anaesth, 69: 162–167 (1992).
126. Hase I, Oda Y, Tanaka K, Mizutani K, Nakamoto T, and Asada A. I.v. fentanyl decreases the clearance of midazolam. Br J Anaesth, 79: 740–743 (1997).
127. Yun CH, Wood M, Wood AJJ, and Guengerich FP. Identification of the pharmacogenetic determinants of alfentanil metabolism: cytochrome P-450 3A4. An explanation of the variable elimination clearance. Anesthesiology, 77: 467–474 (1992).
128. Labroo RB, Thummel KE, Kunze KL, Podoll T, Trager WF, and Kharasch ED. Catalytic role of cytochrome P4503A4 in multiple pathways of alfentanil metabolism. Drug Metab Dispos, 23: 490–496 (1995).

129. Tateishi T, Krivoruk Y, Ueng YF, Wood AJJ, Guengerich FP, and Wood M. Identification of human liver cytochrome p-450 3A4 as the enzyme responsible for fentanyl and sufentanil n-dealkylation. Anesth Analg, 82: 167–172 (1996).
130. Guitton J, Buronfosse T, Desage M, Flinois J-P, Perdrix J-P, Brazier J-L, and Beaune P. Possible involvement of multiple human cytochrome P450 isoforms in the liver metabolism of propofol. Br J Anaesth, 80: 788–795 (1998).
131. Oda Y, Mizutani K, Hase I, Nakamoto T, Hamaoka N, and Asada A. Fentanyl inhibits metabolism of midazolam: competitive inhibition of CYP3A4 in vitro. Brit J Anaesth, 82: 900–903 (1999).
132. Swift R, Davidson D, Rosen S, Fitz E, and Camara P. Naltrexone effects on diazepam intoxication and pharmacokinetics in humans. Psychopharmacology, 135: 256–262 (1998).
133. Tverskoy M, Fleyshman G, Bradley EL, and Kissin I. Midazolam-thiopental anesthetic interaction in patients. Anesth Analg, 67: 342–345 (1988).
134. Short TG, Galletly DC, and Plummer JL. Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. Br J Anaesth, 66: 13–19 (1991).
135. Short TG, and Chui PT. Propofol and midazolam act synergistically in combination. Br J Anaesth, 67: 539–545 (1991).
136. McClune S, McKay AC, Wright PMC, Patterson CC, and Clarke RSJ. Synergistic interaction between midazolam and propofol. Br J Anaesth, 69: 240–245 (1992).
137. Hamaoka N, Oda Y, Hase I, Mizutani K, Nakamoto T, Ishizaki T, and Asada A. Propofol decreases the clearance of midazolam by inhibiting CYP3A4: An in vivo and in vitro stidy. Clin Pharmacol Ther, 66: 110–117 (1999).
138. Miller E, and Park GR. The effect of oxygen on propofol-induced inhibition of microsomal cytochrome P450 3A4. Anaesthesia, 54: 320–322 (1999).
139. Bond A, Silveira JC, and Lader M. Effects of single doses of alprazolam and alcohol alone and in combination on psychological performance. Hum Psychopharmacol, 6: 219–228 (1991).
140. Taeuber K, Badian M, Brettel HF, Royen T, Rupp W, Sittig W, and Uihlein M. Kinetic and dynamic interaction of clobazam and alcohol. Br J Clin Pharmacol, 7: 91 S–97 S (1979).
141. Seppala T, Palva ES, Mattila MJ, Kortilla K, and Shrotriya RC. Tofisopam, a novel 3,4-benzodiazepine: multiple-dose effects on psychomotor skills and memory. Comparison with diazepam and interactions with ethanol. Psychopharmacology, 69: 209–218 (1980).
142. Saario I. Psychomotor skills during subacute treatment with thioridazine and bromazepam, and their combined effects with alcohol. Ann Clin Res, 8: 117–123 (1976).
143. McManus IC, Ankier SI, Norfolk J, Phillips M, and Priest RG. Effects of psychological performance of the benzodiazepine, loprazolam, alone and with alcohol. Br J Clin Pharmacol, 16: 291–300 (1983).
144. Palva ES, and Linnoila M. Effect of active metabolites of chlordiazepoxide and diazepam, alone or in combination with alcohol, on psychomotor skills related to driving. Eur J Clin Pharmacol, 13: 345–350 (1978).
145. Linnoila M, Stapleton JM, Lister R, Moss H, Lane E, Granger A, and Eckardt MJ. Effects of single doses of alprazolam and diazepam, alone and in combination with ethanol, on psychomotor and cognitive performance and on automatic nervous system reactivity in healthy volunteers. Eur J Clin Pharmacol, 39: 21–28 (1990).
146. Linnoila M, and Hakkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. Clin Pharmacol Ther, 15: 368–373 (1974).
147. Sellers EM, Frecker RC, and Romach MK. Drug metabolism in the elderly: confounding of age, smoking, and ethanol effects. Drug Metab Rev, 14: 225–250 (1983).
148. de la Maza MP, Hirsch S, Petermann M, Suazo M, Ugarte G, and Bunout D. Changes in microsomal activity in alcoholism and obesity. Alcohol Clin Exp Res, 24: 605–610 (2000).
149. Kostrubsky VE, Strom SC, Wood SG, Wrighton SA, Sinclair PR, and Sinclair JF. Ethanol and isopentanol increase CYP3A and CYP2E in primary cultures of human hepatocytes. Arch Biochem Biophys, 322: 516–520 (1995).
150. Scavone JM, Greenblatt DJ, Harmatz JS, and Shader RI. Kinetic and dynamic interaction of brotizolam and ethanol. Br J Clin Pharmacol, 21: 197–204 (1986).

151. Linnoila M, Otterstrom S, and Antilla M. Serum chlordiazepoxide, diazepam and thioridazine concentrations after the simultaneous ingestion of alcohol or placebo drink. Ann Clin Res, 6: 4–6 (1974).
152. Dorian P, Sellers EM, Kaplan HL, Hamilton C, Greenblatt DJ, and Abernethy D. Triazolam and ethanol interaction: kinetic and dynamic consequences. Clin Pharmacol Ther, 37: 558–562 (1985).
153. Ochs HR, Greenblatt DJ, Verburg-Ochs B, Harmatz JS, and Grehl H. Disposition of clotiazepam: influence of age, sex, oral contraceptives, cimetidine, isoniazid and ethanol. Eur J Clin Pharmacol, 26: 55–59 (1984).
154. Linnoila M, Erwin CW, Brendle A, and Loque P. Effects of alcohol and flunitrazepam on mood and performance in healthy young men. J Clin Pharmacol, 21: 430–435 (1981).
155. Girre C, Hirschhorn M, Bertaux L, Palombo S, and Fournier PE. Comparison of performance of healthy volunteers given prazepam alone or combined with ethanol. Relation to drug plasma concentrations. Int Clin Psychopharmacol, 6: 227–238 (1991).
156. Hayes SL, Pablo G, Radomoki T, and Palmer RG. Ethanol and oral diazepam absorption. N Engl J Med, 296: 186–189 (1977).
157. Laisi U, Linnoila M, Seppala T, Himberg J-J, and Mattila MJ. Pharmacokinetic and pharmacodynamic interactions of diazepam with different alcoholic beverages. Eur J Clin Pharmacol, 16: 263–270 (1979).
158. Sellers EM, Naranjo CA, Giles HG, Frecker RC, and Beeching M. Intravenous diazepam and oral ethanol interaction. Clin Pharmacol Ther, 28: 638–645 (1980).
159. Morland J, Setekleiv J, Haffner JFW, Stromsaether CE, Danielsen A, and Wethe GH. Combined effects of diazepam and ethanol on mental and psychomotor functions. Acta Pharmacol Toxicol, 34: 5–15 (1974).
160. Greenblatt DJ, Shader RI, Weinberger DR, Allen MD, and MacLaughlin DS. Effect of a cocktail on diazepam absorption. Psychopharmacology, 57: 199–203 (1978).
161. Divoll M, and Greenblatt DJ. Alcohol does not enhance diazepam absorption. Pharmacology, 22: 263–268 (1981).
162. Busby WF, Ackermann JM, and Crespi CL. Effect of methanol, ethanol, dimethyl sulfoxide, and acetonitrile on in vitro activities of cDNA-expressed human cytochromes P-450. Drug Metab Dispos, 27: 246–249 (1999).
163. Perry PJ, Wilding DC, Fowler RC, Helper CD, and Caputo JF. Absorption of oral and intramuscular chlordiazepoxide by alcoholics. Clin Pharmacol Ther, 23: 535–541 (1978).
164. Sellers EM, Greenblatt DJ, Zilm DH, and Degani N. Decline in chlordiazepoxide plasma levels during fixed-dose therapy of alcohol withdrawal. Br J Clin Pharmacol, 6: 370–372 (1978).
165. Sellman R, Pekkarinen A, Kangas L, and Raijola E. Reduced concentrations of plasma diazepam in chronic alcoholic patients following an oral administration of diazepam. Acta Pharmacol Toxicol, 36: 25–32 (1975).
166. Sellman R, Kanto J, Raijola E, and Pekkarinen A. Human and animal study on elimination from plasma and metabolism of diazepam after chronic alcohol intake. Acta Pharmacol Toxicol, 36: 33–38 (1975).
167. Pond SM, Phillips M, Benowitz NL, Galinsky RE, Tong TG, and Becker CE. Diazepam kinetics in acute alcohol withdrawal. Clin Pharmacol Ther, 25: 832–836 (1979).
168. Nair SG, Gamble JAS, Dundee JW, and Howard PJ. The influence of three antacids in the absorption and clinical action of oral diazepam. Br J Anaesth, 48: 1175–1180 (1976).
169. Elliot P, Dundee JW, Elwood RJ, and Collier PS. The influence of H2 receptor antagonists on the plasma concentration of midazolam and temazepam. Eur J Anesth, 1: 245–251 (1984).
170. Greenblatt DJ, Shader RI, Harmatz JS, Franke K, and Koch-Weser J. Influence of magnesium and aluminum hydroxide mixture on chlordiazepoxide absorption. Clin Pharmacol Ther, 19: 234–239 (1976).
171. Chun AHC, Carrigan PJ, Hoffman DJ, Kershner RP, and Stuart JD. Effect of antacids on absorption of clorazepate. Clin Pharmacol Ther, 22: 329–335 (1977).
172. Shader RI, Georgotas A, Greenblatt DJ, Harmatz JS, and Allen MD. Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. Clin Pharmacol Ther, 24: 308–315 (1978).

173. Greenblatt DJ, Allen MD, MacLaughlin DS, Harmatz JS, and Shader RI. Diazepam absorption: effect of antacids and food. Clin Pharmacol Ther, 24: 600–609 (1978).
174. Abruzzo CW, Macasieb T, Weinfeld R, Rider AJ, and Kaplan SA. Changes in the oral absorption characteristics in man of dipotassium clorazepate at normal and elevated gastric pH. J Pharmacokinet Biopharm, 5: 377–390 (1977).
175. Shader RI, Ciraulo DA, Greenblatt DJ, and Harmatz JS. Steady-state plasma desmethyldiazepam during long-term clorazepate use: effect of antacids. Clin Pharmacol Ther, 31: 180–183 (1982).
176. Kroboth PD, Smith RB, Rault R, Silver MR, Sorkin MI, Puschett JB, and Juhl RP. Effects of end-stage renal disease and aluminum hydroxide on temazepam kinetics. Clin Pharmacol Ther, 37: 453–459 (1985).
177. Kroboth PD, Smith RB, Silver MR, Rault R, Sorkin MI, Puschett JB, and Juhl RP. Effects of end stage renal disease and aluminium hydroxide on triazolam pharmacokinetics. Br J Clin Pharmacol, 19: 839–842 (1985).
178. Lima DR, Santos RM, Werneck E, and Andrade GN. Effect of orally administered misoprostol and cimetidine on the steady state pharmacokinetics of diazepam and nordiazepam in human volunteers. Eur J Drug Metab Pharmacokinet, 16: 161–170 (1991).
179. Bateman DN. The action of cispride on gastric emptying and the pharmacodynamics and pharmacokinetics of diazepam. Eur J Clin Pharmacol, 30: 205–208 (1986).
180. Dal Negro R. Pharmacokinetic drug interactions with anti-ulcer drugs. Clin Pharmacokinet, 35: 135–150 (1998).
181. Flockhart DA, Desta Z, and Mahal SK. Selection of drugs to treat gastro-oesophageal reflux disease – The role of drug interactions. Clin Pharmacokinet, 39: 295–309 (2000).
182. Knodell RG, Browne DG, Gwozdz GP, Brian WR, and Guengerich FP. Differential inhibition of individual human liver cytochromes P-450 by cimetidine. Gastroenterology, 101: 1680–1691 (1991).
183. Martinez C, Albet C, Agundez JAG, Herrero E, Carrillo JA, Marquez M, Benitez J, and Ortiz JA. Comparative in vitro and in vivo inhibition of cytochrome P450 CYP1A2, CYP2D6, and CYP3A by H_2-receptor antagonists. Clin Pharmacol Ther, 65: 369–376 (1999).
184. Klotz U, Arvela P, Pasanen, Kroemer H, and Pelkonen O. Comparative effects of H_2-receptor antagonists on drug metabolism in vitro and in vivo. Pharmacol Ther, 33: 157–161 (1987).
185. Hulhoven R, Desager JP, Cox S, and Harvengt C. Influence of repeated administration of cimetidine on the pharmacokinetics and pharmacodynamics of adinazolam in healthy subjects. Eur J Clin Pharmacol, 35: 59–64 (1988).
186. Abernethy DR, Greenblatt DJ, Divoll M, Moschitto LJ, Harmatz JS, and Shader RI. Interaction of cimetidine with triazolobenzodiazepines alprazolam and triazolam. Psychopharmacology, 80: 275–278 (1983).
187. Pourbaix S, Desager JP, Hulhoven R, Smith RB, and Harvengt C. Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. Int J Clin Pharmacol Ther Toxicol, 23: 447–451 (1985).
188. Ochs HR, Greenblatt DJ, Friedman H, Burstein ES, Locniskar A, Harmatz JS, and Shader RI. Bromazepam pharmacokinetics: influence of age, gender, oral contraceptives, cimetidine and propranolol. Clin Pharmacol Ther, 41: 562–570 (1987).
189. Desmond PV, Patwardhan RV, Schenker S, and Speeg KV. Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. Ann Intern Med, 93: 266–268 (1980).
190. Pullar T, Edwards D, Haigh JRM, Peaker S, and Feely MP. The effect of cimetidine on the single dose pharmacokinetics of oral clobazam and N-desmethylclobazam. Br J Clin Pharmacol, 23: 317–321 (1987).
191. Divoll M, Greenblatt DJ, Abernethy DR, and Shader RI. Cimetidine impairs clearance of antipyrine and desmethyldiazepam in the elderly. J Am Geriatr Soc, 30: 684–689 (1982).
192. Klotz U, and Reimann I. Delayed clearance of diazepam due to cimetidine. N Engl J Med, 302: 1012–1014 (1980).
193. Klotz U, and Reimann I. Elevation of steady-state diazepam levels by cimetidine. Clin Pharmacol Ther, 30: 513–517 (1981).

194. Gough PA, Curry SH, Araujo OE, Robinson JD, and Dallman JJ. Influence of cimetidine on oral diazepam elimination with measurement of subsequent cognitive change. Br J Clin Pharmacol, 14: 739–742 (1982).
195. Abernethy DR, Greenblatt DJ, Divoll M, Ameer B, and Shader RI. Differential effect of cimetidine on drug oxidation (antipyrine and diazepam) vs. conjugation (acetaminophen and lorazepam): prevention of acetaminophen toxicity by cimetidine. J Pharmacol Exp Ther, 224: 508–513 (1983).
196. Greenblatt DJ, Abernethy DR, Morse DS, Harmatz JS, and Shader RI. Clinical importance of the interaction of diazepam and cimetidine. N Eng J Med, 310: 1639–1643 (1984).
197. Andersson T, Andren K, Cederberg C, Edvardsson G, Heggelund A, and Lundborg P. Effect of omeprazole and cimetidine on plasma diazepam levels. Eur J Clin Pharmacol, 39: 51–54 (1990).
198. Greenblatt DJ, Abernethy DR, Koepke HH, and Shader RI. Interaction of cimetidine with oxazepam, lorazepam, and flurazepam. J Clin Pharmacol, 24: 187–193 (1984).
199. Fee JPH, Collier PS, Howard PJ, and Dundee JW. Cimetidine and ranitidine increase midazolam bioavailability. Clin Pharmacol Ther, 41: 80–84 (1987).
200. Ochs HR, Greenblatt DJ, Gugler R, Muntefering G, Locniskar A, and Abernethy DR. Cimetidine impairs nitrazepam clearance. Clin Pharmacol Ther, 34: 227–230 (1983).
201. Klotz U, and Reimann I. Influence of cimetidine on the pharmacokinetics of desmethyldiazepam and oxazepam. Eur J Clin Pharmacol, 18: 517–520 (1980).
202. Cox SR, Kroboth PD, Anderson PH, and Smith RB. Mechanism for the interaction between triazolam and cimetidine. Biopharm Drug Dispos, 7: 567–575 (1986).
203. McGowan WAW, and Dundee JW. The effect of intravenous cimetidine on the absorption of orally administered diazepam and lorazepam. Br J Clin Pharmacol, 14: 201–211 (1982).
204. Klotz U, Arvela P, and Rosenkranz B. Effect of single doses of cimetidine and ranitidine on the steady-state plasma levels of midazolam. Clin Pharmacol Ther, 38: 652–655 (1985).
205. Salonen M, Aantaa E, Aaltonen L, and Kanto J. Importance of the interaction of midazolam and cimetidine. Acta Pharmacol Toxicol, 58: 91–95 (1986).
206. Patwardhan RV, Yarborough GW, Desmond PV, Johnson RF, Schenker S, and Speeg KV, Jr. Cimetidine spares the glucuronidation of lorazepam and oxazepam. Gastroenterology, 79: 912–916 (1980).
207. Greenblatt DJ, Abernethy DR, Divoll M, Locniskar A, Harmatz JS, and Shader RI. Noninteraction of temazepam and cimetidine. J Pharm Sci, 73: 399–401 (1984).
208. Klotz U, reimann IW, and Ohnhaus EE. Effect of ranitidine on the steady state pharmacokinetics of diazepam. Eur J Clin Pharmacol, 24: 357–360 (1983).
209. Elwood RJ, Hildebrand PJ, Dundee JW, and Collier PS. Ranitidine influences the uptake of oral midazolam. Br J Clin Pharmacol, 15: 743–745 (1983).
210. Vanderveen RP, Jirak JL, Peters GR, Cox SR, and Bombardt PA. Effect of rantidine on the disposition of orally and intravenously administered triazolam. Clin Pharmacy, 10: 539–543 (1991).
211. Abernethy DR, Greenblatt DJ, Eshelman FN, and Shader RI. Ranitidine does not impair oxidative or conjugative drug metabolism: Noninteraction with antipyrine, diazepam, and lorazepam. Clin Pharmacol Ther, 35: 188–192 (1984).
212. Klotz U, Gottlieb W, Keohane PP, and Dammann HG. Nocturnal doses of ranitidine and nizatidine do not affect the disposition of diazepam. J Clin Pharmacol, 27: 210–212 (1987).
213. Suttle AB, Songer SS, Dukes GE, Hak LJ, Koruda M, Fleishaker JC, and Brouwer KLR. Ranitidine does not alter adinazolam pharmacokinetics or pharmacodynamics. J Clin Psychopharmacol, 12: 282–287 (1992).
214. Klotz U, Arvela P, and Rosenkranz B. Famotidine, a new H_2-receptor antagonist, does not affect hepatic elimination of diazepam or tubular secretion of procainamide. Eur J Clin Pharmacol, 28: 671–675 (1985).
215. Locniskar A, Greenblatt DJ, Harmatz JS, Zinny MA, and Shader RI. Interaction of diazepam with famotidine and cimetidine, two H_2-receptor antagonists. J Clin Pharmacol, 26: 299–303 (1986).
216. VandenBranden M, Ring BJ, Binkley SN, and Wrighton SA. Interaction of human liver cytochromes P450 in vitro with LY307640, a gastric proton pump inhibitor. Pharmacogenetics, 6: 81–91 (1996).

217. Ko J-W, Sukhova N, Thacker D, Chen P, and Flockhart DA. Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. Drug Metab Dispos, 25: 853–862 (1997).
218. Tucker GT. The interaction of proton pump inhibitors with cytochromes P450. Aliment Pharmacol Ther, 8: (Suppl. 1) 33–38 (1994).
219. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors: focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet, 31: 9–28 (1996).
220. Gugler R, and Jensen JC. Omeprazole inhibits oxidative drug metabolism. Gastroenterology, 89: 1235–1241 (1985).
221. Andersson T, Cederberg C, Edvardsson G, Heggelund A, and Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. Clin Pharmacol Ther, 47: 79–85 (1990).
222. Caraco Y, Tateishi T, and Wood AJJ. Interethnic difference in omeprazole's inhibition of diazepam metabolism. Clin Pharmacol Ther, 58: 62–72 (1995).
223. Lefebvre RA, Flouvat B, Karola-Tamisier S, Moerman E, and Van Ganse E. Influence of lansoprazole treatment on diazepam plasma concentrations. Clin Pharmacol Ther, 52: 458–463 (1992).
224. Gugler R, Hartmann M, Rudi J, Brod I, Huber R, Steinijans VW, Bliesath H, Wurst W, and Klotz U. Lack of pharmacokinetic interaction of pantoprazole with diazepam in man. Br J Clin Pharmacol, 42: 249–252 (1996).
225. Venkatakrishnan K, von Moltke LL, and Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism – Clinical relevance. Clin Pharmacokinet, 38: 111–180 (2000).
226. Maurice M, Pichard L, Daujat M, Fabre I, Joyeux H, Domergue J, and Maurel P. Effects of imidazole derivatives on cytochromes P450 from human hepatocytes in primary culture. FASEB J, 6: 752–758 (1992).
227. von Moltke LL, Greenblatt DJ, Duan SX, Harmatz JS, and Shader RI. Inhibition of triazolam hydroxylation by ketoconazole, itraconazole, hydroxyitraconazole and fluconazole in vitro. Pharm Pharmacol Commun, 4: 443–445 (1998).
228. Jurima-Romet M, Crawford K, Cyr T, and Inaba T. Terfenadine metabolism in human liver: in vitro inhibition by macrolide antibiotics and azole antifungals. Drug Metab Dispos, 22: 849–857 (1994).
229. Tassaneeyakul W, Birkett DJ, and Miners JO. Inhibition of human hepatic cytochrome P4502E1 by azole antifungals, CNS-active drugs and non-steroidal anti-inflammatory agents. Xenobiotica, 28: 293–301 (1998).
230. Greenblatt DJ, Wright CE, von Moltke LL, Harmatz JS, Ehrenberg BL, Harrel LM, Corbett K, Counihan M, Tobias S, and Shader RI. Ketoconazole inhibition of triazolam amd alprazolam clearance: Differential kinetic and dynamic consequences. Clin Pharmacol Ther, 64: 237–247 (1998).
231. Schmider J, Brockmoller J, Arold G, Bauer S, and Roots I. Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. Pharmacogenetics, 9: 725–734 (1999).
232. Brown MW, Maldonado AL, Meredith CG, and Speeg KV. Effect of ketoconazole on hepatic oxidative metabolism. Clin Pharmacol Ther, 37: 290–297 (1985).
233. Olkkola KT, Backman JT, and Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther, 55: 481–485 (1994).
234. Varhe A, Olkkola KT, and Neuvonen PJ. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther, 56: 601–607 (1994).
235. Olkkola KT, Ahonen J, and Neuvonen PJ. The effect of systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Anesth Analges, 82: 511–516 (1996).
236. Ahonen J, Olkkola KT, and Neuvonen PJ. Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. Eur J Clin Pharmacol, 51: 415–419 (1997).

237. Varhe A, Olkkola KT, and Neuvonen PJ. Effect of fluconazole dose on the extent of fluconazole-triazolam interaction. Br J Clin Pharmacol, 42: 465–470 (1996).
238. Ohtani Y, Kotegawa T, Tsutsumi K, Morimoto T, Hirose Y, and Nakano S. Effect of fluconazole on the pharmacokinetics and pharmacodynamics of oral and rectal bromazepam: An application of electroencephalography as the pharmacodynamic method. J Clin Pharmacol, 42: 183–191 (2002).
239. Yasui N, Kondo T, Otani K, Furukori H, Kaneko S, Ohkubo T, Nagasaki T, and Sugawara K. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. Psychopharmacology, 139: 269–273 (1998).
240. Ahonen J, Olkkola KT, and Neuvonen PJ. The effect of the antimycotic itraconazole on the pharmacokinetics and pharmacodynamics of diazepam. Fund Clin Pharmacol, 10: 314–318 (1996).
241. Ahonen J, Olkkola KT, and Neuvonen PJ. Effect of itraconazole and terbinafine on the pharmacokinetics and pharmacodynamics of midazolam in healthy volunteers. Br J Clin Pharmacol, 40: 270–272 (1995).
242. Neuvonen PJ, Varhe A, and Olkkola KT. The effect of ingestion time interval on the interaction between itraconazole and triazolam. Clin Pharmacol Ther, 60: 326–331 (1996).
243. Blyden GT, Scavone JM, and Greenblatt DJ. Metronidazole impairs clearance of phenytoin but not of alprazolam or lorazepam. J Clin Pharmacol, 28: 240–245 (1988).
244. Jensen JC, and Gugler R. Interaction between metronidazole and drugs eliminated by oxidative metabolism. Clin Pharmacol Ther, 37: 407–410 (1985).
245. Wang JS, Backman JT, Kivisto KT, and Neuvonen PJ. Effects of metronidazole on midazolam metabolism in vitro and in vivo. Eur J Clin Pharmacol, 56: 555–559 (2000).
246. Varhe A, Olkkola KT, and Neuvonen PJ. Fluconazole, but not terbinafine, enhances the effects of triazolam by inhibiting its metabolism. Br J Clin Pharmacol, 41: 319–323 (1996).
247. Crewe HK, Lennard MS, Tucker GT, Woods FR, and Haddock RE. The effect of selective serotonin re-uptake inhibitors on Cytochrome P4502D6 (CYP2D6) activity in (HLM). Br J Clin Pharmacol, 34: 262–265 (1992).
248. Otton SV, Ball SE, Cheung SW, Inaba T, Rudolph RL, and Sellers EM. Venlafaxine oxidation in vitro is catalysed by CYP2D6. Br J Clin Pharmacol, 41: 149–156 (1996).
249. Schmider J, Greenblatt DJ, von Moltke LL, Harmatz JS, and Shader RI. Inhibition of cytochrome P450 by nefazodone in vitro: studies of dextromethorphan O- and N-demethylation. Br J Clin Pharmacol, 41: 339–343 (1996).
250. Brosen K, and Naranjo CA. Review of the pharmacokinetic and pharmacodynamic interaction studies with citalopram. Eur Neuropsychopharmacol, 11: 275–283 (2001).
251. Schmider J, Greenblatt DJ, von Moltke LL, Karsov D, and Shader RI. Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: studies of phenytoin p-hydroxylation. Br J Clin Pharmacol, 44: 495–498 (1997).
252. Lasher TA, Fleishaker JC, Steenwyk RC, and Antal EJ. Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. Psychopharmacology, 104: 323–327 (1991).
253. Greenblatt DJ, Preskorn SH, Cotreau MM, Horst WD, and Harmatz JS. Fluoxetine impairs clearance of alprazolam but not of clonazepam. Clin Pharmacol Ther, 52: 479–486 (1992).
254. Lemberger L, Rowe H, Bosomworth JC, Tenbarge JB, and Bergstrom RF. The effect of fluoxetine on the pharmacokinetics and psychomotor responses of diazepam. Clin Pharmacol Ther, 43: 412–419 (1988).
255. Wright CE, Lasher-Sisson TA, Steenwyk RC, and Swanson CN. A pharmacokinetic evaluation of the combined administration of triazolam and fluoxetine. Pharmacotherapy, 12: 103–106 (1992).
256. Perucca E, Gatti G, Cipolla G, Spina E, Barel S, Soback S, Gips M, and Bialer M. Inhibition of diazepam metabolism by fluvoxamine: A pharmacokinetic study in normal volunteers. Clin Pharmacol Ther, 56: 471–476 (1994).
257. Kashuba ADM, Nafziger AN, Kearns GL, Leeder JS, Gotschall R, Rocci ML, Kulawy RW, Beck DJ, and Bertino JS. Effect of fluvoxamine therapy on the activities of CYP1A2, CYP2D6, and CYP3A as determined by phenotyping. Clin Pharmacol Ther, 64: 257–268 (1998).

258. Kroboth PD, Folan MM, Lush RM, Chaikin PC, Shukla UA, Barbhaiya R, and Salazar DE. Coadministration of nefazodone and benzodiazepines: I. Pharmacodynamic assessment. J Clin Psychopharmacol, 15: 306–319 (1995).
259. Greene DS, Salazar DE, Dockens RC, Kroboth PD, and Barbhaiya RH. Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. J Clin Psychopharmacol, 15: 399–408 (1995).
260. Barbhaiya RM, Shukla UA, Kroboth PD, and Greene DS. Coadministration of nefazodone and benzodiazepines: II. A pharmacokinetic interaction study with triazolam. J Clin Psychopharmacol, 15: 320–326 (1995).
261. Greene DS, Salazar DE, Dockens RC, Kroboth PD, and Barbhaiya RH. Coadministration of nefazodone and benzodiazepines: IV. A pharmacokinetic interaction study with lorazepam. J Clin Psychopharmacol, 15: 409–416 (1995).
262. Bonate PL, Kroboth PD, Smith RB, Suarez E, and Oo C. Clonazepam and sertraline: Absence of drug interaction in a multiple-dose study. J Clin Psychopharmacol, 20: 19–27 (2000).
263. Gardner MJ, Baris BA, Wilner KD, and Preskorn SH. Effect of sertraline on the pharmacokinetics and protein binding of diazepam in healthy volunteers. Clin Pharmacokinet, 32: (suppl. 1) 43–49 (1997).
264. Amchin J, Zarycranski W, Taylor KP, Albano D, and Klockowski PM. Effect of venlafaxine on the pharmacokinetics of alprazolam. Psychopharmacology Bull, 34: 211–219 (1998).
265. Troy SM, Lucki I, Peirgies AA, Parker VD, Klockowski PM, and chiang ST. Pharmacokinetic and pharmacodynamic evaluation of the potential drug interaction between venlafaxine and diazepam. J Clin Pharmacol, 35: 410–419 (1995).
266. Shenfield GM, and Griffin JM. Clinical pharmacokinetics of contraceptive steroids: an update. Clin Pharmacokinet, 20: 15–37 (1991).
267. Guengerich FP. Oxidation of 17α-ethynylestradiol by human liver cytochrome P–450. Mol Pharmacol, 33: 500–508 (1988).
268. Back DJ, Houlgrave R, Tjia JF, Ward S, and Orme MLE. Effect of the progestogens, gestodene, 3-keto desogestral, levonorgestrel, norethisterone and norgestimate on the oxidation of ethyloestradiol and other substrates by (HLM). J Ster Biochem Mol Biol, 38: 219–225 (1991).
269. Stoehr GP, Kroboth PD, Juhl RP, Wender DB, Phillips JP, and Smith RB. Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. Clin Pharmacol Ther, 36: 683–690 (1984).
270. Roberts RK, Desmond PV, Wilkinson GR, and Schenker S. Disposition of chlordiazepoxide: sex differences and effects of oral contraceptives. Clin Pharmacol Ther, 25: 826–831 (1979).
271. Patwardhan RV, Mitchell MC, Johnson RF, and Schenker S. Differential effects of oral contraceptive steroids on the metabolism of benzodiazepines. Hepatology, 3: 248–253 (1983).
272. Giles HG, Sellers EM, Naranjo CA, Frecker RC, and Greenblatt DJ. Disposition of intravenous diazepam in young men and women. Eur J Clin Pharmacol, 20: 207–213 (1981).
273. Abernethy DR, Greenblatt DJ, Divoll M, Arendt R, Ochs HR, and Shader RI. Impairment of diazepam metabolism by low-dose estrogen containing oral contraceptive steroids. N Engl J Med, 306: 791–792 (1982).
274. Palovaara S, Kivisto KT, Tapanainen P, Manninen P, Neuvonen PJ, and Laine K. Effect of an oral contraceptive preparation containing ethinylestradiol and gestodene on CYP3A4 activity as measured by midazolam 1′-hydroxylation. Brit J Clin Pharmacol, 50: 333–337 (2000).
275. Jochemsen R, Van der Graaff M, Boeijinga JK, and Breimer DD. Influence of sex, menstrual cycle and oral contraception on the disposition of nitrazepam. Br J Clin Pharmacol, 13: 319–324 (1982).
276. Scavone JM, Greenblatt DJ, Locniskar A, and Shader RI. Alprazolam pharmacokinetics in women on low-dose oral contraceptives. J Clin Pharmacol, 28: 454–457 (1988).
277. Holazo AA, Winkler MB, and Patel IH. Effects of age, gender and oral contraceptives on intramuscular midazolam pharmacokinetics. J Clin Pharmacol, 28: 1040–1045 (1988).
278. Belle DJ, Callaghan JT, Gorski JC, Maya JF, Mousa O, Wrighton SA, and Hall SD. The effects of an oral contraceptive containing ethinyloestradiol and norgestrel on CYP3A activity. Br J Clin Pharmacool, 53: 67–74 (2002).

279. Abernethy DR, Greenblatt DJ, Ochs HR, Weyers D, Divoll M, Harmatz JS, and Shader RI. Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. Clin Pharmacol Ther, 33: 628–632 (1983).
280. Gorski JC, Wang ZQ, Heahner-Daniels BD, Wrighton SA, and Hall SD. The effect of hormone replacement therapy on CYP3A activity. Clin Pharmacol Ther, 68: 412–417 (2000).
281. Kroboth PD, Smith RB, Stoehr GP, and Juhl RP. Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. Clin Pharmacol Ther, 38: 525–532 (1985).
282. Kroboth PD, and McAuley JW. Progesterone: Does it affect response to drug. Psychopharmacology Bull, 33: 297–301 (1997).
283. Pichard L, Fabre I, Domergue J, Saint Aubert B, Mourad G, and Maurel P. Cyclosporin A drug interactions: screening for inducers and inhibitors of cytochrome P-450 (cyclosporin A oxidase) in primary cultures of human hepatocytes and in liver microsomes. Drug Metab Dispos, 18: 595–606 (1990).
284. Jawad S, and Richens A. Single dose pharmacokinetic study of clobazam in normal volunteers and epileptic patients. Br J Clin Pharmacol, 18: 873–877 (1984).
285. Dhillon S, and Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. Br J Clin Pharmacol, 12: 841–844 (1981).
286. Backman JT, Olkkola KT, Ojala M, Laaksovirta H, and Neuvonen PJ. Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. Epilepsia, 37: 253–257 (1996).
287. Contin M, Riva R, Albani F, and Baruzzi A. Effect of felbamate on clobazam and its metabolite kinetics in patients with epilepsy. Ther Drug Monit, 21: 604–608 (1999).
288. Wilensky AJ, Levy RH, Troupin AS, Moretti-Ojemann L, and Friel P. Clorazepate kinetics in treated epileptics. Clin Pharmacol Ther, 24: 22–30 (1978).
289. Furukori H, Otani K, Yasui N, Kondo T, Kaneko S, Shimoyama R, Ohkubo T, Nagasaki T, and Sugawara K. Effect of carbamazepine on the single oral dose pharmacokinetics of alprazolam. Neuropsychopharmacology, 18: 364–369 (1998).
290. Levy RH, Lane EA, Guyot M, Brachet-Liermain A, Cenraud B, and Loiseau P. Analysis of parent drug-metabolite relationship in the presence of an inducer: Application to the carbamazepine-clobazam interaction in normal man. Drug Metab Dispos, 11: 286–292 (1983).
291. Lai AA, Levy RH, and Cutler RE. Time-course of interaction between carbamazepine and clonazepam in normal man. Clin Pharmacol Ther, 24: 316–323 (1978).
292. Arana GW, Epstein S, Molloy M, and Greenblatt DJ. Carbamazepine-induced reduction of plasma alprazolam concentrations: a clinical case report. J Clin Psychiatry, 49: 448–449 (1988).
293. Dhillon S, and Richens A. Serum protein binding of diazepam and its displacement by valproic acid in vitor. Br J Clin Pharmacol, 12: 591–592 (1981).
294. Dhillon S, and Richens A. Valproic acid and diazepam interactions in vivo. Br J Clin Pharmacol, 13: 553–560 (1982).
295. Anderson GD, Gidal BE, Kantor ED, and Wilensky AJ. Lorazepam-valproate interaction: Studies in normal subjects and in isolated perfused rat liver. Epilepsia, 35: 221–225 (1994).
296. Samara EE, Granneman RG, Witt GF, and Cavanaugh JH. Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. J Clin Pharmacol, 37: 442–450 (1997).
297. Tija JF, Back DJ, and Breckenridge AM. Calcium channel antagonists and cyclosporin metabolism: in vitro studies with (HLM). Br J Clin Pharmacol, 28: 362–365 (1989).
298. Sutton D, Butler AM, Nadin L, and Murray M. Role of CYP3A4 in human hepatic diltiazem N-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. J Pharmacol Exp Ther, 282: 294–300 (1997).
299. Ma B, Prueksaritanont T, and Lin JH. Drug interactions with calcium channel blockers: Possible involvement of metabolite-intermediate complexation with CYP3A. Drug Metab Dispos, 28: 125–130 (2000).
300. Shaw L, Lennard MS, Tucker GT, Bax NDS, and Woods HF. Irreversible binding and metabolism of propranolol by (HLM) – relationship to polymorphic oxidation. Biochem Pharmacol, 36: 2283–2288 (1987).

301. Ochs HR, Greenblatt DJ, and Verburg-Ochs B. Propranolol interactions with diazepam, lorazepam, and alprazolam. Clin Pharmacol Ther, 36: 451–455 (1984).
302. Hawksworth GM, Betts T, Crowe A, Knight R, Nyemitei-Addo I, Parry K, Petrie JC, Raffle A, and Parsons A. Diazepam / ß-adrenoceptor antagonist interactions. Br J Clin Pharmacol, 17: 69S–76S (1984).
303. Sonne J, Dossing M, Loft S, Olesen KL, Vollmer-Larsen A, Victor MA, Hamberg O, and Thyssen H. Single dose pharmacokinetics and pharmacodynamics of oral oxazepam during concomitant administration of propranolol and labetalol. Br J Clin Pharmacol, 29: 33–37 (1990).
304. Scott AK, Cameron GA, and Hawksworth GM. Interaction of metoprolol with lorazepam and bromazepam. Eur J Clin Pharmacol, 40: 405–409 (1991).
305. Klotz U, and Reimann IW. Pharmacokineitc and pharmacodynamic interaction study of diazepam and metoprolol. Eur J Clin Pharmacol, 26: 223–226 (1984).
306. Ahonen J, Olkkola KT, Salmenpera M, Hynynen M, and Neuvonen PJ. Effect of diltiazem on midazolam and alfentanil disposition in patients undergoing coronary artery bypass grafting. Anesthesia, 85: 1246–1252 (1996).
307. Backman JT, Olkkola KT, Aranko K, Himberg J-J, and Neuvonen PJ. Dose of midazolam should be reduced during diltiazem and verapamil treatments. Br J Clin Pharmacol, 37: 221–225 (1994).
308. Varhe A, Olkkola KT, and Neuvonen PJ. Diltiazem enhances the effects of triazolam by inhibiting its metabolism. Clin Pharmacol Ther, 59: 369–375 (1996).
309. Kosuge K, Nishimoto M, Kimura M, Umemura K, Nakashima M, and Ohashi K. Enhanced effect of triazolam with diltiazem. Br J Clin Pharmac, 43: 367–372 (1997).
310. Backman JT, Wang J-S, Wen X, Kivisto KT, and Neuvonen PJ. Mibefradil but not isradipine substantially elevates the plasma concentrations of the CYP3A4 substrate triazolam. Clin Pharmacol Ther, 66: 401–407 (1999).
311. Venkatesan K. Pharmacokinetic drug interactions with rifampicin. Clin Pharmacokinet, 22: 47–65 (1992).
312. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. Brit J Clin Pharmacol, 50: 285–295 (2000).
313. Yamazaki H, and Shimada T. Comparative studies of in vitro inhibition of cytochrome P450 3A4-dependent testosterone 6ß-hydroxylation by roxithromycin and its metabolites, troleandomycin, and erythromycin. Drug Metab Dispos, 26: 1053–1057 (1998).
314. Zhao XJ, Koyama E, and Ishizaki T. An in vitro study on the metabolism and possible drug interactions of rokitamycin, a macrolide antibiotic, using (HLM). Drug Metab Dispos, 27: 776–785 (1999).
315. Lindstrom TD, Hanssen BR, and Wrighton SA. Cytochrome P-450 complex formation by dirithromycin and other macrolides in rat and human livers. Antimicrob Agents Chemother, 37: 265–269 (1993).
316. Marre F, de Sousa G, Orloff AM, and Rahmani R. In vitro interaction between cyclosporin A and macrolide antibiotics. Br J Clin Pharmacol, 35: 447–448 (1993).
317. Greenblatt DJ, von Moltke LL, Harmatz JS, Counihan M, Graf JA, Durol ALB, Mertzanis P, Duan SX, Wright CE, and Shader RI. Inhibition of triazolam clearance by macrolide antimicrobial agents: In vitro correlates and dynamic consequences. Clin Pharmacol Ther, 64: 278–285 (1998).
318. Wen X, Wang J-S, Neuvonen PJ, and Backman JT. Isoniazid is a mechanism-based inhibitor of P_{450} 1A2, 2A6, 2C19 and 3A4 isoforms in (HLM). Eur J Clin Pharmacol, 57: 799–804 (2002).
319. Edwards DJ, Bowles SK, Svensson CK, and Rybak MJ. Inhibition of drug metabolism by quinolone antibiotics. Clin Pharmacokinet, 15: 194–204 (1988).
320. Fuhr U, Wolff T, Harder S, Schymanski P, and Staib AH. Quinolone inhibition of cytochrome P-450-dependent caffeine metabolism in (HLM). Drug Metab Disposit, 18: 1005–1010 (1990).

321. Sarkar M, Polk RE, Guzelian PS, Hunt C, and Karnes HT. In vitro effect of fluoroquinolones on theophylline metabolism in (HLM). Antimicrob Agents Chemother, 34: 594–599 (1990).
322. Ochs HR, Greenblatt DJ, Roberts GM, and Dengler HJ. Diazepam interaction with antituberculous drugs. Clin Pharmacol Ther, 29: 671–678 (1981).
323. Ohnhaus EE, Brockmeyer N, Dylewicz P, and Habicht H. The effect of antipyrine and rifampin on the metabolism of diazepam. Clin Pharmacol Ther, 42: 148–156 (1987).
324. Ochs HR, Greenblatt DJ, and Knuchel M. Differential effect of isoniazid on triazolam oxidation and oxazepam conjugation. Br J Clin Pharmacol, 16: 743–746 (1983).
325. Backman JT, Olkkola KT, and Neuvonen PJ. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. Clin Pharmacol Ther, 59: 7–13 (1996).
326. Backman JT, Kivisto KT, Olkkola KT, and Neuvonen PJ. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. Eur J Clin Pharmacol, 54: 53–58 (1998).
327. Brockmeyer NH, Mertins L, Klimek K, Goos M, and Ohnhaus EE. Comparative effects of rifampin and/or probenecid on the pharmacokinetics of temazepam and nitrazepam. Int J Clin Pharmacol Ther Toxicol, 28: 387–393 (1990).
328. Villikka K, Kivisto KT, Backman JT, Olkkola KT, and Neuvonen PJ. Triazolam is ineffective in patients taking rifampin. Clin Pharmacol Ther, 61: 8–14 (1997).
329. Yasui N, Otani K, Kaneko S, Ohkubo T, Osanai T, Sugawara K, Chiba K, and Ishizaki T. A kinetic and dynamic study of oral alprazolam with and without erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in alprazolam metabolism. Clin Pharmacol Ther, 59: 514–519 (1996).
330. Luurila H, Olkkola KT, and Neuvonen PJ. Interaction between erythromycin and the benzodiazepines diazepam and flunitrazepam. Pharmacol Toxicol, 78: 117–122 (1996).
331. Vanakoski J, Mattila MJ, Vainio P, Idanpaan-Heikkila JJ, and Tornwall M. 150 mg fluconazole does not substantially increase the effects of 10 mg midazolam or the plasma midazolam concentrations in healthy subjects. Int J Clin Pharmacol Ther Toxicol, 33: 518–523 (1995).
332. Olkkola KT, Aranko K, Luurila H, Hiller A, Saarnivaara L, Himberg J-J, and Neuvonen PJ. A potentially hazardous interaction between erythromycin and midazolam. Clin Pharmacol Ther, 53: 298–305 (1993).
333. Zimmermann T, Yeates RA, Laufen H, Scharpf F, Leitold M, and Wildfeuer A. Influence of the antibiotics erythromycin and azithromycin on the pharmacokinetics and pharmacdynamics of midazolam. Arsch-Forsch Drug Metab, 46: 213–217 (1996).
334. Phillips JP, Antal EJ, and Smith RB. A pharmacokinetic drug interaction between erythromycin and triazolam. J Clin Psychopharmacol, 6: 297–299 (1986).
335. Luurila H, Olkkola KT, and Neuvonen PJ. Lack of interaction of erythromycin with temazepam. Ther Drug Monit, 16: 548–551 (1994).
336. Warot D, Bergougnan L, Lamiable D, Berlin I, Benison G, Danjou P, and Puech AJ. Troleandomycin-triazolam interaction in healthy volunteers: pharmacokinetic and psychometric evaluation. Eur J Clin Pharmacol, 32: 389–393 (1987).
337. Backman JT, Aranko K, Himberg J-J, and Olkkola KT. A pharmacokinetic interaction between roxithromycin and midazolam. Eur J Clin Pharmacol, 46: 551–555 (1994).
338. Kamali F, Thomas SHL, and Edwards C. The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam. Eur J Clin Pharmacol, 44: 365–367 (1993).
339. Wijnands WJA, Trooster JFG, Teunissen PC, Cats HA, and Vree TB. Ciprofloxacin does not impair the elimination of diazepam in humans. Drug Metab Dispos, 18: 954–957 (1990).
340. Barry M, Mulcahy F, Merry C, Gibbons S, and Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. Clin Pharmacokinet, 36: 289–304 (1999).
341. Li XL, and Chan WK. Transport, metabolism and elimination mechanisms of anti-HIV agents. Advan Drug Delivery Rev, 39: 81–103 (1999).

342. Tseng AL, and Foisy MM. Significant interactions with new antiretrovirals and psychotic drugs. Ann Pharmacother, 33: 461–473 (1999).
343. Eagling VA, Back DJ, and Barry MG. Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. Br J Clin Pharmacol, 44: 190–194 (1997).
344. Inaba T, Fischer NE, Riddick DS, Stewart DJ, and Hidaka T. HIV protease inhibitors, saquinavir, indinavir and ritonavir: inhibition of CYP3A4-mediated metabolism of testosterone and benzoxazinorifamycin, KRM-1648, in (HLM). Toxicol Lett, 93: 215–219 (1997).
345. Lillibridge JH, Liang BH, Kerr BM, Webber S, Quart B, Shetty BV, and Lee CA. Characterization of the selectivity and mechanism of human cytochrome P450 inhibition by the human immunodeficiency virus-protease inhibitor nelfinavir mesylate. Drug Metab Dispos, 26: 609–616 (1998).
346. von Moltke LL, Greenblatt DJ, Grassi JM, Granda BW, Duan SX, Fogelman SM, Daily JP, Harmatz JS, and Shader RI. Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. J Clin Pharmacol, 38: 106–111 (1998).
347. Decker CJ, Laitinen LM, Bridson GW, Raybuck SA, Tung RD, and Chaturvedi PR. Metabolism of amprenavir in liver microsomes: role of CYP3A4 inhibition for drug interactions. J Pharm Sci, 87: 803–807 (1998).
348. Zalma A, von Moltke LL, Granda BW, Harmatz JS, Shader RI, and Greenblatt DJ. In vitro metabolism of trazodone by CYP3A: Inhibition by ketoconazole and human immunodeficiency viral protease inhibitors. Biol Psychiat, 47: 655–661 (2000).
349. von Moltke LL, Greenblatt DJ, Granda BW, Giancarlo GM, Duan SX, Daily JP, Harmatz JS, and Shader RI. Inhibition of human cytochrome P450 isoforms by nonnucleoside reverse transcriptase inhibitors. J Clin Pharmacol, 41: 85–91 (2001).
350. Greenblatt DJ, von Moltke LL, Harmatz JS, Durol ALB, Daily JP, Graf JA, Mertzanis P, Hoffman JL, and Shader RI. Differential impairment of triazolam and zolpidem clearance by ritonavir. J Acq Immune Defic Syndr, 24: 129–136 (2000).
351. Greenblatt DJ, von Moltke LL, Harmatz JS, Durol ALB, Daily JP, Graf JA, Mertzanis P, Hoffman JL, and Shader RI. Alprazolam-ritonavir interaction: implications for product labeling. Clin Pharmacol Ther, 67: 335–341 (2000).
352. Palkama VJ, Ahonen J, Neuvonen PJ, and Olkkola KT. Effect of saquinavir on the pharmacokinetics and pharmacodynamics of oral and intravenoud midazolam. Clin Pharmacol Ther, 66: 33–39 (1999).
353. Yeh RF, Gaver VE, Patterson KB, Rezk NL, Baxter-Meheux F, Blake MJ, Eron JJ, Klein CE, Rublein JC, and Kashuba ADM. Lopinavir/ritonavir induces the hepatic activity of cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP1A2 but inhibits the hepatic and intestinal activity of CYP3A as measured by a phenotyping drug cocktail in healthy volunteers. J Acquir Immune Defic Syndr, 42: 52–60 (2006).
354. Fellay J, Marzolini C, Decosterd L, Golay KP, Baumann P, Buclin T, Telenti A, and Eap CB. Variations of CYP3A activity induced by antiretroviral treatment in HIV-1 infected patients. Eur J Clin Pharmacol, 60: 865–873 (2005).
355. Abel S, Russell D, Whitlock LA, Ridgway CE, and Muirhead GJ. Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers. Br J Clin Pharmacol, 65: 19–26 (2008).
356. Nyunt MM, Becker S, Macfarland RT, Chee P, Scarborough R, Everts S, Calandra GB, and Hendrix CW. Pharmacokinetic effect of AMD070, an oral CXCR4 antagonist, on CYP3A4 and CYP2D6 substrates midazolam and dextromethorphan in healthy volunteers. JAIDS, 47: 559–565 (2008).
357. Mathias AA, West S, Hui J, and Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. Clin Pharmacol Ther, 85: 64–70 (2009).
358. Bailey DG, Spence JD, Munoz C, and Arnold JMO. Interaction of citrus juices with felodipine and nifedipine. Lancet, 337: 268–269 (1991).
359. Watkins PB, Wrighton SA, Schuetz EG, Molowa DT, and Guzelian PS. Identification of glucocortisol-inducible cytochrome P-450 in the intestinal mucosa of rats and man. J Clin Invest, 80: 1029–1036 (1987).

360. Kolars JC, Schmiedlin-Ren P, Schuetz JD, Fang C, and Watkins PB. Identification of rifampin-inducible P450IIIA4 (CYP3A4) in human small bowel enterocytes. J Clin Invest, 90: 1871–1878 (1992).
361. Bailey DG, Malcolm J, Arnold O, and Spence JD. Grapefruit juice-drug interactions. Br J Clin Pharmacol, 46: 101–110 (1998).
362. Greenblatt DJ, Patki KC, von Moltke LL, and Shader RI. Drug interactions with grapefruit juice: an update. J Clin Psychopharmacol, 21: 357–359 (2001).
363. Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, Brown MB, Guo W, and Watkins PB. Grapefruit juice increases felodipine oral bioavailability in humans by decreasing intestinal CYP 3A protein expression. J Clin Invest, 99: 1–9 (1997).
364. Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, He K, Lown KS, Woster PM, Rahman A, Thummel KE, Fisher JM, Hollenberg PF, and Watkins PB. Mechanisms of enhanced oral availability of CYP3A substrates by grapefruit constituents: decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. Drug Metab Dispos, 25: 1228–1233 (1997).
365. Guengerich FP, and Kim D-H. In vitro inhibition of dihydropyridine oxidation and aflatoxin B_1 activation in (HLM) by naringenin and other flavonoids. Carcinogenesis, 11: 2275–2279 (1990).
366. Miniscalco A, Lundahl J, Regardh CG, Edgar B, and Eriksson UG. Inhibition of dihydropyridine metabolism in rat and (HLM) by flavonoids found in grapefruit juice. J Pharmacol Exp Ther, 261: 1195–1199 (1991).
367. Ha HR, Chen J, Leuenberger PM, Freiburghaus AU, and Follath F. In vitro inhibition of midazolam and quinidine metabolism by flavonoids. Eur J Clin Pharmacol, 48: 367–371 (1995).
368. Schubert W, Eriksson U, Edgar B, Cullberg G, and Hedner T. Flavonoids in grapefruit juice inhibit the in vitro hepatic metabolism of 17 beta-estradiol. Eur J Drug Metab Pharmacokinet, 20: 219–224 (1995).
369. Eagling VA, Profit L, and Back DJ. Inhibition of the CYP3A4-mediated metabolism and P-glycoprotein-mediated transport of the HIV-I protease inhibitor saquinavir by grapefruit juice components. Br J Clin Pharmacol, 48: 543–552 (1999).
370. Rashid J, McKinstry C, Renwick AG, Dirnhuber M, Waller DG, and George CF. Quercetin, an in vitro inhibitor of CYP3A, does not contribute to the interaction between nifedipine and grapefruit juice. Br J Clin Pharmacol, 36: 460–463 (1993).
371. Bailey DG, Arnold JMO, Munoz C, and Spence JD. Grapefruit juice-felodipine interaction – mechanism, predictability, and effect of naringin. Clin Pharmacol Ther, 53: 637–642 (1993).
372. Edwards DJ, Bellevue FH, and Woster PM. Identification of 6′,7′-dihydroxybergamottin, a cytochrome P-450 inhibitor in grapefruit juice. Drug Metab Dispos, 24: 1287–1290 (1996).
373. Fukuda K, Ohta T, and Yamazoe Y. Grapefruit component interacting with rat and human P450 CYP3A: possible involvement of non-flavonoid components in drug interaction. Biol Pharm Bull, 20: 560–564 (1997).
374. Fukuda K, Ohta T, Oshima Y, Ohashi N, Yoshikawa M, and Yamazoe Y. Specific CYP3A4 inhibitors in grapefruit juice: furocoumarins dimers as components of drug interaction. Pharmacogenetics, 7: 391–396 (1997).
375. Guo L-Q, Fukuda K, Ohta T, and Yamazoe Y. Role of furanocoumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. Drug Metab Dispos, 28: 766–771 (2000).
376. He K, Iyer KR, Hayes RN, Sinz MW, Woolf TF, and Hollenberg PF. Inactivation of cytochrome P450 3A4 by bergamottin, a component of grapefruit juice. Chem Res Toxicol, 11: 252–259 (1998).
377. Fuhr U, Klittich K, and Staib AH. Inhibitory effect of grapefruit juice and its bitter principal, naringenin, on CYP1A2 dependent metabolism of caffeine in man. Br J Clin Pharmacol, 35: 431–436 (1993).
378. Edwards DJ, Fitzsimmons ME, Schuetz EG, Yasuda K, Ducharme MP, Warbasse LH, Woster PM, Schuetz JD, and Watkins P. 6 ′,7 ′-Dihydroxybergamottin in grapefruit juice and Seville orange juice: Effects on cyclosporine disposition, enterocyte CYP3A4, and P-glycoprotein. Clin Pharmacol Ther, 65: 237–244 (1999).

379. Soldner A, Christians U, Susanto M, Wacher VJ, Silverman JA, and Benet LZ. Grapefruit juice activates P-glycoprotein-mediated drug transport. Pharm Res, 16: 478–485 (1999).
380. Kupferschmidt HHT, Ha HR, Ziegler WH, Meier PJ, and Krahenbuhl S. Interaction between grapefruit juice and midazolam in humans. Clin Pharmacol Ther, 58: 20–28 (1995).
381. Andersen V, Pedersen N, Larsen N-E, Sonne J, and Larsen S. Intestinal first pass metabolism of midazolam in kiver cirrhosis – effect of grapefruit juice. Br J Clin Pharmacol, 54: 120–124 (2002).
382. Hukkinen SK, Varhe A, Olkkola KT, and Neuvonen PJ. Plasma concentrations of triazolam are increased by concomitant ingestion of grapefruit juice. Clin Pharmacol Ther, 58: 127–131 (1995).
383. Yasui N, Kondo T, Furukori H, Kaneko S, Ohkubo T, Uno T, Osanai T, Sugawara K, and Otani K. Effects of repeated ingestion of grapefruit juice on the single and multiple oral-dose pharmacokinetics and pharmacodynamics of alprazolam. Psychopharmacology, 150: 185–190 (2000).
384. Vanakoski J, Mattila MJ, and Seppala T. Grapefruit juice does not enhance the effects of midazolam and triazolam in man. Eur J Clin Pharmacol, 50: 501–508 (1996).
385. Backman JT, Maenpaa J, Belle DJ, Wrighton SA, Kivisto KT, and Neuvonen PJ. Lack of correlation between in vitro and in vivo studies on the effects of tangeretin and tangerine juice on midazolam hydroxylation. Clin Pharmacol Ther, 67: 382–390 (2000).
386. Henauer SA, Hollister LE, Gillespie HK, and Moore F. Theophylline antagonizes diazepam-induced psychomotor impairment. Eur J Clin Pharmacol, 25: 743–747 (1983).
387. Tuncok Y, Akpinar O, Guven H, and Akkoclu A. The effects of theophylline on serum alprazolam levels. Int J Clin Pharmacol Ther, 32: 642–645 (1994).
388. Ghoneim MM, Hinrichs JV, Chiang C-K, and Loke WH. Pharmacokinetic and pharmacodynamic interactions between caffeine and diazepam. J Clin Psychopharmacol, 6: 75–80 (1986).
389. Ohnhaus EE, Park BK, Colombo JP, and Heizmann P. The effect of enzyme induction on diazepam metabolism in man. Br J Clin Pharmacol, 8: 557–563 (1979).
390. MacLeod SM, Sellers EM, Giles HG, Billings BJ, Martin PR, Greenblatt DJ, and Marshman JA. Interaction of disulfiram with benzodiazepines. Clin Pharmacol Ther, 24: 583–589 (1978).
391. Diquet B, Gujadhur L, Lamiable D, Warot D, Hayoun H, and Choisy H. Lack of interaction between disulfiram and alprazolam. Eur J Clin Pharmacol, 38: 157–160 (1990).
392. Nakajima M, Suzuki T, Sasaki T, Yokoi T, Hosoyamada A, Yamamoto T, and Kuroiwa Y. Effects of chronic administration of glucocorticoid on midazolam pharmacokinetics in humans. Ther Drug Monit, 21: 507–513 (1999).
393. Villikka K, Kivisto KT, and Neuvonen PJ. The effect of dexamethasone on the pharmacokinetics of triazolam. Pharmacol Toxicol, 83: 135–138 (1998).
394. Mulley BA, Potter BI, Rye RM, and Takeshita K. Interactions between diazepam and paracetamol. J Clin Pharmacy, 3: 25–35 (1978).
395. Abernethy DR, Greenblatt DJ, Ameer B, and Shader RI. Probenecid impairment of acetaminophen and lorazepam clearance: Direct inhibition of ether glucuronide formation. J Pharmacol Exp Ther, 234: 345–349 (1985).
396. Golden PL, Warner PE, Fleishaker JC, Jewell RC, Millikin S, Lyon J, and Brouwer KLR. Effects of probenecid on the pharmacokinetics and pharmacodynamics of adinazolam in humans. Clin Pharmacol Ther, 56: 133–141 (1994).
397. Robertson P, Decory HH, Madan A, and Parkinson A. In vitro inhibition and induction of human hepatic cytochrome P450 enzymes by modafinil. Drug Metab Dispos, 28: 664–671 (2000).
398. Robertson P, Hellriegel ET, Arora S, and Nelson M. Effect of modafinal on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. Clin Pharmacol Ther, 71: 46–56 (2002).
399. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, and Ang CYW. Cytochrome P450 phenotype ratios for predicting herb-drug interactions in humans. Clin Pharmacol Ther, 72: 276–287 (2002).
400. Klee H, Faugier J, Hayes C, Boulton T, and Morris J. AIDS-related risk behavior, polydrug use and temazepam. Br J Addict, 85: 1125–1132 (1990).

401. Navaratnam V, and Foong K. Adjunctive drug use among opiate addicts. Curr Med Res Opin, 11: 611–619 (1990).
402. Metzger D, Woody G, De Philippis D, McLellan AT, O'Brien CP, and Platt JJ. Risk factors for needle sharing among methadone-treated patients. Am J Psychiatry, 148: 636–640 (1991).
403. Darke S, Hall W, Ross M, and Wodak A. Benzodiazepine use and HIV risk-taking behaviour among injecting drug users. Drug Alcohol Depend, 31: 31–36 (1992).
404. Barnas C, Rossmann M, Roessler H, Riemer Y, and Fleishchhacker WW. Benzodiazepines and other psychotropic drugs abused by patients in a methadone maintenance program: familiarity and preferance. J Clin Psychopharmacol, 12: 397–402 (1992).
405. Hall W, Bell J, and Carless J. Crime and drug use among applicants for methadone maintenance. Drug Alcohol Depend, 31: 123–129 (1993).
406. San L, Tato J, Torrens M, Castillo C, Farre M, and Cami J. Flunitrazepam consumption among heroin addicts admitted for in-patient detoxification. Drug Alcohol Depend, 32: 281–286 (1993).
407. Darke S, Swift W, Hall W, and Ross M. Drug use, HIV risk-taking and psychosocial correlates of benzodiazepine use among methadone maintenance clients. Drug Alcohol Depend, 34: 67–70 (1993).
408. Strang J, Griffiths P, Abbey J, and Gossop M. Survey of injected benzodiazepines among drug users in Britain. BMJ, 308: 1082 (1994).
409. Garriott JC, DiMaio VJM, Zumwalt RE, and Petty CS. Incidence of drugs and alcohol in fatally injured motor vehicle drivers. J Forensic Sci, 22: 383–389 (1977).
410. Warren R, Simpson H, Hilchie J, Cimbura G, Lucas D, and Bennett R. Drugs detected in fatally injured drivers in the province of Ontario. Alcohol Drugs Traffic Safety, 1: 203–217 (1980).
411. Fortenberry JC, Brown DB, and Shelvin LT. Analysis of drug involvement in traffic fatalities in Alabama. Am J Drug Alcohol Abuse, 12: 257–267 (1986).
412. McLean S, Parsons RS, Chesterman RB, Johnson MG, and Davies NW. Drugs, alcohol and road accidents in Tasmania. Med J Aust, 147: 6–11 (1987).
413. Logan BK, and Schwilke EW. Drug and alcohol use in fatally injured drivers in Washington state. J Forensic Sci, 41: 505–510 (1996).
414. Finkle BS, Biasotti AA, and Bradford LW. The occurrence of some drugs and toxic agents encountered in drinking driver investigations. J Forensic Sci, 13: 236–245 (1968).
415. Robinson TA. The incidence of drugs in impaired driving specimens in Northern Ireland. J Forensic Sci Soc, 19: 237–241 (1979).
416. White JM, Clardy DO, Graves MH, Kuo MC, MacDonald BJ, Wiersema SJ, and Fitzpatrick G. Testing for sedative-hypnotic drugs in the impaired driver: a survey of 72,000 arrests. Clin Toxicol, 18: 945–957 (1981).
417. Peel HW, Perrigo BJ, and Mikhael NZ. Detection of drugs in saliva of impaired drivers. J Forensic Sci, 29: 185–189 (1984).
418. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, and MacDonald TM. Association of road-traffic accidents with benzodiazepine use. Lancet, 352: 1331–1336 (1998).
419. Liljequist R, Linnoila M, Mattila MJ, Saario I, and Seppala T. Effect of two weeks' treatment with thioridazine, chlorpromazine, sulpiride and bromazepam, alone or in combination with alcohol, on learning and memory in man. Psychopharmacologia, 44: 205–208 (1975).
420. Hughes FW, Forney RB, and Richards AB. Comparative effect in human subjects of chlordiazepoxide, diazepam, and placebo on mental and physical performance. Clin Pharmacol Ther, 6: 139–145 (1965).
421. Staak M, Raff G, and Strohm H. Pharmacopsychological investigation of changes in mood induced by dipotassium chlorazepate with and without simultaneous alcohol administration. Int J Clin Pharmacol Ther Toxicol, 18: 283–291 (1980).
422. Lawton MP, and Cahn B. The effects of diazepam (Valium®) and alcohol on psychomotor performance. J Nerv Ment Dis, 136: 550–554 (1963).
423. Molander L, and Duvhok C. Acute effects of oxazepam, diazepam and methylperone, alone and in combination with alcohol on sedation, coordination and mood. Acta Pharmacol Toxicol, 38: 145–160 (1976).

424. van Steveninck AL, Gieschke R, Schoemaker RC, Roncari G, Tuk B, Pieters MSM, Breimer DD, and Cohen AF. Pharmacokinetic and pharmacodynamic interactions of bretazenil and diazepam with alcohol. Br J Clin Pharmacol, 41: 565–573 (1996).
425. van Steveninck AL, Gieschke R, Schoemaker HC, Pieters MSM, Kroon JM, Breimer DD, and Cohen AF. Pharmacodynamic interactions of diazepam and intravenous alcohol at pseudo steady state. Psychopharmacology, 110: 471–478 (1993).
426. Saario I, and Linnoila M. Effect of subacute treatment with hypnotics, alone or in combination with alcohol, on psychomotor skills related to driving. Acta Pharmacol Toxicol, 38: 382–392 (1976).
427. Lichter JL, Korttila K, Apfelbaum J, Rupani G, Ostman P, Lane B, Hendren M, Dohrn C, Kemen M, and Villalabos T. Alcohol after midazolam sedation: does it really matter. Anesth Analges, 70: S 237 (1990).
428. Saario I, Linnoila M, and Maki M. Interaction of drugs with alcohol on human psychomotor skills related to driving: effect of sleep deprivation or two weeks' treatment with hypnotics. J Clin Pharmacol, 15: 52–59 (1975).
429. Grigoleit HG, Hajdu P, Hundt HKL, Koeppen D, Malerczyk V, Meyer BH, Muller FO, and Witte PU. Pharmacokinetic aspects of the interaction between clobazam and cimetidine. Eur J Clin Pharmacol, 25: 139–142 (1983).
430. Sanders LD, Whitehead C, Gildersleve CD, Rosen M, and Robinson JO. Interaction of H_2-receptor antagonists and benzodiazepine sedation: a double-blind placebo-controlled investigation of the effects of cimetidine and rantidine on recovery after intravenous midazolam. Anaesthesia, 48: 286–292 (1993).
431. Wilson CM, Robinson FP, Thompson EM, Dundee JW, and Elliot P. Effect of pretreatment with ranitidine on the hypnotic action of single doses of midazolam, temazepam and zopiclone. Br J Anaesth, 58: 483–486 (1986).
432. Van Hecken AM, Tjandramaga TB, Verbesselt R, and De Schepper PJ. The influence of diflunisal on the pharmacokinetics of oxazepam. Br J Clin Pharmacol, 20: 225–234 (1985).
433. Huang W, and Moody DE. Immunoassay detection of benzodiazepines and benzodiazepine metabolites in blood. J Anal Toxicol, 19: 333–342 (1995).
434. Back DJ, Tjia JF, Karbwang J, and Colbert J. In vitro inhibition studies of tolbutamide hydroxylase activity of (HLM) by azoles, sulphonamides and quinilines. Br J Clin Pharmacol, 26: 23–29 (1988).
435. Erickson DA, Mather G, Trager WF, Levy RH, and Keirns JJ. Characterization of the in vitro biotransformation of the HIV-1 reverse transcriptase inhibitor nevirapine by human hepatic cytochromes P-450. Drug Metab Dispos, 27: 1488–1495 (1999).

Chapter 3
Antiepileptic Drugs

Nathan L. Kanous II and Barry E. Gidal

Abstract Epilepsy is a chronic neurological disorder characterized by recurrent seizures. Estimates indicate that approximately 120 in 100,000 people in the USA seek medical attention each year as the result of experiencing a seizure. While not every patient that has a seizure has epilepsy, approximately 125,000 new cases of epilepsy are diagnosed every year. Several types of antiepileptic drugs (AEDs) with different modes of action are used in clinical practice to treat patients with epilepsy, depending on the exact underlying cause of the condition. Although these drugs provide relief for most epileptics, many of the drugs have significant side-effects, drug interactions and toxicities. This chapter provides an outline of the pharmacokinetics and pharmacodynamics of AEDs, as well as their toxicities and drug interactions, and wil provide the reader with a general outline which can be used to assist in the treatment of clinical patients as well as a guide to assist forensic toxicologists.

Keywords Epilepsy • Etiology

Epidemiology of Epilepsy

Epilepsy is a chronic neurologic disorder characterized by recurrent seizures. Estimates indicate that approximately 120 in 100,000 people in the USA seek medical attention each year as the result of experiencing a seizure. While not every patient that has a seizure has epilepsy, approximately 125,000 new cases of epilepsy are diagnosed every year [1–3].

The incidence of epilepsy in the general population is highest in newborn and young children with a second peak occurring in patients older than 65 years. It has

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been suggested that there may be some genetic predisposition to the development of seizures and epilepsy. While the incidence of epilepsy is higher among patients with mental retardation and cerebral palsy, neither condition is synonymous with epilepsy [1].

Etiology

Epilepsy is recognized as a syndrome of disturbed electrical activity in the brain which can be caused by a variety of stimuli. This disturbed electrical activity leads to the development of seizures. Seizures occur because of the abnormal discharge of neurons within the central nervous system. Even slight abnormal discharges can destabilize the electrical homeostasis of neurons, thus increasing the propensity for other abnormal activity and the propagation of seizure activity [3].

Precipitation of seizures in predisposed patients can occur as the result of a variety of inciting factors. Hyperventilation, sleep, sleep deprivation, and sensory and emotional stimuli have all been implicated. Hormonal changes associated with menses and several prescription drugs and drug classes may also influence the onset or frequency of seizure activity in patients with epilepsy. In addition, many antiepileptic drugs (AEDs) are known to cause seizures at excessive concentrations [3].

Medications Utilized in the Treatment of Epilepsy

AEDs act within the central nervous system in one of two ways: by reducing pathologic electrical discharges or by inhibiting the propagation of aberrant electrical activity. This may occur through effects on specific ion channels, inhibitory neurotransmitters or excitatory neurotransmitters. While multiple neurophysiological effects of AEDs have been theorized and hypothesized, it is important to recognize that the true mechanisms of action of these agents are poorly understood and may be multifactorial [4].

Testing to determine the serum concentration of AEDs is commonly employed. The widespread availability of this technology makes the determination of serum concentrations an attractive method for use in forensic science. For most AEDs there is poor correlation between maintenance doses and their resulting serum concentrations [5]. In addition there is important interindividual variability in both therapeutic and toxic response to medications [5–7]. Therefore, knowledge of the pharmacokinetics of AEDs is essential for understanding and interpreting serum concentrations of AEDs. This includes issues related to all aspects of drug disposition: absorption, distribution, metabolism, and excretion.

This situation is further complicated by the fact that AEDs are subject to pharmacokinetic interactions with one another and many other drugs and foods [5]. Interactions with other drugs may lead to loss of efficacy or toxic effects from either the AED or the other interacting drug. This can be particularly important with the

initiation or discontinuation of either drug, and careful attention should be paid to the time course of initiation or discontinuation of any drug in the interpretation of the effects of drugs and serum drug concentrations [8].

AEDs are well known for their side effects. Side effects are generally classified as acute or chronic. Further, these effects may be described as being concentration-dependant or idiosyncratic. Concentration-dependant effects are usually relatively common and well characterized. Allergic reactions are typically mild but may be severe in some cases. Other idiopathic reactions are rare but can be serious and life-threatening [9]. Knowledge of the mechanism(s) of the toxic effects of AEDs and their relationship to serum concentration data are also important for the practicing forensic scientist.

Lastly, it is important to recognize that many AEDs are frequently employed for off-label use. The majority of off-label use involves the treatment of psychiatric disorders, particularly bipolar affective disorder or manic depressive disorder [10]. Other off-label uses include such things as migraine prophylaxis, attention-deficit disorder, and neuropathic pain.

Phenytoin and Fosphenytoin

Chemistry

Phenytoin is a hydantoin anticovulsant medication that is structurally related to the barbiturates. Although similar, the monoacylurea structure of phenytoin makes it a much weaker organic acid than the barbiturates [11]. This results in very poor aqueous solubility of phenytoin.

Parenteral phenytoin must be formulated as a highly alkaline aqueous solution to maintain adequate solubility. This is accomplished through the use of an aqueous vehicle consisting of 40% propylene glycol and 10% ethanol in water buffered with sodium hydroxide to a pH of 12. Parenteral phenytoin is incompatible with dextrose-based intravenous solutions. Preparation of intravenous phenytoin in dextrose-based solutions results in immediate precipitation of the free acid [12].

Oral phenytoin is available in a variety of formulations as the free acid or sodium salt in both immediate and extended release formulations.

Fosphenytoin is a phenytoin prodrug. This drug was developed and formulated specifically to improve the solubility of phenytoin for parenteral use. Fosphenytoin is a disodium phosphate ester of phenytoin. As such, fosphenytoin is freely soluble in aqueous solution and is rapidly and completely converted to phenytoin in vivo through the action of serum phosphatase enzymes [13].

Pharmacology

Phenytoin and fosphenytoin are effective at reducing seizure frequency and severity without causing generalized central nervous system depression. This action is mediated through effects on voltage-activated Na^+ channels in neuronal cell membranes [11].

Depolarization of the neuronal cell membrane triggers the voltage-activated Na^+ channel to open, thus facilitating transmission of the action potential down the axon and, ultimately, from cell to cell. After opening, these voltage-activated Na^+ channels will spontaneously close. This is termed inactivation of the Na^+ channel. This inactivation is thought to cause the refractory period, a period of time after an action potential during which another action potential cannot be evoked [11].

These drugs effectively limit repetitive firing of action potentials by prolonging inactivation, thus slowing the rate of repolarization of neuronal cells. At therapeutic concentrations, these effects are selective with no effect on spontaneous firing or responses to gamma-amino butyric acid or glutamate [14]. Thus, they limit the propagation of the aberrant electrical discharges which characterize epilepsy.

Pharmacokinetics

The pharmacokinetics of phenytoin (and also fosphenytoin) are strongly influenced by its limited aqueous solubility and saturable enzymatic elimination. The inactivation of these drugs by cytochrome P450 isozymes predisposes them to the influence of drug interactions.

Absorption

Due to its broad effectiveness in the management of epilepsy and the nature of epilepsy as a clinical disorder, phenytoin is available in a variety of formulations. Differences in physicochemical properties of the various formulations results in significant variability in both the rate and extent of absorption from each preparation.

Several factors including pK_a and lipid solubility, pH of the dissolution medium, solubility in the medium, and phenytoin concentration influence the rate and extent of absorption in the gastrointestinal tract. These factors are commonly altered by the presence of food or drugs in the gastrointestinal tract and the individual formulation [12, 13, 15].

Phenytoin is poorly absorbed in the stomach due to the low pH of gastric juice (approximately 2.0) which renders it insoluble even though it may be present in a non-ionized form. The duodenum serves as the primary source of absorption with its higher pH increasing the solubility of the drug. Absorption slows within the jejunum and ileum and is again poor in the colon [12, 13, 15].

Also due to poor solubility, intramuscular administration of phenytoin results in drug precipitation and the formation of an insoluble mass. This effect, coupled with the pain associated with intramuscular injection of a high pH solution mandate that phenytoin be administered intravenously when a parenteral route is necessary [16].

Due to its improved solubility profile, fosphenytoin can be administered either intramuscularly or intravenously. Comparison of area under the curve measures for total or free phenytoin concentrations between fosphenytoin and phenytoin sodium

are nearly identical, indicating complete bioavailability of fosphenytoin by either route [13].

In an effort to facilitate simple and rapid utilization of parenteral fosphenytoin for the more problematic phenytoin, fosphenytoin is packaged and dosed as milligram phenytoin equivalents (mPE) [13]. While this facilitates accurate conversion between parenteral dosage forms, this conversion is less accurate when converting oral phenytoin to parenteral mPEs. This is because oral phenytoin is formulated as a sodium salt. Thus, a 100 mg capsule of phenytoin sodium only delivers 92 mg of actual phenytoin [13]. This represents an approximately 9% difference in total dose when oral phenytoin is converted to parenteral fosphenytoin or phenytoin. This may result in increased serum concentrations of phenytoin after conversion, particularly in light of the unpredictable nonlinear kinetics of phenytoin metabolism.

Distribution

Phenytoin is approximately 90% protein bound in the plasma, primarily to albumin. The remaining 10% is unbound or "free" phenytoin and is pharmacologically active because that which is bound to plasma proteins is unable to cross the blood-brain barrier. Due to the passive diffusion of phenytoin into the cerebrospinal fluid (CSF), the concentration of phenytoin in the CSF is considered equivalent to the unbound plasma concentration [15].

The generally recognized therapeutic range for phenytoin is 10–20 mcg/mL, which includes both bound and unbound drug. The 10% of phenytoin which remains unbound corresponds to an equivalent unbound therapeutic range of 1–2 mcg/mL [17].

Protein binding of phenytoin is dependent upon albumin concentration and can also be influenced by a variety of clinical conditions and situations. Low serum albumin, renal failure, or concomitant use of other protein-bound drugs may change the protein binding and serum concentration of phenytoin [17, 18].

Metabolism

Phenytoin is extensively metabolized via the cytochrome P450 system. This occurs primarily through the 2 C19 and 2 C9 isozymes and accounts for the involvement of phenytoin in a variety of drug interactions [12]. Of note is the fact that the metabolism of phenytoin involves the intermediate formation of an arene oxide. This arene oxide intermediate has been implicated as the source of various toxicities and teratogenicity associated with the use of phenytoin [19].

Phenytoin is also known for its saturable enzyme pharmacokinetics. At low doses phenytoin exhibits a first-order dose-dependent kinetic profile. As the enzyme system becomes saturated, the maximal rate of metabolism is exceeded which leads to disproportionate increases in serum concentration with relatively small changes in dosing rate [12]. In most patients, the usual therapeutic range exceeds the concentration at which metabolism is half-maximal which causes phenytoin to exhibit a

nonlinear profile in the majority of patients. A variety of situations such as concurrent illness, medications, pregnancy, age, or genetics may influence the maximal rate of metabolism and thus may alter the pharmacokinetic profile of phenytoin in a given patient [20].

Excretion

Approximately 95% of an administered dose is excreted in the urine or feces as metabolites [12, 20].

Adverse Reactions

With initial therapy, the CNS depressant effects of phenytoin are most prominent and may cause lethargy, fatigue, incoordination, blurred vision, and drowsiness (Table 3.1). Slow dose titration can minimize these effects [9].

At high serum concentrations (>20 g/mL), many patients exhibit lateral gaze nystagmus. Other adverse effects known to occur at excessive plasma concentrations include ataxia, mental status changes, and coma. Further phenytoin has the ability to precipitate seizures or status epilepticus at extreme concentrations.

Chronic adverse effects include gingival hyperplasia which can occur in up to 50% of patients receiving long-term therapy. Other long-term effects include hirsutism, acne, coarsening of facial features, vitamin D deficiency, osteomalacia, folic acid deficiency (with resultant macrocytosis), hypothyroidism, and peripheral neuropathy.

Contraindications and Precautions

Patients with hypersensitivity reactions to any hydantoin AED may react to other hydantoin AEDs such as phenytoin. In addition, some patients exhibit cross-sensitivity to other compounds with similar chemical structures such as barbiturates, succinimides, and oxazolidinediones.

Prenatal exposure to hydantoin AEDs may result in the development of cleft palate, cleft lip, cardiac malformations and of a constellation of physical abnormalities referred to as the fetal anticovulsant syndrome; prenatal growth deficiency, microcephaly, hypophasia of the fingernails and craniofacial abnormalities [21].

The use of parenteral phenytoin can alter automaticity of cardiac tissue and may result in the development of ventricular arrhythmias and should only be used with extreme caution in patients with second- or third-degree AV blockade, bradycardia, or significant cardiac disease [22].

Due to the risk of myelosuppression, the use of phenytoin in immunosuppressed patients or patients with blood dyscrasias may increase the risk of infection or exacerbation of the hematologic abnormality.

Table 3.1 Antiepileptic drug side effects

Acute side effects			
AED	Concentration dependent	Idiosyncratic	Chronic side effects
Carbamazepine	Diplopia	Blood dyscrasias	Hyponatremia
	Dizziness	Rash	
	Drowsiness		
	Nausea		
	Unsteadiness		
	Lethargy		
Ethosuximide	Ataxia	Blood dyscrasias	Behavior changes
	Rash	Headache	
	Drowsiness		
	GI distress		
	Unsteadiness		
	Hiccoughs		
Felbamate	Anorexia	Aplastic anemia	Not established
	Nausea	Acute hepatic failure	
	Vomiting		
	Insomnia		
	Headache		
Gabapentin	Dizziness		Weight gain
	Fatigue		
	Somnolence		
	Ataxia		
Lamotrigine	Diplopia	Rash	Not established
	Dizziness		
	Unsteadiness		
	Headache		
Levetiracetam	Sedation	Not established	Not established
	Behavioral disturbance		
Oxcarbazepine	Sedation	Rash	Hyponatremia
	Dizziness		
	Ataxia		
	Nausea		
Phenobarbital	Ataxia	Blood dyscrasias	Behavior changes
	Hyperactivity	Rash	Connective tissue disorders
	Headache		Intellectual blunting
	Unsteadiness		Metabolic bone disease
	Sedation		Mood change
	Nausea		Sedation
Phenytoin	Ataxia	Blood dyscrasias	Behavior changes
	Nystagmus	Rash	Cerebellar syndrome
	Behavior changes	Immunologic reaction	Connective tissue changes
	Dizziness		Skin thickening
	Headache		Folate deficiency
	Incoordination		Gingival hyperplasia

(continued)

Table 3.1 (continued)

Acute side effects			
	Sedation		Hirsutism
	Lethargy		Coarsening of facial features
	Cognitive impairment		Acne
	Fatigue		Cognitive impairment
	Visual blurring		Metabolic bone disease
			Sedation
Primidone	Behavior changes	Blood dyscrasias	Behavior change
	Headache	Rash	Connective tissue disorders
	Nausea		Cognitive impairment
	Sedation		Sedation
	Unsteadiness		
Tiagabine	Dizziness	Not established	Not established
	Fatigue		
	Difficulties concentrating		
	Nervousness		
	Tremor		
	Blurred vision		
	Depression		
	Weakness		
Topiramate	Difficulties concentrating	None established	Kidney stones
	Psychomotor slowing		
	Speech or language problems		
	Somnolence, fatigue		
	Dizziness		
	Headache		
Valproic acid	GI upset	Acute hepatic failure	Polycystic ovary-like syndrome
	Sedation	Acute pancreatitis	Alopecia
	Unsteadiness		Weight gain
	Tremor		Hyperammonemia
	Thrombocytopenia		
Zonisamide	Sedation	Rash	Kidney stones
	Dizziness	Oligohydrosis	
	Cognitive impairment		
	Nausea		

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The metabolism of phenytoin may be impaired in patients with active liver disease or active alcoholism with subsequent toxic effects associated with elevated serum concentrations [6, 12, 23].

Drug Interactions

Phenytoin is involved in many drug interactions (Tables 3.2 and 3.3). These interactions are well characterized and phenytoin may be the target or cause of interactions. Pharmacokinetic drug interactions affecting absorption, metabolism, or excretion have the potential to either increase or decrease the plasma concentration of phenytoin. While food may slightly alter the rate of absorption of phenytoin, it is well recognized that enteral feedings can dramatically decrease the bioavailability of phenytoin suspension when administered via a feeding tube [24].

Although phenytoin is highly protein bound, protein-binding interactions are generally of minimal significance. As phenytoin is displaced from plasma proteins, the free fraction of phenytoin increases. This is followed by an increase in the clearance of phenytoin, a decrease in total phenytoin concentration, and subsequent reestablishment of baseline free phenytoin concentration [17]. It is important that clinicians understand the mechanism of this interaction and do not react to decreases in total concentration without considering the possibility that free concentrations remain therapeutic.

Long-term use of phenytoin decreases folic acid absorption [9]. Replacement of folic acid effectively increases the clearance of phenytoin and thereby decreases phenytoin concentrations. Supplementation of folic acid, alone or as a vitamin, has the potential to decrease plasma phenytoin concentrations and subsequently decrease seizure control [25].

Carbamazepine and Oxcarbazepine

Chemistry

The chemical structure of carbamazepine is tricyclic in nature, with two benzene rings flanking one azepine ring which contains a double bond. This structure is most closely related to antipsychotic and antidepressant drugs such as chlorpromazine, imipramine, and maprotiline. Carbamazepine differs from other heterocyclic AEDs by being tricyclic, lacking an amide group in the heterocyclic ring, and not possessing a saturated carbon atom in the cyclic structure [26].

Carbamazepine is insoluble in water although easily soluble in many organic solvents including benzene, chloroform, and dichloromethane. This lipophilicity strongly influences drug transport across biological membranes.

Oxcarbazepine, a biological prodrug, is a keto analog of carbamazepine. This change in structure alters the solubility of the compound and renders it only slightly

Table 3.2 Interactions between antiepileptic drugs

AED	Added drug	Effect
Carbamazepine (CBZ)	Felbamate	Incr. 10, 11 epoxide
	Felbamate	Decr. CBZ
	Phenobarbital	Decr. CBZ
	Phenytoin	Decr. CBZ
Felbamate (FBM)	Carbamazepine	Decr. FBM
	Phenytoin	Decr. FBM
	Valproic acid	Incr. FBM
Gabapentin	No known interactions	
Lamotrigine (LTG)	Carbamazepine	Decr. LTG
	Phenobarbital	Decr. LTG
	Phenytoin	Decr. LTG
	Primidone	Decr. LTG
	Valproic acid	Incr. LTG
Levetiracetam	No known interactions	
Oxcarbazepine	Carbamazepine	Decrease MHD
	Phenytoin	Decrease MHD
	Phenobarbital	Decrease MHD
Phenobarbital (PB)	Felbamate	Incr. PB
	Phenytoin	Incr. or decr. PB
	Valproic acid	Incr. PB
Phenytoin (PHT)	Carbamazepine	Decr. PHT
	Felbamate	Incr. PHT
	Methsuximide	Incr. PHT
	Phenobarbital	Incr. or decr PHT
	Valproic acid	Decr. total PHT
	Vigabatrin	Decr. PHT
Primidone (PRM)	Carbamazepine	Decr. PRM
		Incr. PB
	Phenytoin	Decr. PRM
		Incr. PB
	Valproic acid	Incr. PRM
		Incr. PB
Tiagabine (TGB)	Carbamazepine	Decr. TGB
	Phenytoin	Decr. TGB
Topiramate (TPM)	Carbamazepine	Decr. TPM
	Phenytoin	Decr. TPM
	Valproic acid	Decr. TPM
Valproic acid (VPA)	Carbamazepine	Decr. VPA
	Lamotrigine	Decr. VPA
	Phenobarbital	Decr. VPA
	Primidone	Decr. VPA
	Phenytoin	Decr. VPA
Zonisamide	Carbamazepine	Decrease zonisamide
	Phenytoin	Decrease zonisamide
	Phenobarbital	Decrease zonisamide

Incr increased, *Decr* decreased, *MHD* 10

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Table 3.3 Interactions with other drugs

AED	Altered by	Result	Alters	Result
Carbamazepine	Cimetidine	Incr. CBZ	Oral contraceptives (OC)	Decr. efficacy of OC
	Erythromycin	Incr. CBZ	Doxycycline	Decr. doxycycline
	Fluoxetine	Incr. CBZ	Theophylline	Decr. theophylline
	Isoniazid	Incr. CBZ	Warfarin	Decr. warfarin
	Propoxyphene	Incr. CBZ		
Oxcarbazepine			OC	Decr. efficacy of OC
Phenobarbital	Acetazolamide	Incr. PB	OC	Decr. efficacy of OC
Phenytoin	Antacids	Decr. absorption of PHT	Oral contraceptives	Decr. efficacy of OC
	Cimetidine	Incr. PHT	Bishydroxycoumarin	Decr. anticoagulation
	Chloramphenicol	Incr. PHT	Folic acid	Decr. folic acid
	Disulfiram	Incr. PHT	Quinidine	Decr. quinidine
	Ethanol (acute)	Incr. PHT	Vitamin D	Decr. vitamin D
	Fluconazole	Incr. PHT		
	Isoniazid	Incr. PHT		
	Propoxyphene	Incr. PHT		
	Warfarin	Incr. PHT		
	Alcohol (chronic)	Decr. PHT		
Primidone	Isonazid	Decr. metabolism of primidone	Chlorpromazine	Decr. chlorpromazine
	Nicotinamide	Decr. metabolism of primidone	Corticosteroids	Decr. corticosteroids
				Quinidine
				Decr. quinidine
			Tricyclics	Decr. tricyclics
			Furosemide	Decr. renal sensitivity to furosemide
Topiramate			OC	Decr. efficacy of OC
Valproic acid	Cimetidine	Incr. VPA	OC	Decr. efficacy of OC
	Salicylates	Incr. free VPA		

Incr increased, *Decr* decreased
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soluble in chloroform, dichloromethane, acetone, and methanol while it is practically insoluble in water ethanol and ether [27].

Pharmacology

Carbamazepine enhances the inactivation of voltage-activated Na^+ channels by slowing their recovery. This results in a net decrease in high-frequency repetitive firing of action potentials. These effects are evident and selective at serum concentrations within the therapeutic range [28]. No effect of carbamazepine on exogenously administered GABA or glutamate has been identified. The 10, 11 epoxycarbamazepine metabolite also contributes a similar therapeutic effect [29].

The pharmacologic effect of oxcarbazepine is due to a principal metabolite, 10-hydroxy-oxcarbazepine [27]. The mechanism of action is similar to that of carbamazepine but may also include increased potassium conduction and modulation of high-voltage calcium channels [30, 31].

Pharmacokinetics

It is well known that absorption of carbamazepine varies significantly from one dosage form to another [32]. Further, the effects of carbamazepine on the cytochrome P450 isozyme system warrants close assessment of the pharmacokinetics of this drug in clinical use.

Absorption

Carbamazepine tablets are incompletely and erratically absorbed. The time to maximal serum concentration (t_{mas}) is eight or more hours for tablets but 3–5 h for the suspension [33]. That means that the full effects of a given oral dose of carbamazepine tablets may not be recognized until eight or more hours after the dose has been ingested, while a similar dose of the suspension reaches maximal concentration in just 3–5 h and may influence the interpretation of serum concentration data. In addition to delayed absorption of carbamazepine from tablets, it has also been recognized that tablet formulations can be adversely effected by humidity and moisture content, thus further delaying or decreasing absorption [34].

Carbamazepine exhibits both zero-order and first-order absorption characteristics. Approximately 35% of an oral dose is absorbed in zero-order fashion (no effect of dose on absorption) while the remainder of the dose is absorbed according to a first-order kinetics. At doses greater than 20 mg/kg, an inverse relationship between dose and absorption begins to occur [35].

Absolute bioavailability of carbamazepine is approximately 75% of the dose administered. This is similar between all dosage forms.

Distribution

Carbamazepine is highly protein bound with 75–80% bound to albumin and other plasma proteins with an apparent volume of distribution of 0.8–2 L/kg. Unbound concentrations of CBZ vary inversely with the concentration of α_1-acid glycoprotein [36].

CBZ is readily distributed into cerebrospinal fluid and these concentrations vary linearly with plasma levels. While there may be wide variability in CBZ concentration between patients, the ratio of plasma:CSF concentration is relatively constant between patients [37].

CBZ is also readily distributed into amniotic fluid and breast milk [38]. While the use of CBZ is not contraindicated among pregnant women, it must be recognized that the newborn may be susceptible to adverse effects associated with exposure to CBZ.

Consistent with its lower lipid solubility, 10, 11 epoxycarbamazepine has a lower apparent volume of distribution and increased fraction unbound of 48–53% [39]. The commonly accepted therapeutic range for carbamazepine in adults is 4–12 mcg/mL [40]. To date, no accepted therapeutic range for the use of oxcarbazepine in treating epilepsy has been established [41]. Clinical trials in patients treated for neurologic pain have reported serum 10-hydroxy-carbazepine concentrations between 50 and 100 mcg/mL [42].

Metabolism

Carbamazepine is essentially completely metabolized in humans through both oxidative and conjugative pathways. The primary metabolite, carbamazepine epoxide, is pharmacologically active and may accumulate in patients using CBZ over long periods of time [36]. This may potentially lead to the development of toxicity in a patient who manifests no change in plasma CBZ level after an increase in daily CBZ dose.

A comparison of patients reveals a lower ratio of CBZ epoxide to CBZ among patients receiving monotherapy when compared to those receiving multiple AEDs [43].

Autoinduction

After initial dosing, CBZ induces its own metabolism significantly leading to increased clearance, decreased serum half-life, and a subsequent decline in plasma concentration over time. Studies have shown that while the elimination half-life of CBZ in single-dose studies varied from 20 to 65 h, the half-life was decreased by approximately 50% after multiple dosing for 10–20 days [44, 45].

There is a time dependence of CBZ kinetics secondary to this phenomenon of autoinduction. As the autoinduction progresses, changes in daily dose are required to maintain adequate plasma concentrations. Autoinduction is expected to be complete within 20–30 days and is dependent upon CBZ dose [44, 45].

Excretion

Approximately 72% of a given dose of CBZ is eliminated as metabolites in the urine. The remaining 28% is eliminated in the feces.

Adverse Reactions

The most common side effects of carbamazepine include dizziness, drowsiness, ataxia, dyskinesia, diplopia, and headache. These effects are typically dose-related and may resolve with continued administration only to recur with significant increases in plasma concentration [9].

Idiopathic reactions to carbamazepine include blood dyscrasias and hypersensitivity reactions. Aplastic anemia, agranulocytosis, and pancytopenia have been reported to occur rarely with the use of CBZ and more often when CBZ is used in combination with other medications. Leukopenia is reported to occur in nearly 10% of patients. While somewhat common, there appears to be no association between the presence of leukopenia and an increased incidence of infection. This has been hypothesized to occur as a result of WBC redistribution [9].

Hypersensitivity manifests most commonly as the development of an eczematous rash which can progress in some patients to Stevens–Johnson syndrome [46].

Dilutional hyponatremia and the syndrome of inappropriate antidiuretic hormone have been reported. The incidence of this phenomenon may increase with the age of the patient and appears somewhat dose-related although low-dose therapy does not preclude the development of hyponatremia [47].

Contraindications and Precautions

Some patients with a history of hypersensitivity to tricyclic antidepressants may be sensitive to carbamazepine and should only be treated with carbamazepine when the risk of benefit outweighs the risk of hypersensitivity.

The use of CBZ in patients with absence seizures has been associated with worsening of seizures while using CBZ and should be avoided. Similarly, CBZ is considered ineffective for the treatment of Lennox–Gastaut syndrome [11].

Congenital abnormalities have been reported to occur in infants of mothers who take CBZ. Current evidence indicates a higher risk of malformations with combination therapy which may result in higher plasma CBZ concentrations [48].

Drug Interactions

Carbamazepine's metabolic fate and its influence on the cytochrome p450 system make carbamazepine the subject of many significant drug interactions [5]. Interestingly, valproic acid can effectively increase the plasma concentration of the

10, 11 epoxide metabolite without changing the concentration of carbamazepine. Erythromycin inhibits the metabolism of CBZ resulting in clinically significant increases in plasma CBZ concentration. CBZ can induce the metabolism of many other drugs potentially leading to loss of therapeutic effect. Several examples include valproic acid, theophylline, warfarin, and ethosuximide.

Lamotrigine

Chemistry

Lamotrigine is a phenyltriazine AED unrelated to other currently available AEDs. As a tertiary amine, lamotrigine is only very slightly soluble in water and slightly soluble in 0.1 M HCl [49].

Pharmacology

Lamotrigine effectively inhibits the reactivation of voltage-activated Na^+ channels, similar to phenytoin and carbamazepine. Further, this action appears greater during repetitive activation, such as may occur during an epileptic seizure (double check that). However, unlike carbamazepine and phenytoin, lamotrigine also competitively blocks high-voltage Ca^+ flux which may be due to blocking presynaptic-type Ca^+ channels. Lamotrigine is also effective at inhibiting the release of glutamate and GABA from neurons, although this effect is much more pronounced for glutamate than for GABA [49].

Pharmacokinetics

The pharmacokinetics of lamotrigine are unique when compared to other AEDs in that while it is not a subject of drug interactions related to oxidative metabolism through the cytochrome P-450 system, it is subject to interaction with drugs that may alter its glucuronide conjugation.

Absorption

Lamotrigine is readily and completely absorbed from the gastrointestinal system. The bioavailability is 98%. Plasma concentrations peak 1–3 h after oral administration, and absorption appears to be linearly related to dose up to approximately 700 mg. Food does not alter the absorption of lamotrigine and systemic absorption can occur with rectal administration although to a more limited extent than with oral dosing [50].

Distribution

Lamotrigine is approximately 56% bound to plasma proteins which remains constant throughout the range of concentrations from 1 to 10 g/mL. The apparent volume of distribution is 0.9–1.2 L/kg and is independent of dose administered. Although lamotrigine serum concentrations can be determined, no therapeutic range has been established for this drug and it is advised that treatment decisions be guided by therapeutic response without concern for serum concentration [51].

Metabolism

Lamotrigine undergoes hepatic metabolism by uridine diphosphate (UDP)-glucuronosyl-transferase (UGT 1A4). Metabolism can occur at either heterocyclic nitrogen atom to form one of two glucuronide conjugates. These glucuronide conjugates are pharmacologically inactive [51].

The half-life of lamotrigine is approximately 24–29 h in healthy volunteers. While some evidence suggests that lamotrigine may undergo autoinduction, the relatively slow onset of autoinduction and the slow, tapered dosing schedule make this autoinduction clinically insignificant.

Excretion

Single-dose studies indicate that approximately 70% of a given dose is eliminated in the urine, almost entirely as glucuronide conjugates. Less than 10% of an administered dose is renally eliminated as unchanged drug [51].

Adverse Reactions

Lamotrigine can cause a number of CNS side effects including drowsiness, ataxia, diplopia, and headache. These effects occur significantly less frequently when compared to other AEDs [52].

A hallmark side effect of lamotrigine is the development of a rash. While several types of rash have been reported, the most common is a generalized erythematous morbilliform rash that is typically mild to moderate in severity. Case reports of the development of Stevens–Johnson syndrome have been reported. Rash appears to occur more frequently in patients receiving concomitant valproic acid and with rapid dose escalation [53].

Contraindications and Precautions

Dermatologic reactions to lamotrigine appear to be more frequent in children when compared to adults. Safety and efficacy in patients up to the age of 16 years has not been proven. As noted previously the development of rash is more common among patients receiving valproic acid.

Significant interindividual differences in pharmacokinetics of lamotrigine have been observed in patients with renal dysfunction and careful consideration should be given that the benefits outweigh the risks of treatment in this patient population [51].

Drug Interactions

As lamotrigine is not metabolized by the cytochrome p450 system, it is not involved in precipitating drug interactions. Lamotrigine clearance is increased by phenytoin and carbamazepine. Valproic acid decreases lamotrigine clearance and increases its half-life. Conversely, the addition of lamotrigine to valproic acid can decrease valproic acid concentrations by as much as 25% [51].

Valproate

Chemistry

Valproate is a short-chain branched fatty acid with low water solubility. Clinically, this compound is available as a sodium salt (valproate sodium, Depakene®) with high water solubility and also as a complex of valproic acid and sodium valproate (divalproate, Depakote®). This complex rapidly dissociates in the gastrointestinal tract to two molecules of valproate.

Pharmacology

Similar to phenytoin and carbamazepine, valproic acid prolongs the recovery of voltage-activated Na^+ channels. This effectively reduces propagation of rapid firing action potentials. Some evidence exists to suggest that valproic acid blocks calcium currents in T-type calcium channels similar to that seen with ethosuximide [54].

Valproic acid has no direct modulatory effect on GABAergic neurotransmission. However, valproic acid may alter CNS GABA concentrations via two mechanisms. First, valproic acid may stimulate glutamic acid decarboxylase, thus increasing GABA synthesis.

Second, valproic acid may inhibit the action of GABA transaminase and succinic semialdehyde dehydrogenase, therefore decreasing the degradation of GABA in the CNS. In either case, the net result is an increase in the concentration of GABA in the CNS [54].

Pharmacokinetics

Valproic acid is a widely used AED and is available in multiple formulations for oral and parenteral administration. Oral formulations include capsules, tablets, and syrup

with immediate release characteristics, enteric-coated tablets of sodium valproate or divalproex sodium, enteric-coated sprinkles of divalproex sodium Knowledge of the differences in pharmacokinetics between formulations is important.

Absorption

Oral valproic acid is essentially 100% bioavailable. However, due to difficulties associated with gastric irritation, enteric-coated and delayed release formulations have been developed to improve tolerability [54]. Multiple oral formulations of valproic acid are available: immediate release capsules, tablets, and syrup; enteric-coated tablets; and sprinkles of divalproex sodium. The rate of absorption of valproic acid differs among the various formulations [54].

Immediate release formulations are rapidly absorbed with peak concentrations reached within 2 h. Enteric-coated tablets delay absorption but remains rapid once the tablet reaches the small intestine. The time of onset for absorption of delayed release formulations is dependent upon the state of gastric emptying with peak plasma concentrations occurring between 3 and 8 h after oral administration. In patients taking delayed release VPA, true trough concentrations may not occur until after administration of a morning dose. No difference in bioavailability has been noted between immediate or delayed release formulations [54].

Distribution

VPA is highly bound to plasma proteins with an apparent volume of distribution of 0.13–0.19 L/kg for adults and 0.2–0.3 L/kg in children. Protein binding is saturable and therapeutic concentrations and the free fraction of VPA increases with increasing total concentration. This effect can be quite dramatic with a threefold increase in total concentration leading to a near tenfold increase in the concentration of free VPA [5].

Serum concentrations of valproic acid are expected to be above 50 mcg/mL to achieve therapeutic response. However, some controversy exists as to what the maximum concentration of the therapeutic range is. The most commonly cited maximal concentration of valproic acid is 100 mcg/mL [5]. While some reports have linked the emergence of adverse effects to concentrations greater than 80 mcg/mL, higher concentrations may be required and tolerated in the management of difficult-to-control patients.

Metabolism

VPA is metabolized extensively by the liver with a glucuronide conjugate and a 3-oxo-VPA metabolite accounting for over 70% of an administered dose. One metabolite, a 4-ene-VPA causes marked hepatotoxicity in rats and may be responsible for reports of hepatotoxicity in humans although this has not been entirely substantiated.

It should also be noted that higher concentrations of the 4-ene-VPA may be present in patients taking enzyme-inducing drugs such as phenobarbital [54].

Excretion

The majority of VPA (70–80%) is excreted in the urine as metabolites. In addition, portions of VPA are excreted in bile (7%) and through the lung (2–18%) [5].

Adverse Reactions

The most common side effects encountered with the use of valproic acid are mild and gastrointestinal in nature: nausea, vomiting, gastrointestinal distress, and anorexia. CNS-related side effects such as drowsiness, ataxia, and tremor appear to be dose-related. Any of these dose-related side effects may recur with changes in plasma concentration. Hair loss is occasionally seen early in therapy but generally resolves with continued use [5, 9].

The most serious idiosyncratic effect of valproic acid is hepatotoxicity. Risk factors for death due to hepatotoxicity include age <2 years, mental retardation and use of multiple AEDs. These events also occurred early in therapy [55]. Hyperammonemia is a very common finding among patients using valproic acid but is not considered to be a consequence of hepatic damage [9, 55]. Pancreatitis is very rare.

Thrombocytopenia and other blood dyscrasias have been commonly reported to occur in patients receiving valproic acid but rarely lead to drug discontinuation. Bleeding can occur in some patients as a result [56].

Excessive weight gain is a common side effect associated with chronic use of valproic acid [9].

Contraindications and Precautions

Valproate crosses the placenta and observational studies have revealed that first trimester use of valproate is associated with an increased risk of neural tube defects. Careful consideration of the use of this medication during pregnancy is warranted [57].

Pediatric use of valproic acid is associated with an increased risk of hepatotoxicity. Risk factors include age <2 years, multiple AED use, and mental retardation. In addition, valproic acid should not be used in patients with current hepatic disease [9, 55].

Valproic acid does alter platelet aggregation [9]. Caution should be exercised when using valproic acid with other drugs that may affect platelet aggregation and by patients with a history of thrombocytopenia and other risk factors for bleeding.

The use of valproic acid in combination with lamotrigine significantly increases the risk of dermatologic reactions to lamotrigine and caution is warranted [52].

Drug Interactions

Because valproic acid is extensively metabolized, alterations in liver enzyme function can change the clearance of valproic acid. Common enzyme-inducing drugs such as phenytoin, carbamazepine, primidone, and phenobarbital increase valproic acid metabolism. Highly protein-bound drugs such as aspirin and phenytoin have a propensity to displace valproic acid from binding sites and may change plasma VPA concentrations [5].

Valproic acid inhibits the metabolism of phenobarbital resulting in a significant decrease in phenobarbital clearance and subsequent toxic effects. As mentioned previously, valproic acid has the potential to increase the concentration of the 10, 11 epoxide metabolite of CBZ without altering the concentration of CBZ [5].

Ethosuximide

Ethosuximide is indicated for the treatment of absence seizures. In this capacity, it is considered the drug of first choice. Combination therapy with valproic acid is indicated in patients with difficult to control absence seizures despite monotherapy with ethosuximide.

Chemistry

Ethosuximide is a monocyclic AED which contains a five-member ring structure with two carbonyl oxygen atoms flanking a ring nitrogen. This compound is considered soluble in ethanol or ether, freely soluble in water or chloroform, and only very slightly soluble in hexane [58]. While containing a chiral center, ethosuximide is utilized clinically as a racemic mixture of the two compounds.

Pharmacology

Ethosuximide exhibits antiseizure activity by reducing low threshold Ca^{++} currents in the thalamic region. There is no effect on recovery of voltage-activated Na^{+} channels and thus no change in sustained repetitive firing. Ethosuximide has no influence on the action or concentration of GABA in the CNS. As a result of this unique mechanism of action, the use of ethosuximide is limited to the treatment of absence seizures [59].

Pharmacokinetics

Absorption

Absorption of ethosuximide is rapid and nearly complete (90–95%) and does not appear to be effected by long-term administration. Peak concentrations are reached

within 1–4 h after oral administration [5, 59]. While the rate of absorption of oral syrup may be faster than that of oral tablets, the formulations are considered bioequivalent.

Distribution

Ethosuximide distributes widely and homogeneously throughout the body. Based on this phenomenon, several studies have concluded that saliva concentrations of ethosuximide can be evaluated in lieu of plasma concentrations for therapeutic monitoring [59, 60].

The apparent volume of distribution is 0.62–0.65 L/kg in adults and 0.69 L/kg in children. Protein binding of ethosuximide is very low, ranging from 0% to 10% in humans [60].

Serum concentrations of ethosuximide can be useful in monitoring therapy. The generally accepted therapeutic range is 40–100 mcg/mL [5, 59].

Metabolism

Ethosuximide is extensively metabolized via hepatic oxidation with 80–90% of an administered dose transformed to inactive metabolites. Biotransformation is catalyzed through the action of CYP3A in a first-order fashion. Ethosuximide does not induce hepatic microsomal enzymes or the uridine diphosphate glucuronosyl transferase (UDPGT) system [5, 59].

Excretion

Approximately 10–20% of an administered dose of ethosuximide is renally eliminated with nonrenal routes accounting for the majority of elimination. The apparent half-life of the parent compound is 30–60 h in adults and 30–40 h in children [58].

Adverse Reactions

Adverse reactions from use of ethosuximide are relatively benign when compared to other AEDs. Most of these effects are dose-related, predictable, and resolve with a decrease in dose. Nausea and vomiting occur in up to 40% of patients taking ethosuximide. CNS side effects such as drowsiness, dizziness, fatigue, lethargy, and hiccups are also relatively common. Various behavioral changes have been reported but not well correlated with ethosuximide use [9, 59].

Episodes of psychosis have been reported to occur in young adults with a history of mental disorders who are treated with ethosuximide. These psychotic reactions typically occur after the onset of seizure control and resolve after discontinuation of the drug and recurrence of seizures. This phenomenon is called forced normalization [61].

Dermatologic adverse effects are the most common idiosyncratic reactions and range from mild dermatitis and rash to erythema multiforme and Stevens–Johnson syndrome [62]. Other rare effects include systemic lupus erythematosus, a lupus-like syndrome, and various blood dyscrasias [63].

Contraindications and Precautions

Although teratogenic effects in humans have not been documented with the use of ethosuximide, caution is warranted as birth defects have been associated with the use of other AEDs.

Patients with active hepatic or renal disease may be at increased risk of side effects due to altered pharmacokinetics of ethosuximide.

Drug Interactions

Few drug interactions have been reported with ethosuximide. CBZ may induce the metabolism of ethosuximide resulting in loss of seizure control. When ethosuximide metabolism reaches saturation, valproic acid may interfere by inhibiting the metabolism of ethosuximide and prolonging its half-life [5].

Gabapentin

Chemistry

The chemical structure of gabapentin is that of GABA covalently bound to a cyclohexane ring. The inclusion of a lipophilic cyclohexane ring was employed to facilitate transfer of the GABA moiety into the central nervous system. Gabapentin is freely soluble in water [64].

Pharmacology

Despite the fact that gabapentin was synthesized to serve as a GABA agonist in the CNS, this compound does not mimic the effects of GABA in experimental models [65]. Gabapentin appears to stimulate non-vesicular release of GABA through an unknown mechanism. Although it binds to a protein similar to the L-type voltage-sensitive Ca^{++} channels, gabapentin has no effect on calcium currents in root ganglion cells. Further, gabapentin does not effectively reduce sustained repetitive firing of action potentials as is seen with some other AEDs.

Pharmacokinetics

Absorption

Gabapentin is primarily absorbed in the small intestine. The L-amino acid carrier protein is responsible for absorption from the gut and distribution into the CNS. As a result of a saturable carrier-mediated absorption mechanism, bioavailability of gabapentin is dose-dependent [66].
Oral bioavailability is reported as being 60%. In one multi-dose study of 1,600 mg three times daily, bioavailability was reduced to approximately 35%. Maximal plasma concentrations are reached within 2–3 h of oral administration [66].

Distribution

Gabapentin is not appreciably bound to plasma proteins and exhibits an apparent volume of distribution of 0.65–1.04 L/kg. CSF concentrations of gabapentin range from 10% to 20% of plasma concentrations and distribution is limited by active transport through the L-amino acid carrier protein [66]. Optimal concentrations for therapeutic response to gabapentin have not been established.

Metabolism

Gabapentin is not metabolized nor has it been found to interfere with the metabolism of other AEDs.

Excretion

Gabapentin is excreted exclusively in the urine. The reported half-life of gabapentin is 5–7 h but this may be significantly prolonged in patients with renal dysfunction [67]. Renal elimination of gabapentin is closely related to creatinine clearance and glomerular filtration rate. For this reason, dosage adjustments may be necessary for patients with renal disease.

Adverse Reactions

CNS side effects of gabapentin are the most common, tend to occur with initiation of therapy, and subside with continued use. The most common of these effects are somnolence, dizziness, and fatigue. Ataxia has also been reported. Other rare CNS effects include nystagmus, tremor, and diplopia [68].

Neuropsychiatric reactions including emotional lability, hostility, and thought disorders have been reported and may be more common among children and mentally retarded patients [66]. Weight gain is becoming more widely recognized as a long-term side effect of gabapentin use.

Contraindications and Precautions

Elderly patients or patients with impaired renal function should be monitored closely for the development of side effects secondary to reduced clearance and accumulation of gabapentin.

Drug Interactions

As previously mentioned, gabapentin is not appreciably metabolized by the cytochrome p450 system, nor does it alter the function of those enzymes. Cimetidine can decrease the renal clearance of gabapentin by 10%, and aluminum-based antacids can decrease the bioavailability of gabapentin by as much as 20% [66].

Topiramate

Chemistry

Topiramate is chemically unique from the more traditional AEDs in that it is a sulfamate-substituted monosaccharide. Topiramate is freely soluble in acetone, chloroform, dimenthylsulfoxide, and ethanol. It is most soluble in aqueous environments with an alkaline pH [69].

Pharmacology

Topiramate appears to have several mechanisms by which it exerts its antiseizure effects. First, topiramate reduces currents through voltage-gated Na^+ channels and may act on the inactivated state of these channels similar to phenytoin thus reducing the frequency of repetitive firing action potentials. In addition, topiramate increases postsynaptic $GABA_a$ currents while also enhancing Cl^- channel activity. Further, topiramate decreases the activity of AMPA-kainate subtypes of glutamate receptors. Lastly, topiramate has been shown to function as a weak carbonic anhydrase inhibitor [70, 71].

Pharmacokinetics

Absorption

Topiramate is readily absorbed with an estimated bioavailability of 80%. Food may delay absorption but does not alter bioavailability. Time to peak concentration ranges from 1.5 to 4 h after an oral dose [72].

Distribution

Topiramate is minimally bound to plasma proteins but does bind to erythrocytes. This unique phenomenon may lead to nonlinear changes in serum concentration until red cell binding sites have become saturated. The apparent volume of distribution is 0/6–0.8 L/kg [72].

Topiramate dosage adjustments should be based upon therapeutic response as no defined therapeutic range has been established.

Metabolism

Topiramate metabolism accounts for the disposition of <50% of an administered dose. Hepatic metabolism involves several pathways including hydroxylation, hydrolysis, and glucuronidation. Administration of enzyme-inducing drugs such as carbamazepine can increase the apparent hepatic clearance of topiramate by 50–100% with a corresponding decrease in the fraction excreted in the urine [73].

Excretion

Greater than 50% of an administered does of topiramate is eliminated unchanged in the urine. The elimination half-life ranges from 15 to 24 h. Clearance of topiramate may be reduced in patients with renal failure [70].

Adverse Reactions

Primary side effects of topiramate are usually either related to the CNS or carbonic anhydrase inhibition. CNS side effects are common and patients may become tolerant to them with continued use. These include fatigue, somnolence, dizziness, ataxia, confusion, psychomotor retardation, and difficulty concentrating. Visual disturbances such as diplopia and blurred vision and acute closed-angle glaucoma have also been reported [74].

Side effects related to carbonic anhydrase inhibition include paresthesias and nephrolithiasis. Paresthesias are generally mild and transient. Renal stones were reported to occur in 1.5% of patients in premarketing studies but have been less frequent in postmarketing analyses [70].

Two unique side effects have been attributed to topiramate. In contrast to other AEDs, long-term use of topiramate is associated with a decrease in body weight from 1 to 6 kg. This weight loss typically begins within the first 3 months of therapy and peaks between 12 and 18 months of use. Higher degrees of weight loss tend to occur in patients with higher pretreatment weight [70].

Lastly, some users of topiramate report difficulty with word-finding while talking. This has been attributed to the effects on psychomotor function and is not a specific effect on language or speech [74].

No significant metabolic, hematologic, or hepatic effects have been attributed to the use of topiramate.

Contraindications and Precautions

Topiramate has demonstrated various teratogenic effects in animal models. Postmarketing surveillance has identified select cases of hypospadias in infants born to women taking topiramate alone or in combination with other AEDs during pregnancy. Topiramate is classified in the FDA Pregnancy Category C [69].

Patients with impaired renal function may be at risk of toxicity due to accumulation of topiramate and should be monitored appropriately.

Drug Interactions

Topiramate does not appear to alter the metabolism or elimination of other AEDs. CBZ induces the metabolism of topiramate thus necessitating adjustment of the dosage of topiramate when used concomitantly. Other potent enzyme-inducing drugs such as phenytoin or phenobarbital may exhibit similar effects. It should also be noted that dose adjustments would be necessary upon discontinuation of an enzyme-inducing drug while continuing the topiramate [75].

Tiagabine

Chemistry

Tiagabine is a nipecotic acid derivative synthesized by linking nipecotic acid to a lipophilic anchor compound. The addition of this anchor compound facilitates transfer of the nipecotic acid moiety across the blood–brain barrier. Tiagabine is sparingly soluble in water and practically insoluble in most organic solvents. However, it does remain soluble in ethanol [76].

Pharmacology

Tiagabine reduces GABA uptake into presynaptic neurons by inhibiting the GABA transport protein, GAT-1. Inhibiting the re-uptake of GABA results in increased extracellular concentrations of GABA and a prolongation of the inhibitory effect of GABA on neurons [77].

Pharmacokinetics

Absorption

Tiagabine is readily absorbed with oral bioavailability approaching 90%. Absorption is linear with maximum plasma concentrations occurring between 45 and 90 min after administration in the fasting state and after a mean of 2.6 h when taken with food. While food may delay the absorption of tiagabine, the extent of absorption is unaffected. It is recommended by the manufacturer that tiagabine be administered with food to avoid side effects associated with high plasma concentrations [78, 79].

Distribution

Tiagabine is highly bound to plasma proteins (96%) and is widely distributed throughout the body. The apparent volume of distribution is 1 L/kg [78, 79].

While no therapeutic range for tiagabine has been established, because of the risk of drug interactions the manufacturer suggests that monitoring concentrations of tiagabine before and after the addition or discontinuation of interacting drugs may be useful [76].

Metabolism

Tiagabine is extensively metabolized in the liver via the CYP3A isozyme system with less than 2% of an administered dose excreted unchanged. The half-life of tiagabine ranges from 5 to 8 h in patients receiving monotherapy but may be reduced to 2–3 h in patients taking enzyme-inducing medications [80].

Excretion

Approximately 25% of an administered dose of tiagabine is eliminated in the urine with 40–65% of a dose eliminated in the feces within 3–5 days. This extended elimination may be due to enterohepatic recycling of tiagabine metabolites [80].

Adverse Reactions

Side effects that occur more commonly with tiagabine than placebo include dizziness, asthenia, nervousness, tremor, diarrhea, and depression. These side effects are usually mild and transient [81].

More severe side effects such as ataxia, confusion, and itching or rash have been reported although rarely and should resolve upon discontinuation of tiagabine [81].

Contraindications and Precautions

Animal teratogenicity studies demonstrate increased risks of embryo-fetal development abnormalities but no evidence of teratogenicity in humans has been seen. Tiagabine is classified as FDA Pregnancy Category C.

Drug Interactions

Many drugs are known to inhibit or induce the 3A isozyme family of the cytochrome system. The use of drugs which alter metabolism through these isozymes should be expected to alter the metabolism of tiagabine. Plasma concentrations of tiagabine will decrease with the addition of enzyme-inducing drugs such as carbamazepine and phenytoin while concentrations will increase with the addition of enzyme-inhibiting drugs such as cimetidine [77].

Although tiagabine is highly protein bound, plasma concentrations are low enough that significant displacement interactions do not occur.

Felbamate

Chemistry

Felbamate is a dicarbamate AED with a chemical structure similar to that of meprobamate. While meprobamate incorporates an aliphatic chain at the 2-carbon position, felbamate includes a phenyl group at that position. Felbamate is a lipophilic compound that is only very slightly soluble in water and increasingly soluble in ethanol, methanol, and dimethyl sulfoxide [82].

Pharmacology

Felbamate has a dual mechanism of action, inhibiting excitatory neurotransmission and potentiating inhibitory effects. Felbamate inhibits NMDA-evoked responses in rat hippocampal neurons. In addition, felbamate potentiates the effects of GABA in the same cell line [83]. By decreasing the spread of seizures to other neurons and increasing the seizure threshold, felbamate exhibits broad effects on various seizure types.

Pharmacokinetics

Absorption

Felbamate is readily absorbed from the gastrointestinal tract. Neither the rate nor the extent of absorption are altered by the presence of food. Greater than 90% of an

orally administered dose of felbamate or its metabolites can be recovered in the urine or feces [82].

Distribution

Felbamate is approximately 20–25% bound to plasma proteins and this is independent of total concentration. It readily crosses the blood-brain barrier with CSF concentrations nearly equal to plasma concentrations in animal models. No significant displacement of other compounds from protein-binding sites occurs with the use of felbamate [84]. The apparent volume of distribution of felbamate is 0.7–1 L/kg.

While no therapeutic range has been defined for felbamate, it is suggested that concentrations of phenytoin, carbamazepine be monitored when used concurrently with felbamate [85].

Metabolism

Approximately 50% of an administered dose of felbamate is metabolized in the liver by hydroxylation and conjugation. One metabolite, atropaldehyde, has been implicated in the development of aplastic anemia associated with the use of felbamate. Atropaldehyde has been shown to alkylate proteins which produces antigens which can generate a dangerous immune response in some individuals. Variations in the metabolism of felbamate as well as detoxification of atropaldehyde make it very difficult to predict which patients may be subject to this dangerous effect [82].

Excretion

Urinary excretion of unchanged felbamate accounts for the disposition of 30–50% of an administered dose. This fraction can decrease to 9–22% in patients with renal dysfunction. The apparent half-life of felbamate has been reported to be between 16 and 22 h. This half-life may increase in patients with decreasing renal function [85].

Adverse Reactions

Gastrointestinal upset, headache, anorexia, and weight loss have been reported to occur commonly among patients using felbamate. While most adverse effects will subside over time, anorexia and insomnia are more likely to persist with continued use.

Less common side effects such as diplopia, dizziness, and ataxia have been reported. However, these side effects occur more commonly with polytherapy than monotherapy and may be related to the other medications used, particularly carbamazepine [86].

Postmarketing surveillance identified an increased risk of the development of aplastic anemia and hepatic failure among users of felbamate. Emerging risk factors for the development of these reactions are history of cytopenia, AED allergy or significant toxicity, viral infection, and/or immunologic problems [82].

Contraindications and Precautions

Cross-sensitivity between felbamate and other carbamate drugs has been demonstrated. Caution is advised when treating a patient with carbamate hypersensitivity with felbamate.

Two known animal carcinogens, ethyl carbamate (urethane) and methyl carbamate, are found in felbamate tablets as a consequence of the manufacturing process. Quantities of these substances have been shown to be inadequate to stimulate tumor development in rats and mice. The implications of this in humans remains unknown [82, 87].

Teratogenicity studies in rats and mice revealed decreased rat pup weight and increased mortality during lactation but no effects on fetal development were identified. Felbamate is classified as FDA Pregnancy Category C.

Patients suffering from blood dyscrasias characterized by abnormalities in blood counts, platelet count, or serum iron concentrations should not receive felbamate without close evaluation of the risks and benefits of its use. Similarly, patients with a history of or current bone marrow suppression should not receive felbamate. This would also apply to patients receiving chemotherapy with agents known to cause bone marrow suppression [82, 88].

Due to the synthesis of atropaldehyde during felbamate metabolism and subsequent potential for immunologic response, patients with hepatic disease may be at increased risk for exacerbation of their condition [82].

Caution should be exercised when patients with a history of myelosuppression or hematologic toxicity to any medication are prescribed felbamate as these patients may be at increased risk of felbamate-induced hematologic toxicity.

Drug Interactions

Felbamate has been reported to inhibit the metabolism of both phenytoin and valproic acid. As felbamate increases the metabolism of carbamazepine serum concentrations decrease while epoxide metabolite concentrations increase. Doses of phenytoin, CBZ, and valproic acid should be decreased by approximately 30% when felbamate is co-administered [86, 89].

Enzyme inducers like phenytoin and CBZ can increase the metabolism of felbamate. Felbamate has also been shown to decrease the metabolism of phenobarbital and warfarin [86, 89].

Vigabatrin

Chemistry

Vigabatrin, gamma-vinyl GABA, is a structural analogue of GABA. Vigabatrin is a racemic mixture of *R*(−) and *S*(+) isomers in equal proportions with no evident optical rotational activity. While this compound is highly soluble in water, it is only slightly soluble in ethanol or methanol and remains insoluble in hexane or toluene [90].

Pharmacology

Vigabatrin has been shown to effectively increase CNS concentrations of GABA in both animal models and humans with epilepsy in a dose-dependent fashion. Increased concentrations of other markers of GABA concentration (homocarnosine) are also been reported to occur in patients taking vigabatrin. The proposed mechanism by which vigabatrin facilitates these increases is through the inhibition of GABA transaminase, the primary enzyme involved in GABA metabolism. This inhibition occurs in an irreversible manner [90]. Therefore, despite a relatively short half-life, vigabatrin can be administered on a once-daily basis.

Pharmacokinetics

Absorption

Vigabatrin is readily absorbed from the gastrointestinal tract. Peak concentrations occur within 2 h of oral administration. Oral bioavailability is reported to be approximately 60%. Food has no effect on either the rate or extent of absorption of vigabatrin [91].

Distribution

Vigabatrin has an apparent volume of distribution of 0.8 L/kg. There is virtually no binding to plasma proteins. CSF concentrations of vigabatrin are approximately 10% of concentrations in plasma samples. Uniquely, vigabatrin distributes into red blood cells with subsequent red blood cell concentrations approximating 30–80% of plasma concentrations [90, 91].

Metabolism

No human metabolites of vigabatrin have been identified and no therapeutic range has been established [90, 91].

Excretion

The manufacturer reports that up to 82% of an orally administered dose is recovered unchanged in the urine. The terminal half-life of vigabatrin is approximately 7 h which can be significantly prolonged in patients with renal dysfunction. Although it has been suggested that doses of vigabatrin be reduced in patients with renal dysfunction, no guidelines in this regard have been published [90, 91].

Adverse Reactions

Vigabatrin is well tolerated with sedation and fatigue being the primary adverse effects associated with its use. It has been shown to have no effect on cognitive abilities [90, 92].

Psychiatric and behavioral effects of vigabatrin have been reported. Agitation, irritability, depression, or psychosis has been reported in up to 5% of patients taking the drug with no prior history of psychosis [90].

The development of visual field defects has occurred in patients taking vigabatrin. These visual field defects are commonly asymptomatic and appear to be irreversible. The time course of the onset, relationship with dose, influence of other AEDs, and progression of visual field deficits are unknown. It is suggested that patients treated with vigabatrin undergo visual field testing regularly during therapy [90].

Contraindications and Precautions

No evidence of carcinogenicity has been demonstrated in animal studies. Serious fetal neurotoxicity has been shown to occur in animal studies and vigabatrin is NOT recommended to be used during pregnancy [90]. Vigabatrin is classified as FDA Pregnancy Category D.

Vigabatrin should be used with caution in patients with aggressive tendencies or evidence of psychosis as these patients may be at higher risk for these types of episodes while using vigabatrin [90, 92].

Due to the risk of accumulation, patients with impaired renal function or a creatinine clearance <60 mL/min should be monitored closely for the development of adverse effects [92].

Drug Interactions

Few clinically significant drug interactions have been identified with vigabatrin. Vigabatrin use can increase serum concentrations of phenytoin by as much as 30% although the mechanism of this interaction is unknown [92].

Levetiracetam

Chemistry

Levetiracetam is a unique AED which is chemically unrelated to any of the other currently available AEDs. This single *S*-enantiomer pyrrolidine compound is very soluble in water and decreasingly less soluble in chloroform or methanol, ethanol, acetonitrile, and practically insoluble in *n*-hexane [93].

Pharmacology

The mechanism of action of levetiracetam is distinct and unrelated to the effects of other AEDs. No evidence supports any effect on voltage-gated Na^+ channels or on GABA or benzodiazepine receptors. Levetiracetam has been shown to bind in a stereospecific, saturable, and reversible manner to unknown binding sites in the CNS. These binding sites do appear to be confined to synaptic membranes in the CNS and not the peripheral nervous system. Phenylenetetrazole and piracetam can effectively displace levetiracetam from these binding sites while there is no effect on binding caused by other antiepileptic drugs, picrotoxin, or bicucculline. Midazolam, a benzodiazepine receptor antagonist has no discernible effect on binding of levetiracetam to synaptic membranes [94].

Pharmacokinetics

Absorption

Levetiracetam is readily and completely absorbed after oral administration. Peak concentrations occur within 20–120 min of administration. Clinical studies have shown that although food does not decrease the extent of absorption, it can cause a delay in time to peak concentration by up to 1.5 h and decrease the peak concentration by as much as 20% [94].

Distribution

The apparent volume of distribution of levetiracetam is 0.7 L/kg. This drug and its metabolites are <10% bound to plasma proteins and protein displacement drug interactions are unlikely to occur. There has been no therapeutic range established for levetiracetam [93, 94].

Metabolism

Levetiracetam is minimally metabolized in humans via a hydrolysis reaction. This metabolism does not involve hepatic microsomal enzymes and therefore is unlikely to be involved in metabolic drug interactions [95].

Excretion

Renal excretion of parent drug accounts for 66% of the disposition of an orally administered dose of levetiracetam with an additional 25% of administered dose eliminated renally as metabolites. The elimination half-life is 6–8 h and may be prolonged as much as 2.5 h in elderly subjects due to changes in renal function. In addition, half-life is prolonged in patients with documented renal disease [95].

Adverse Reactions

Common adverse effects of levetiracetam include somnolence, dizziness, asthenia, and fatigue. Somnolence has been reported in up to 45% of patients receiving the drug. Coordination difficulties including ataxia, abnormal gait, and incoordination are also more common with levetiracetam than placebo. Behavioral symptoms have also been reported and include reactions such as psychosis, agitation, anxiety, hostility, emotional lability, depression, and others. These adverse effects typically appear early in therapy and may resolve with dose reduction [93].

Little information is available regarding idiosyncratic reactions on hematologic and hepatic systems.

Contraindications and Precautions

Animal studies show that levetiracetam can cause developmental abnormalities at doses near that used in humans [93]. Levetiracetam is classified as FDA Pregnancy Category C.

Levetiracetam dose should be reduced in patients with evidence of renal function impairment.

Drug Interactions

Pharmacokinetic studies of levetiracetam indicate that no clinically significant interactions of this sort occur. Levetiracetam neither induces nor inhibits cytochrome p450 isozymes nor does it alter UDP-glucuronidation [95].

Zonisamide

Chemistry

Zonisamide is a unique AED with a sulfonamide structure. This compound is only moderately soluble in water and 0.1 N HCl [96].

Pharmacology

Zonisamide exhibits antiseizure effects similar to other AEDs. It has been shown to inhibit T-type calcium currents as well as prolonging the inactivation of voltage-gated Na^+ channels, thus inhibiting sustained repetitive firing of neurons. These mechanisms are similar to those of phenytoin and carbamazepine. In addition, Zonisamide may have some minimal carbonic anhydrase inhibitory activity [94, 96].

Pharmacokinetics

Absorption

Peak serum concentrations occur within 2–6 h of administration of an oral dose of zonisamide. Food may prolong the time to peak concentration (4–6 h) but has no effect on the extent of absorption [94, 96].

Distribution

Studies indicate that zonisamide is 40–50% protein-bound. In addition, zonisamide is extensively bound to erythrocytes with erythrocyte concentrations eight times higher than serum concentrations. This binding to erythrocytes is saturable and may result in disproportionate increases in serum concentration with a given change in dose at higher doses. The volume of distribution is reported to be 1.4 L/kg. No therapeutic range has been established [94, 97].

Metabolism

The primary route of metabolism of zonisamide is reduction to 2-sulfamoylacetyl phenol (SMAP) by the CYP3A4 isozyme system. A minor metabolic route involves hydroxylation and acetylation to 5-*N*-acetylzonisamide. Zonisamide does not induce its own metabolism [94, 97].

Excretion

Renal elimination is the primary route for clearance of zonisamide. Thirty-five percent of an administered dose is recovered unchanged while the remaining 65% is eliminated in the urine as metabolites. The terminal half-life of zonisamide is 63 h which may be prolonged in patients with renal or hepatic dysfunction [94, 97].

Adverse Reactions

Adverse effects most common with the use of zonisamide include somnolence, dizziness, ataxia, anorexia, headache, nausea, and anger/irritability. Other CNS effects include psychomotor slowing, difficulty concentrating, and word finding difficulties [94, 98].

Severe reactions including Stevens–Johnson syndrome, toxic epidermal necrosis, hepatic failure, aplastic anemia, agranulocytosis, and other blood dyscrasias have been reported in patients taking sulfonamides and should be considered potential side effects of zonisamide [94, 98].

Oligohydrosis and hyperthermia have been reported to occur in 13 pediatric patients during the first 11 years of marketing of zonisamide in Japan. Although zonisamide is not approved for pediatric use in the USA, it is important to recognize that oligohydrosis and hyperthermia are potential adverse effects associated with the use of zonisamide [98].

Contraindications and Precautions

Studies in rats and mice have shown teratogenic effects when zonisamide is administered during organogenesis in pregnancy. Embryolethality has been demonstrated during the treatment of cynomolgus monkeys. Strong caution is advised against the use of zonisamide during pregnancy. Zonisamide is categorized as FDA Pregnancy Category C [96].

Oligohydrosis and hyperthermia were reported to occur in Japanese children treated with zonisamide but has not occurred in Caucasians.

Decreases in clearance will occur in patients with impaired renal function and zonisamide should only be used under close supervision in patients with a glomerular filtration rate of <50 mL/min. In addition, metabolism of zonisamide may be decreased in patients with hepatic dysfunction.

Drug Interactions

Although zonisamide is metabolized via the CYP3A4 isozyme system, it has not been shown to alter the pharmacokinetics of other drugs metabolized through that isozyme. In contrast, carbamazepine, phenytoin, fosphenytoin, and phenobarbital

have been shown to increase the clearance of zonisamide. The clinical impact of these interactions are unknown as no therapeutic level for zonisamide has been determined [94, 97].

References

1. Hauser, W. A. (1992). Seizure disorders: the changes with age. *Epilepsia* 33 Suppl 4, S6-14.
2. Hauser, W. A. (1994). The prevalence and incidence of convulsive disorders in children. *Epilepsia* 35 Suppl 2, S1-6.
3. Leppik, I. E. (1993). *Contemporary diagnosis and management of the patient with epilepsy*. 1st edit, Handbooks in Health Care, Newtown, Pa., USA.
4. Dichter, M. A. (1994). Emerging insights into mechanisms of epilepsy: implications for new antiepileptic drug development. *Epilepsia* 35 Suppl 4, S51-7.
5. Garnett, W. R. (1995). Antiepileptics. In *Therapeutic drug monitoring* (Schumacher, G. E., ed.), pp. 345–395. Appleton & Lange, Norwalk, Conn.
6. Schmidt, D. & Haenel, F. (1984). Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. *Neurology* 34, 1252–5.
7. Schmidt, D., Einicke, I. & Haenel, F. (1986). The influence of seizure type on the efficacy of plasma concentrations of phenytoin, phenobarbital, and carbamazepine. *Archives of Neurology* 43, 263–5.
8. Juul-Jensen, P. (1968). Frequency of recurrence after discontinuance of anticonvulsant therapy in patients with epileptic seizures: a new follow-up study after 5 years. *Epilepsia* 9, 11–6.
9. Camfield, P. & Camfield, C. (1994). Acute and chronic toxicity of antiepileptic medications: a selective review. *Canadian Journal of Neurological Sciences* 21, S7-11.
10. Bowden, C. L. (1996). Role of newer medications for bipolar disorder. *Journal of Clinical Psychopharmacology* 16, 48 S-55 S.
11. McNamara, J. O. (2001). Drugs effective in the therapy of the epilepsies. In *Goodman & Gilman's the pharmacological basis of therapeutics* 10th / edit. (Goodman, L. S., Gilman, A., Hardman, J. G., Limbird, L. E. & Gilman, A. G., eds.), pp. xxvii, 2148. McGraw-Hill, New York.
12. Browne, T. & LeDuc, B. (1995). Phenytoin: chemistry and biotransformation. In *Antiepileptic drugs* 4th edit. (Levy, R. H., Mattson, R. H. & Meldrum, B. S., eds.), pp. 283–300. Raven Press, New York.
13. Browne, T. R., Kugler, A. R. & Eldon, M. A. (1996). Pharmacology and pharmacokinetics of fosphenytoin. *Neurology* 46, S3-7.
14. McLean, M. J. & Macdonald, R. L. (1983). Multiple actions of phenytoin on mouse spinal cord neurons in cell culture. *Journal of Pharmacology & Experimental Therapeutics* 227, 779–89.
15. Treiman, D. & Woodbury, D. (1995). Phenytoin: absorption, distribution, and excretion. In *Antiepileptic drugs* 4th edit. (Levy, R. H., Mattson, R. H. & Meldrum, B. S., eds.), pp. 301–314. Raven Press, New York.
16. Kostenbauder, H. B., Rapp, R. P., McGovren, J. P., Foster, T. S., Perrier, D. G., Blacker, H. M., Hulon, W. C. & Kinkel, A. W. (1975). Bioavailability and single-dose pharmacokinetics of intramuscular phenytoin. *Clinical Pharmacology & Therapeutics* 18, 449–56.
17. Vajda, F., Williams, F. M., Davidson, S., Falconer, M. A. & Breckenridge, A. (1974). Human brain, cerebrospinal fluid, and plasma concentrations of diphenylhydantoin and phenobarbital. *Clinical Pharmacology & Therapeutics* 15, 597–603.
18. Wallace, S. & Brodie, M. J. (1976). Decreased drug binding in serum from patients with chronic hepatic disease. *European Journal of Clinical Pharmacology* 09, 429–32.

19. Spielberg, S. P., Gordon, G. B., Blake, D. A., Mellits, E. D. & Bross, D. S. (1981). Anticonvulsant toxicity in vitro: possible role of arene oxides. *Journal of Pharmacology & Experimental Therapeutics* 217, 386–9.
20. Tozer, T. N. & Winter, M. E. (1992). Phenytoin. In *Applied pharmacokinetics : principles of therapeutic drug monitoring* 3rd edit. (Evans, W. E., Schentag, J. J. & Jusko, W. J., eds.), pp. Chapter 25. Applied Therapeutics, Vancouver, WA.
21. Kaneko, S., Battino, D., Andermann, E., Wada, K., Kan, R., Takeda, A., Nakane, Y., Ogawa, Y., Avanzini, G., Fumarola, C., Granata, T., Molteni, F., Pardi, G., Minotti, L., Canger, R., Dansky, L., Oguni, M., Lopes-Cendas, I., Sherwin, A., Andermann, F., Seni, M. H., Okada, M. & Teranishi, T. (1999). Congenital malformations due to antiepileptic drugs. *Epilepsy Research* 33, 145–58.
22. Mattson, R. H. (1996). Parenteral antiepileptic/anticonvulsant drugs. *Neurology* 46, S8-13.
23. Liponi, D. F., Winter, M. E. & Tozer, T. N. (1984). Renal function and therapeutic concentrations of phenytoin. *Neurology* 34, 395–7.
24. Olsen, K. M., Hiller, F. C., Ackerman, B. H. & McCabe, B. J. (1989). Effect of enteral feedings on oral phenytoin absorption. *Nutrition in Clinical Practice* 4, 176–8.
25. Berg, M. J., Fincham, R. W., Ebert, B. E. & Schottelius, D. D. (1988). Decrease of serum folates in healthy male volunteers taking phenytoin. *Epilepsia* 29, 67–73.
26. Kutt, H. (1975). Carbamazepine: chemistry and methods of determination. *Advances in Neurology* 11, 249–61.
27. Grant, S. M. & Faulds, D. (1992). Oxcarbazepine. A review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. *Drugs* 43, 873–88.
28. MacDonald, R. (1989). Carbamazepine. Mechanisms of action. In *Antiepileptic drugs* 3rd edit. (Levy, R. H., Mattson, R. H. & Meldrum, B. S., eds.), pp. 447–455. Raven Press, New York.
29. Waldmeier, P. C., Baumann, P. A., Wicki, P., Feldtrauer, J. J., Stierlin, C. & Schmutz, M. (1995). Similar potency of carbamazepine, oxcarbazepine, and lamotrigine in inhibiting the release of glutamate and other neurotransmitters. *Neurology* 45, 1907–13.
30. McLean, M. J., Schmutz, M., Wamil, A. W., Olpe, H. R., Portet, C. & Feldmann, K. F. (1994). Oxcarbazepine: mechanisms of action. *Epilepsia* 35 Suppl 3, S5-9.
31. Schmutz, M., Brugger, F., Gentsch, C., McLean, M. J. & Olpe, H. R. (1994). Oxcarbazepine: preclinical anticonvulsant profile and putative mechanisms of action. [see comments.]. *Epilepsia* 35 Suppl 5, S47-50.
32. Morselli, P. (1989). Carbamazepine: absorption, distribution, and excretion. In *Antiepileptic drugs* 3rd/edit. (Levy, R. H., ed.), pp. 473–490. Raven Press, New York.
33. Meinardi, H. (1972). CBZ. In *Antiepileptic drugs* (Woodbury, D. M., Penry, J. K. & Schmidt, R. P., eds.), pp. 487–496. Raven Press, New York.
34. Bell, W. L., Crawford, I. L. & Shiu, G. K. (1993). Reduced bioavailability of moisture-exposed carbamazepine resulting in status epilepticus. *Epilepsia* 34, 1102–4.
35. Riad, L. E., Chan, K. K., Wagner, W. E., Jr. & Sawchuk, R. J. (1986). Simultaneous first- and zero-order absorption of carbamazepine tablets in humans. *Journal of Pharmaceutical Sciences* 75, 897–900.
36. Morselli, P. L. & Frigerio, A. (1975). Metabolism and Pharmacokinetics of Carbamazepine. *Drug Metabolism Reviews* 4, 97–113.
37. Morselli, P. L., Baruzzi, A., Gerna, M., Bossi, L. & Porta, M. (1977). Carbamazepine and carbamazepine-10, 11-epoxide concentrations in human brain. *British Journal of Clinical Pharmacology* 4, 535–40.
38. Wisner, K. L. & Perel, J. M. (1998). Serum levels of valproate and carbamazepine in breast-feeding mother-infant pairs. *Journal of Clinical Psychopharmacology* 18, 167–9.
39. Kerr, B. & Levy, R. (1989). Carbamazepine: carbamazepine and carbamazepine-epoxide. In *Antiepileptic drugs* 3rd/edit. (Levy, R. H., ed.), pp. 505–520. Raven Press, New York.
40. Hundt, H. K., Aucamp, A. K., Muller, F. O. & Potgieter, M. A. (1983). Carbamazepine and its major metabolites in plasma: a summary of eight years of therapeutic drug monitoring. *Therapeutic Drug Monitoring* 5, 427–35.

41. Lloyd, P., Flesch, G. & Dieterle, W. (1994). Clinical pharmacology and pharmacokinetics of oxcarbazepine. *Epilepsia* 35 Suppl 3, S10-3.
42. Zakrzewska, J. M. & Patsalos, P. N. (1989). Oxcarbazepine: a new drug in the management of intractable trigeminal neuralgia. *Journal of Neurology, Neurosurgery & Psychiatry* 52, 472–6.
43. Bertilsson, L. & Tomson, T. (1986). Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide. An update. *Clinical Pharmacokinetics* 11, 177–98.
44. Bertilsson, L., Hojer, B., Tybring, G., Osterloh, J. & Rane, A. (1980). Autoinduction of carbamazepine metabolism in children examined by a stable isotope technique. *Clinical Pharmacology & Therapeutics* 27, 83–8.
45. Bertilsson, L., Tomson, T. & Tybring, G. (1986). Pharmacokinetics: time-dependent changes--autoinduction of carbamazepine epoxidation. *Journal of Clinical Pharmacology* 26, 459–62.
46. Konishi, T., Naganuma, Y., Hongo, K., Murakami, M., Yamatani, M. & Okada, T. (1993). Carbamazepine-induced skin rash in children with epilepsy. *European Journal of Pediatrics* 152, 605–8.
47. Van Amelsvoort, T., Bakshi, R., Devaux, C. B. & Schwabe, S. (1994). Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. *Epilepsia* 35, 181–8.
48. Lander, C. M. & Eadie, M. J. (1990). Antiepileptic drug intake during pregnancy and malformed offspring. *Epilepsy Research* 7, 77–82.
49. Messenheimer, J. A. (1995). Lamotrigine. *Epilepsia* 36 Suppl 2, S87-94.
50. Goa, K. L., Ross, S. R. & Chrisp, P. (1993). Lamotrigine. A review of its pharmacological properties and clinical efficacy in epilepsy. *Drugs* 46, 152–76.
51. Rambeck, B. & Wolf, P. (1993). Lamotrigine clinical pharmacokinetics. *Clinical Pharmacokinetics* 25, 433–43.
52. Richens, A. (1994). Safety of lamotrigine. *Epilepsia* 35 Suppl 5, S37-40.
53. Messenheimer, J., Mullens, E. L., Giorgi, L. & Young, F. (1998). Safety review of adult clinical trial experience with lamotrigine. *Drug Safety* 18, 281–96.
54. Davis, R., Peters, D. H. & McTavish, D. (1994). Valproic acid. A reappraisal of its pharmacological properties and clinical efficacy in epilepsy. *Drugs* 47, 332–72.
55. Dreifuss, F. E., Santilli, N., Langer, D. H., Sweeney, K. P., Moline, K. A. & Menander, K. B. (1987). Valproic acid hepatic fatalities: a retrospective review. *Neurology* 37, 379–85.
56. May, R. B. & Sunder, T. R. (1993). Hematologic manifestations of long-term valproate therapy. *Epilepsia* 34, 1098–101.
57. Bjerkedal, T., Czeizel, A., Goujard, J., Kallen, B., Mastroiacova, P., Nevin, N., Oakley, G., Jr. & Robert, E. (1982). Valproic acid and spina bifida. *Lancet* 2, 1096.
58. Pisani, F., Narbone, M. & Trunfio, C. (1995). Ethosuximide: chemistry and biotransformation. In *Antiepileptic drugs* 4th edit. (Levy, R. H., Mattson, R. H. & Meldrum, B. S., eds.), pp. 655–658. Raven Press, New York.
59. Glauser, T. (2001). Ethosuximide. In *The treatment of epilepsy : principles and practice* 3rd edit. (Wyllie, E., ed.), pp. 881–891. Williams & Wilkins, Baltimore.
60. Horning, M. G., Brown, L., Nowlin, J., Lertratanangkoon, K., Kellaway, P. & Zion, T. E. (1977). Use of saliva in therapeutic drug monitoring. *Clinical Chemistry* 23, 157–64.
61. Yamamoto, T., Pipo, J. R., Akaboshi, S. & Narai, S. (2001). Forced normalization induced by ethosuximide therapy in a patient with intractable myoclonic epilepsy. *Brain & Development* 23, 62–4.
62. Gibaldi, M. (1992). Adverse drug effect-reactive metabolites and idiosyncratic drug reactions: Part I. *Annals of Pharmacotherapy* 26, 416–21.
63. Dreifuss, F. (1995). Ethosuximide: toxicity. In *Antiepileptic drugs* 4th edit. (Levy, R. H., Mattson, R. H. & Meldrum, B. S., eds.), pp. 675–679. Raven Press, New York.
64. Schmidt, B. (1989). Potential new antiepileptic drugs: gabapentin. In *Antiepileptic Drugs* 3rd edit. (Levy, R. H., Mattson, R. H. & Meldrum, B. S., eds.), pp. 925–935. Raven Press, New York.

65. Taylor, C. P., Gee, N. S., Su, T. Z., Kocsis, J. D., Welty, D. F., Brown, J. P., Dooley, D. J., Boden, P. & Singh, L. (1998). A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Research* 29, 233–49.
66. McLean, M. J. (2001). Gabapentin. In *The treatment of epilepsy: principles and practice* 3rd edit. (Wyllie, E., ed.), pp. 915–932. Lippincott Williams & Wilkins, Philadelphia.
67. Wong, M. O., Eldon, M. A., Keane, W. F., Turck, D., Bockbrader, H. N., Underwood, B. A., Sedman, A. J. & Halstenson, C. E. (1995). Disposition of gabapentin in anuric subjects on hemodialysis. *Journal of Clinical Pharmacology* 35, 622–6.
68. Goa, K. L. & Sorkin, E. M. (1993). Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. *Drugs* 46, 409–27.
69. (March 1998). Package insert: topamax. Ortho-McNeil Pharmaceuticals, Raritan, NJ.
70. Privitera, M., Ficker, D. & Welty, T. (2001). Topiramate. In *The treatment of epilepsy: principles and practice* 3rd edit. (Wyllie, E., ed.), pp. 939–945. Lippincott Williams & Wilkins, Philadelphia.
71. Coulter, D., Sombati, S. & DeLorenzo, R. (1993). Selective effects of topiramate on sustained repetitive firing and spontaneous bursting in cultured hippocampal neurons. *Epilepsia* 34, 123.
72. Doose, D. R., Walker, S. A., Gisclon, L. G. & Nayak, R. K. (1996). Single-dose pharmacokinetics and effect of food on the bioavailability of topiramate, a novel antiepileptic drug. *Journal of Clinical Pharmacology* 36, 884–91.
73. Sachdeo, R. C., Sachdeo, S. K., Walker, S. A., Kramer, L. D., Nayak, R. K. & Doose, D. R. (1996). Steady-state pharmacokinetics of topiramate and carbamazepine in patients with epilepsy during monotherapy and concomitant therapy. *Epilepsia* 37, 774–80.
74. Walker, M. C. & Sander, J. W. (1996). Topiramate: a new antiepileptic drug for refractory epilepsy. *Seizure* 5, 199–203.
75. Bourgeois, B. F. (1996). Drug interaction profile of topiramate. *Epilepsia* 37 Suppl 2, S14-S17.
76. Schachter, S. (2001). Tiagabine. In *The treatment of epilepsy: principles and practice* 3rd edit. (Wyllie, E., ed.), pp. 930–938. Lippincott Williams & Wilkins, Philadelphia.
77. Schachter, S. C. (1999). A review of the antiepileptic drug tiagabine. *Clinical Neuropharmacology* 22, 312–7.
78. Mengel, H. (1994). Tiagabine. *Epilepsia* 35 Suppl 5, S81-4.
79. Gustavson, L. E. & Mengel, H. B. (1995). Pharmacokinetics of tiagabine, a gamma-aminobutyric acid-uptake inhibitor, in healthy subjects after single and multiple doses. *Epilepsia* 36, 605–11.
80. Bopp, B., Gustavson, L. E. & Johnson, M. (1995). Pharmacokinetics and metabolism of [14 C tiagabine] after oral administration to human subjects. *Epilepsia* 36, S158.
81. Leppik, I. E. (1995). Tiagabine: the safety landscape. *Epilepsia* 36 Suppl 6, S10-S13.
82. Faught, E. (2001). Felbamate. In *The treatment of epilepsy: principles and practice* 3rd edit. (Wyllie, E., ed.), pp. 953-960xxvii, 1188. Lippincott Williams & Wilkins, Philadelphia.
83. White, H. S., Wolf, H. H., Swinyard, E. A., Skeen, G. A. & Sofia, R. D. (1992). A neuropharmacological evaluation of felbamate as a novel anticonvulsant. *Epilepsia* 33, 564–72.
84. Adusumalli, V. E., Wichmann, J. K., Kucharczyk, N., Kamin, M., Sofia, R. D., French, J., Sperling, M., Bourgeois, B., Devinsky, O. & Dreifuss, F. E. (1994). Drug concentrations in human brain tissue samples from epileptic patients treated with felbamate. *Drug Metabolism & Disposition* 22, 168–70.
85. Wilensky, A. J., Friel, P. N., Ojemann, L. M., Kupferberg, H. J. & Levy, R. H. (1985). Pharmacokinetics of W-554 (ADD 03055) in epileptic patients. *Epilepsia* 26, 602–6.
86. Graves, N. M. (1993). Felbamate. *Annals of Pharmacotherapy* 27, 1073–81.
87. McGee, J. H., Butler, W. H., Erikson, D. J. & Sofia, R. D. (1998). Oncogenic studies with felbamate (2-phenyl-1,3-propanediol dicarbamate). *Toxicological Sciences* 45, 146–51.
88. Kaufman, D. W., Kelly, J. P., Anderson, T., Harmon, D. C. & Shapiro, S. (1997). Evaluation of case reports of aplastic anemia among patients treated with felbamate. [see comments.]. *Epilepsia* 38, 1265–9.

89. Wagner, M. L., Remmel, R. P., Graves, N. M. & Leppik, I. E. (1993). Effect of felbamate on carbamazepine and its major metabolites. *Clinical Pharmacology & Therapeutics* 53, 536–43.
90. Ben-Menachem, E. (2001). Vigabatrin. In *The treatment of epilepsy : principles and practice* 3rd edit. (Wyllie, E., ed.), pp. 961–968. Lippincott Williams & Wilkins, Philadelphia.
91. Durham, S. L., Hoke, J. F. & Chen, T. M. (1993). Pharmacokinetics and metabolism of vigabatrin following a single oral dose of [14 C]vigabatrin in healthy male volunteers. *Drug Metabolism & Disposition* 21, 480–4.
92. Grant, S. M. & Heel, R. C. (1991). Vigabatrin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. [erratum appears in Drugs 1991 Aug;42(2):330.]. *Drugs* 41, 889–926.
93. (March 2000). Package insert: keppra. UCB Pharma, Smyrna, GA.
94. Delanty, N. & French, J. (2001). Newer antiepileptic drugs. In *The treatment of epilepsy: principles and practice* 3rd edit. (Wyllie, E., ed.), pp. 977–983. Lippincott Williams & Wilkins, Philadelphia.
95. Patsalos, P. N. (2000). Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacology & Therapeutics* 85, 77–85.
96. (May 2000). Package insert: zonegran. Elan pharmaceuticals, San Francisco, CA.
97. Perucca, E. & Bialer, M. (1996). The clinical pharmacokinetics of the newer antiepileptic drugs. Focus on topiramate, zonisamide and tiagabine. *Clinical Pharmacokinetics* 31, 29–46.
98. Mimaki, T. (1998). Clinical pharmacology and therapeutic drug monitoring of zonisamide. *Therapeutic Drug Monitoring* 20, 593–7.
99. Gidal, B. E., Garnett, W. R. & Graves, N. M. (1999). Epilepsy. In *Pharmacotherapy: a pathophysiologic approach* 5th edit. (DiPiro, J. T., ed.), pp. 1031–1060. McGraw-Hill, New York.

Chapter 4
Opioids and Opiates

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Abstract The term "opioid" applies to any substance, whether endogenous or synthetic, that produces morphine-like effects. Opiates are restricted to synthetic morphine-like drugs with non-peptidic structure. Opium is an extract of the juice of the poppy *Papaver somniferum*, which has been used socially and medicinally as early as 400 to 300 BC. In the early 1800s, morphine was isolated, and in the 1900s, its chemical structure was determined. Opium contains many alkaloids related to morphine. Many semisynthetic and fully synthetic compounds have been made and studied. The main groups of drugs include morphine analogues such as oxymorphone, codeine, oxycodone, hydrocodone, heroin (diamorphine), and nalorphine, and the synthetic derivatives such as meperidine, fentanyl, methadone, propoxyphene, butorphanol, pentazocine, diphenoxylate, and loperamide (Herz, A., Opioids Handbook of Experimental Pharmacology, Vol. 104, Berlin, Springer Verlag, 1993).

Keywords Opioids • Opiates • Drug interaction • Pharmacology • Toxicology

Pharmacokinetics

Some of the pharmacokinetic parameters for opioids are summarized in Table 4.1 [1, 2]. Most opioids are readily absorbed from the gastrointestinal tract; they are also absorbed from the nasal mucosa, the lungs, rectum, and vagina and after subcutaneous or intramuscular injection. With most opioids and due to significant but variable first-pass effect, the effect of a given dose is more after parenteral than after

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Table 4.1 Pharmacokinetic parameters and receptor subtype activities of some opioids

Generic name	Brand name	Dose (mg)	Administration	Duration of analgesia (h)	Addiction/ abuse potential	Opioid receptor		
						μ	δ	κ
Buprenorphine	Buprenex	0.3	IM, IV, SC	4–8	Low	P	–	
Butorphanol	Stadol	2	IM, IV, Nasal Spray	3–4	Low	P	+++	
Codeine		30–60	Oral, SC	3–4	Medium	+	+	
Fentanyl	Sublimaze	0.1	IM, IV, Transdermal	1–2	High	+++		
Hydro-morphone	Dilaudid	1.5	Oral, SC	4–5	High	+++	+	
Mepridine	Demerol	50–100	Oral, IM	1–3	High	++		
Methadone	Dolphine	10	Oral, SC	3–5	High	+++		
Morphine	Statex, Kadian	10	Oral, IM, IV, SC	4–5	High	+++	+	
Naloxone	Narcan	0.4	IM, IV	–	–	–	–	–
Oxycodone	Percodan	5	Oral	3–5	Medium	+	+	
Oxymorphone	Numorphan	1–2	IM, IV, SC	3–5	High	+++	+	
Pentazocine	Talwin	25–50	Oral, IM	3–4	Low	P	++	
Propoxyphene	Darvon	60–120	Oral	2–4	Low	++		
Tramadol	Ultram	50–100	Oral, IM	1–6	Low		+	

Data compiled from various sources
+ agonist, – antagonist, *P* partial agonist

oral administration. The enzyme activity responsible for opioids metabolism in the liver varies considerably in different individuals. Thus, the effective oral dose in a particular patient may be difficult to predict.

All opioids bind to plasma proteins with varying affinity. However, the drugs rapidly leave the blood and localize in highest concentrations in tissues that are highly perfused. Brain concentrations of opioids are usually relatively low in comparison to most other organs. In neonates, the blood–brain barrier for opioids is effectively lacking. Because of this, easy transport of opioids through the placenta, and the low conjugating capacity in neonates, opioids used in obstetrics analgesia have a much longer duration of action and can easily cause respiratory depression in neonates [3].

Hepatic metabolism is the main mode of inactivation, usually by conjugation with glucuronide. Esters (e.g., heroin) are rapidly hydrolyzed by common tissue esterases. Heroin is hydrolyzed to monoacetylmorphine and finally to morphine, which is then conjugated with glucuronic acid. These metabolites were originally thought to be inactive, but is now believed that morphine-6-glucuronide is more active as analgesic than morphine. Accumulation of these active metabolites may occur in patients with renal failure and may lead to prolonged and more profound analgesia even though central nervous system entry is limited [2, 4].

Some opioids are also *N*-demethylated by CYP3A and *O*-demethylated by CYP2D6 in the liver but these are minor pathways of metabolism. Codeine, oxycodone, and hydrocodone are converted to metabolites of increased activity by

CYP2D6. Genetic variability of CYP2D6 and other CYP isozymes may have clinical consequences in patients taking these compounds. Accumulation of a demethylated metabolite of meperidine, normeperidine, may occur in patients with decreased renal function or those receiving multiple high doses of the drug. In sufficiently high concentrations, the metabolite may cause seizures, especially in children. However, these are exceptions, and opioid metabolism usually results in compounds with little or no pharmacologic activity [2]. Minor metabolic pathways in human subjects have been shown to exist for the conversion of codeine to hydrocodone, and recently, the metabolic conversion of morphine to hydromorphone has also been reported [5].

Hepatic oxidative metabolism, mainly *N*-dealkylation by CYP3A4, is the primary route of degradation of the phenylpiperidine opioids (e.g., fentanyl) and eventually leaves only small quantities of the parent compound unchanged for excretion [2].

Pharmacodynamics

Morphine and most other opioids elicit a mixture of stimulatory and inhibitory effects, with the major sites of action being the brain and the gastrointestinal tract. Areas of the brain receiving input from the ascending spinal pain-transmitting pathways are rich in opioids receptors.

Opioid Receptors

Three major classes of opioid receptors have been identified in various nervous system sites and in other tissues. They are mu (μ), delta (δ), and kappa (κ). The newly discovered N/OFQ receptor, initially called the opioid-receptor-like 1 (ORL-1) receptor or "orphan" opioid receptor, has added a new dimension to the study of opioids. Each major opioid receptor has a unique anatomical distribution in brain, spinal cord, and the periphery. These distinctive patterns of localization suggest specific possible functions. There is little agreement regarding the exact classification of opioid receptor subtypes. Pharmacological studies have suggested the existence of multiple subtypes of each receptor. Behavioral and pharmacological studies suggested the presence of μ_1, μ_2, and μ_3 subtypes. μ_3 has only been found in macrophages, and its clinical effects has not been reported. The μ_1 site is proposed to be a very high affinity receptor with little discrimination between μ and δ ligands. The data supporting the existing of δ-opioid receptor subtypes are derived mainly from behavioral studies. In the case of κ receptor, numerous reports indicate the presence at least one additional subtype [3].

Opioids show different activities at these receptors (Table 4.1). Most of the clinically used opioids are relatively selective for μ receptors. It is crucial to note that opioids that are relatively selective at standard doses will interact with additional receptor subtypes when given at sufficiently high doses, leading to possible changes

Table 4.2 Classification of opioid receptors and their effects

Functional effects	μ_1	μ_2	δ	κ
Analgesia				
Supraspinal	++	–	+	+
Spinal	++	–	++	+
Respiratory depression	+++	++	+	–
Reduced GI motility	++	++	+	++
Pupil constriction	+	++	–	+
Euphoria	+++	++	–	–
Sedation	++	–	–	++
Physical dependence	+++	++	–	–

in their pharmacological profile. Classification of opioid receptor subtypes and actions is shown in Table 4.2 [2, 3]. Opioid receptors have been cloned and belong to the G protein–coupled family of receptor proteins [3].

Endorphins

Opioid alkaloids (e.g., morphine) produce analgesia through actions at regions in the brain that contain peptides which have opioid-like pharmacologic properties. The general term currently used for these endogenous substances is *endogenous opioid peptides,* which replaces the other term *endorphin.* There are three families of endogenous opioid peptides. The best-characterized of the opioid peptides possessing analgesic activity are the pentapeptides methionine-enkephalin (met-enkephalin) and leucine-enkephalin (leu-enkephalin), which were the first opioid peptides to be isolated and purified. Leu- and met-enkephalins have slightly higher affinity for the δ than for the μ opioid receptor. Two recently discovered peptides, endomorphin I and endomorphin II, have very high μ receptor selectivity [2, 3].

These endogenous peptides are derived by proteolysis from much larger precursor proteins. The principal precursor proteins are prepro-opiomelanocortin (POMC), preproenkephalin (proenkephalin A), and preprodynorphin (proenkephalin B). POMC contains the met-enkephalin sequence, β-endorphin, and several nonopioid peptides, including ACTH, β-lipotropin, and melanocyte-stimulating hormone. Preproenkephalin contains six copies of met-enkephalin and one copy of leu-enkephalin. Preprodynorphin yields several active opioid peptides that contain the leu-enkephalin sequence. These are dynorphin A, dynorphin B, and alpha and beta neoendorphins [2, 3].

The endogenous opioid precursor molecules are present at brain sites that have been implicated in pain modulation. Evidence suggests that they can be released during stress such as pain or the anticipation of pain. The precursor peptides are also found in the adrenal medulla and neural plexuses of the gut. Recent studies indicate that several

phenanthrene opioids (morphine, codeine) may also be found as endogenous substances at very low (picomolar) concentrations in mammalian tissues; their role at such sites has not been established [2, 3].

Mechanism of Action

Activation of opioids receptors has a number of cellular consequences, including inhibition of adenyl cyclase activity, leading to a reduction in intracellular cAMP concentration. This fall in neuronal cAMP is believed to account mostly for the analgesic effect of opioids.

Opioids vary not only in their receptor specificity, but also in their efficacy at different types of receptors. Some agents act as agonists on one type of receptor and antagonists or partial agonists at another, producing a very complicated pharmacological picture. Most opioids are pure agonists, pentazocine and nalorphine are partial agonists, and naloxone and naltrexone act as antagonists (Table 4.1).

The opioids have two well-established direct actions on neurons. They either close a voltage-gated Ca^{2+} channel on presynaptic nerve terminals and thereby reduce transmitter release, or they hyperpolarize and thus inhibit postsynaptic neurons by opening K^+ channels [2, 3]. The presynaptic action (depressed transmitter release) has been demonstrated for release of a large number of neurotransmitters, including acetylcholine, norepinephrine, glutamate, serotonin, and substance P [2].

All three major receptors are present in high concentrations in the dorsal horn of the spinal cord. Receptors are present on both spinal cord pain transmission neurons and on the primary afferents that relay the pain message to them. Opioid agonists inhibit the release of excitatory transmitters from these primary afferents, and they directly inhibit the dorsal horn pain transmission neuron. Thus, opioids exert a powerful analgesic effect directly upon the spinal cord. This spinal action has been exploited clinically by direct application of opioid agonists to the spinal cord, which provides a regional analgesic effect while minimizing the unwanted respiratory depression, nausea and vomiting, and sedation that may occur from the supraspinal actions of systematically administered drugs [2]. Different combinations of opioid receptors are found in supraspinal regions implicated in pain transmission and modulation. Of particular importance are opioid-binding sites in pain-modulating descending pathways, including the rostral ventral medulla, the locus ceruleus, and the midbrain periaqueductal gray area. At these sites as at others, opioids directly inhibit neurons, yet neurons that send processes to the spinal cord and inhibit pain transmission neurons are activated by the drugs. In addition, part of the pain-relieving action of exogenous opioids involves the release of endogenous opioid peptides [2].

Clinical use of opioid analgesics consists primarily in balancing the analgesia against adverse side effects. Their depressive effect on neuronal activity, increase in pain threshold, and sedation is often accompanied by euphoria. A summary of opioid pharmacological effects is shown in Table 4.3 [1, 2].

Table 4.3 Pharmacodynamic properties of opioids

Central nervous system effects
Suppression of pain; analgesia
Drowsiness and decreased mental alertness; sedation
Respiratory function depression (at the same dose that produce analgesia)
Euphoria
Psychotomimetic effects (nightmares, hallucinations)
Increased intracranial pressure
Suppression of cough; codeine is used primarily as antitussive
Miosis, mediated by parasympathetic pathways
Nausea and vomiting, by activating the brain stem chemoreceptor trigger zone
Antimuscarinic effects by Meperedine
Peripheral effects
Hypotension, if cardiovascular system is stressed
Bradycardia
Decreased peristalsis; constipation
Decreased gastric acid secretion
Inhibition of fluid and electrolyte accumulation in intestinal lumen
Increased tone of intestinal smooth muscle
Increased tone of sphincter of Oddi; increased biliary pressure
Increased tone of detrusor muscle and vesical sphincter
Decreased uterine tone
Stimulation of the release of antidiuretic, prolactin, and somatotrophin hormones
Inhibition of luteinizing hormone release
Skin flushing and warming; sweating; itching
Immune system modulation

Opioid Use and Abuse

Introduction: The Size of the Problem

Man has used drugs for recreational purposes as long as history itself. Arabic traders smoked opium in the third century BC. In the last 30 years, the number of people using recreational drugs, particularly opioids, appears to have increased. In 2007, an estimated 19.9 million Americans aged 12 or older were current (past month) illicit drug users. In 2006, there have been 1.8 million annual admissions to treatment for abuse of alcohol and drugs in USA, of which 324,000 cases were related to opiates (primarily heroin). In 2003, there were 237,000 admissions for injection drug use (13% of all admissions). Opiates accounted for 77% of admissions for injection drug use, followed by stimulants (16%) and cocaine (6%). Admissions for injected opiates rose 23% between 1992 and 2003. Injection drug users tended to use drugs for many years before entering the substance abuse treatment system. Heroin treatment admission rates between 1993 and 1999 increased by 200% or more in 6 States and by 100–199% in another 11 States. The West and Northeast had the highest heroin treatment admission rates between

1993 and 1999 [6]. As an example of 1 state in USA, a report indicated that the total unintentional drug overdose death rate in New Mexico increased from 5.6 per 100,000 in 1990 to 15.5 per 100,000 in 2005. Deaths caused by heroin, prescription opioids, cocaine, and alcohol/drug combinations together ranged from 89 % to 98% of the total. Heroin caused the most deaths during 1990–2005, with a notable rate increase in prescription opioid overdose death during 1998–2005 (58%). During 1990–2005, the 196% increase in single drug category overdose death was driven by prescription opioids alone and heroin alone; the 148% increase in multi-drug category overdose death was driven by heroin/alcohol and heroin/cocaine [7]. Use and abuse of prescription narcotic analgesics have increased dramatically in the United States since 1990. The effect of this pharmacoepidemic has been most pronounced in rural states which experienced the nation's largest increase in drug overdose mortality rates during 1999–2004. Concurrent with the increase in legitimate sales of opioids, diversion of these drugs to nonmedical uses has also increased. The National Survey on Drug Use and Health discovered that an annual average of 4.8% of persons 12 years or older consumed a prescription pain reliever for nonmedical reasons in the previous year during 2002–2005 [8]. Rates of emergency department visits for opioid analgesic overdoses have also increased [9]. Unintentional drug poisoning deaths increased 68% during 1999–2004 [10]; the majority of this increase has been attributed to deaths associated with opioid analgesics [11].

There are numerous medical consequences to recreational drug use. Follow-up studies of heroin addicts indicate an annual mortality of 4%. Thus, physicians should consider substance abuse in any unexplained illness. Recent evidence suggests that more than 40% of young people in the UK have tried illicit drugs at some time [12]. It is estimated that 9.5% of total mortality in Australians aged 15–39 years can be attributed to regular use of illicit opiates. Australian mortality data for 1992 indicate that approximately 401 male deaths and 161 female deaths occurred as a result of opiate use. This represents some 15,429 and 6,261 person-years of life lost to age 70, for males and females, respectively [13]. In the UK in 1991, 44 heroin deaths out of 113,620 yields a mortality of 1 in 2,582 and 74 methadone deaths of 9,880 gives a mortality of 1 in 134. Thus, methadone would appear to be 19 times more fatal than heroin, similar to previous findings in New York. Yet methadone is a manufactured pharmaceutical product, whereas heroin is usually adulterated from the street [14]. Although methadone has been used as a maintenance therapy for opiate addicts, several reports on the fatal methadone overdose have been published [15, 16]. Serious side effects of some opioids such as hydrocodone have been reported. This powerful and potentially addictive painkiller used by millions of Americans is causing rapid hearing loss and even deafness [17]. In another report, sublingual buprenorphine caused 20 fatalities in France over a 6 month period in 5 urban areas. Buprenorphine and its metabolites were found in postmortem fluids and viscera [18]. In several European countries and in Canada, clinical trials are being conducted in which heroin-addicted patients are treated with pharmaceutically prepared heroin in order to reduce the destructive behavior that is so often associated with this drug [19–21].

Fentanyl is an extremely potent narcotic analgesic that is becoming more popular as a drug of abuse. Because of the unique way in which the drug is packaged and delivered, unusual methods of abuse including digestion [22, 23], chewing [24], and rectal insertion [25] have been reported [26]. More recently, fentanyl-related deaths have created havoc with public health and safety, especially in the United States. With this increasingly apparent role as a drug of abuse in cases of overdose and death, the drug has acquired the reputation of "killer fentanyl" [27–29].

Tramadol is one of the opioids that is extensively used and is considered a safe drug devoid of many serious adverse effects of traditional opioids. However, recently, toxicity and an abuse potential of tramadol have been reported. In a study that examined fatal unintentional tramadol intoxications among Swedish forensic autopsy cases between 1995 and 2005, it was found that fatal intoxications with tramadol may occur unintentionally and that subjects with a history of substance abuse may be at certain risk [30].

In summary, the size of the problem is increasing at alarming levels and becoming critical to the medical and patient communities. This has led authorities to intensify their efforts to warn physicians, other health professionals, and the public [31]. The health authorities in each country and the International organizations such as WHO should put more efforts in controlling substances of abuse, particularly opiates.

Pathophysiology of Opiate Use

The physiologic effects of opioids are actually the result of interaction between the individual agent and multiple receptors. These interactions exert their primary effects on the CNS and the respiratory system; however, other organs particularly the cardiovascular system and the gastrointestinal system may also be affected [3].

Central Nervous System

The CNS effects include analgesia, via altered pain tolerance, sedation, euphoria, and dysphoria. Morphine-like drugs produce analgesia, drowsiness, changes in mood, and mental clouding. A significant feature of the analgesia is that it occurs without loss of consciousness, although drowsiness commonly occurs. Nausea and vomiting are secondary to stimulating the chemoreceptor trigger zone in the medulla. As the dose is increased, the subjective analgesic and toxic effects, including respiratory depression, become more pronounced. Morphine does not possess anticonvulsant activity and usually does not cause slurred speech [32].

Respiratory System

Opioids depress respiration by a number of mechanisms and neuronal sites of action. It is therefore not surprising that there has been such difficulty in combating

opioid-induced respiratory depression. Both hypoxic and hypercapnic responses are strongly affected by opioids and appear to be strongly mediated in the brainstem [33]. Respiratory depression occurs by direct effect on the medullary/respiratory center. The diminished sensitivity at this region results in an elevation of pCO_2 with resultant cerebral vasodilatation, increased cerebral perfusion pressure, and increased intracranial pressure. Hypoxic stimulation of the chemoreceptors still may be effective when opioids have decreased the responsiveness to CO_2, and the inhalation of O_2 may thus produce apnea [3]. In human beings, death from morphine poisoning is nearly always due to respiratory arrest. Therapeutic doses of morphine depress all phases of respiratory activity (rate, minute volume, and tidal exchange) and may also produce irregular and periodic breathing. The diminished respiratory volume is due primarily to a slower rate of breathing [34]. Toxic doses may pronounce the above effects, and the respiratory rate may fall even to less than 3 or 4 breaths per minute. Although respiratory effects can be documented readily with standard doses of morphine, respiratory depression occurs occasionally in the absence of underlying pulmonary dysfunction [35]. The combination of opiates with other medications such as general anesthetics, alcohol, or sedative – hypnotics may present a greater risk of respiratory depression due to the synergic effects of these drugs on the respiratory center.

Morphine and related opioids also depress the cough reflex at least in part by a direct effect on a cough center in the medulla. There is no positive relationship between depression of respiration and depression of coughing. Effective antitussive agents such as dextrometorphan do not depress respiration. Suppression of cough by such agents appears to involve the medulla that is less sensitive to naloxone than to the other opioid analgesics [3].

Cardiovascular System

Cardiovascular effects are trivial at therapeutic doses. However, peripheral vasodilation resulting in orthostatic hypertension may occur. Histamine release may contribute to the hemodynamic changes as well as dermal pruritus. Transient bradycardia and hypotension secondary to occasional vasovagal episodes may accompany nausea and vomiting. In supine patients, therapeutic doses of morphine-like opioids have no major effect on blood pressure and cardiac rate and rhythm. Such doses do produce peripheral vasodilation, reduced peripheral resistance, and inhibition of baroreceptor reflexes. When supine patients assume the head-up position, orthostatic hypotension and fainting may occur. The peripheral, arteriolar, and venous dilatation produced by morphine involves several mechanisms. It provokes release of histamine, which sometimes plays a central role in hypotension. However, vasodilation is usually only partially blocked by H_1 antagonists, but is effectively reversed by naloxone. Morphine also attenuates the reflex vasoconstriction caused by increased pCO_2 [3]. Myocardial damage and rhabdomyolysis associated with prolonged hypoxic coma, following opiate overdose, has been reported [36].

Gastrointestinal System

Gastrointestinal effects result in gastric motility. Increased antral and proximal duodenal muscle tone results in delayed gastric emptying. This may also contribute to the observed nausea and vomiting. Increased segmental tone and decreased longitudinal peristaltic contractions in the small intestine and colon may result in the common side effect of constipation. Spasm of the Oddi sphincter may also occur with certain narcotics, resulting in symptoms which are characteristics of biliary colic. Morphine and other μ agonists usually decrease the secretion of HCl, although stimulation is sometimes evident. It also diminishes biliary, pancreatic, and intestinal secretions [37]. Morphine delays ingestion of food in the small intestine. The upper part of the small intestine particularly the duodenum is more affected than the ileum. In a recent population-based survey of adults in the USA who use opioids to manage pain unrelated to cancer, 57% of participants reported having had constipation that they associated with opioid treatment and less reported nausea, abdominal pain, and gas [38]. Recently, the Food and Drug Administration has approved methylnaltrexone bromide for opioid-induced constipation [39, 40]. Currently, Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist, is being investigated for the treatment of opioid-induced bowel dysfunction [41].

Immune System

Due to opioids' widespread and expanding use, the immunological effects of opioids are receiving considerable attention because of concerns that opioid-induced changes in the immune system may affect the outcome of surgery or of variety of disease processes, including bacterial and viral infections and cancer [42]. The potent opioid fentanyl also exerts a relevant immunosuppression, while the partial agonist buprenorphine appears to have a more favorable immune profile [43, 44]. The impact of the opioid-mediated immune effects could be particularly dangerous in selective vulnerable populations, such as the elderly or immunocompromised patients.

Tolerance and Physical Dependence

Tolerance and dependence are physiological responses observed in all patients and are not predictors of abuse. For example, cancer pain often requires prolonged treatment with high doses of opioids leading to tolerance and dependence, although abuse in this setting is very unusual. Neither the presence of tolerance and dependence nor the fear that it may develop should interfere with the appropriate use of opioids. Opiate dependence is initially psychological and thus can be discontinued in the early stage without subjecting to withdrawal syndrome. Suppression of withdrawal syndrome at a later stage with initial physical dependence may require only minimal doses of an opiate. Clinically, the dose can be decreased by 50%

every several days and eventually stopped, without severe signs and symptoms of withdrawal. However, decreases in dosage may lead to reduction of the degree of pain control. Blockade of glutamate actions by noncompetitive and competitive NMDA (*N*-Methyl D Aspartate) antagonist receptors inhibits morphine tolerance [45]. Although the role of the NMDA receptor in the development and expression of opiate tolerance, dependence, and withdrawal is well established in adults, but different mechanisms may exist in infants [46].

Nitric oxide production has also been implicated in morphine tolerance, as inhibition of nitric oxide synthesis also blocks morphine tolerance [47]. These studies indicate that several important aspects of tolerance and dependence are involved. Firstly, the selective actions of drugs on tolerance and dependence demonstrate that analgesia can be dissociated from theses two unwanted actions. Secondly, the reversal of preexisting tolerance by NMDA antagonists and nitric oxide synthetase inhibitors indicates that tolerance is a balance between activation of processes and reversal of those processes.

The clinical importance of these observations is speculative, but they suggest that in the future, tolerance and dependence in the clinical management of pain can be minimized.

Clinical Presentations of Opioid Overdose

Opioid overdose may occur in children as accidental or in adults as intentional and rarely as a criminal act. The body packers, who present with the leakage of drugs from the packets that are being transported with the gastrointestinal tract, may also be encountered. Opium body packing is a health problem in Iran [48]. Overdoses in addicts generally occur in two ways. The first is the user who unknowingly uses a more potent grade of opioid. The second is the uninitiated or abstaining user who had administered a dose beyond his or her perceived tolerance. In both ways, excessive opioid effects are observed and excessive respiratory depression may result. The patient is typically found or presents in an obtuse state with worrying degrees of respiratory depression. Diagnosis is usually aided by the presence of miosis, loss of consciousness, respiratory depression and track mark (scaring from prior IV administration) or evidence of skin popping (scaring from prior subcutaneous administration). Positive rapid response to the administration of naloxone is usually confirmatory.

Pediatric patients often present with overdose resulting from access to pain medication or methadone from a family member or other individual in the household. Interpretation of clinical manifestations in this situation is very important as the available history maybe very limited or nonexistent, particularly in cases in which illicit drugs are involved.

The suicidal patient may present with a mixed picture, resulting from polysubstance ingestion, frequently accompanied by the co-ingestion of alcohol. History may be more helpful than in the prior scenarios. The patient is frequently accompanied by family members or friends, who confirm the use of medication by

the patient, or may simply have found pill bottles. Toxic doses of opioids may be difficult to assess in this situation, as tolerance, underlying medical conditions, and the other substances abused play a role in the severity of poisoning. Patients with mild overdose present with slight depression in mental status, miosis, and minimal respiratory depression. Severe overdoses result in the triad of coma, miosis, and respiratory depression. Effects on respiration usually begin with a decrease in respiratory rate while the tidal volume is maintained. In more severe overdoses, respiratory arrest may occur. Hypoxia due to respiratory depression is the main cause of most deaths of opioid drugs.

Certain opiates, particularly heroin, can cause a fulminant but rapidly reversible pulmonary edema. Noncardiogenic pulmonary edema (NCPE) has been described as the most frequent complication of heroin overdose that is observed in up to 48% of the patients [49]. In contrast, a later study reported NCPE was diagnosed in only 2.4% of patients presenting to the emergency departments [50]. The wide range may be reflective of numerous factors including changes in heroin purity and methods of administration. Pneumonia, the next leading complication of heroin overdose (up to 30%), may also play a role in this discrepancy [51].

The etiology of heroin-induced NCPE in heroin overdose remains unclear but may include a hypersensitivity reaction, an acute hypoxemia-induced capillary vasoconstriction resulting in increased hydrostatic pressure or capillary injury, secondary to the drug or adultery [52]. NCPE is characterized by tachypnea, tachycardia, hypoxia, and rales on lungs auscultation. Pulmonary capillary wedged pressure is typically normal. Laboratory abnormalities include respiratory acidosis and hypoxia. Radiographic evaluation usually demonstrates bilateral patchy infiltrates. Onset of intoxication may occur from minutes to several hours after heroin use. Prior review indicates that onset maybe delayed as much as 24 h after heroin administration [53], whereas a further study reported a much earlier onset [49]. Methadone and other opiates have also been linked to NCPE, although its occurrence is uncommon [54, 55].

Other complications from opioid overdose include seizures most often attributed to propoxifen [56, 57], or meperidine overdose [58]. Heroin also appears to be a potential causative agent [59]. The mechanism for opioid-induced seizures is not totally clear. However, two distinct causes have been postulated based on therapy with opioid antagonists. Although seizures from heroin, morphine, and propoxifen overdoses have been treated successfully with naloxone, animal studies indicate that naloxone will lower seizure threshold in meperidine overdoses. The toxic metabolite normeperidine has been implicated in cases involving meperidine [60, 61].

Cardiac conduction disturbances have also been reported and are primarily attributed to propoxifen and its metabolites [62, 63].

Diagnosis of Opioid Overdose

Diagnosis of opioid overdose should be based initially on history and clinical presentation. Additional laboratory analyses are useful particularly in the IV drug users who may have additional underlying conditions or complications. Drug screens of

mixed utility depend on the information being obtained, clinical manifestations, and the time after exposure. The results may guide the physician in clinical management of the patient. In patients with specific signs such as miosis, CNS, and respiratory depression, particularly in severe poisoning with coma and respiratory insufficiency, IV administration of naloxone is a good diagnostic tool.

Situations involving poly-substance usage maybe less straightforward, but clinical judgment and supportive measures are usually employed before receiving results of a drug screen. However, in complicated cases, opioid screens as well as other CNS depressants screening could be beneficial. Screening techniques must be able to detect parent compounds and their active metabolites in serum or urine. Urine drug screens can provide a qualitative method to detect many opioids, including propoxyphene, codeine, methadone, meperidine, and morphine. Screens for fentanyl and its derivatives are usually negative. Quantitative results on opiates from serum are not helpful in the routine management of overdoses. The serum drug screen may be helpful in detecting the presence of agents other than opiates, such as acetaminophen, that may require its specific antidote (*N*-acetyl cysteine) therapy.

Management of Opioid Overdose

Management of opioid overdoses focuses on stabilization of respiration. Initial assessment and establishment of effective ventilation and oxygenation followed by insuring adequate homodynamic support are followed. Initial support with a bag-valve-mask (BMV) is appropriate along with 100% oxygen supplementation. Oral or nasal airway placement may be required and in fact is vital in comatose patients. However, caution is advised with their use, to prevent vomiting and or aspiration. Suction apparatus should be available for immediate use at the patient's bedside. Ventilatory support can usually be provided with a BMV device while awaiting the reversal of respiratory depression by an opioid antagonist.

Endotracheal intubation is indicated in severely compromised patients in whom there is a real risk in aspiration or in patients who do not respond satisfactorily to opioid antagonists. Treatment of NCPE will require 100% oxygen therapy with positive end expiratory pressure (PEEP), if necessary to reverse hypoxia. Diuretics and digoxin have no role in treatment of NCPE. The options for opioid antagonists include naloxone, and the longer-acting antagonist nalmefene [64, 65]. These pure opiate antagonists with great affinity to μ receptors should be titrated according to the severity of poisoning.

Naloxone remains the drug of choice as the initial reversal agent in suspected opioid overdose, given its short half-life and ability to titrate for the effect. The need for immediate results (usually in the form of increased ventilation) is balanced by the potential unpleasant effects inducing withdrawal symptoms in the chronic abuser. In the patient who presents with respiratory arrest, precipitation of some acute withdrawal symptoms may be unavoidable. To minimize this risk, naloxone should be given in small increments, titrated to the response. Naloxone can be administered IV, IM, SC, endotracheally, or intralingually [66–68].

Naloxone dose is based on the severity of poisoning. It generally ranges from 0.4 to 2.0 mg IV in the adult patient. For respiratory depression or arrest, 2 mg IV is suggested initially (provided that the patient was not dependent to opiate), to be repeated 2–5 min (or sooner if the patient is indeed in respiratory arrest) up to 10 mg. If no response is observed after 10 mg of he naloxone, it is unlikely that opioids by themselves are playing a significant role in the patient's clinical status. Certain opiate overdoses such as codeine, propoxifen, pentazocine, methadone, and diphenoxylate may require repetitive or continuous administration. In cases of leaked opium body packing, repetitive or continuous naloxone administration is needed.

Nalmefene may provide an alternative to naloxone infusion, given its longer half-life (4–8 h) compared to (1 h) with naloxone. Initial dose of 0.5-mg nalmefene IV reverses respiratory depression in the adult patients. A repeat dose of 1.0 mg can be given 2–5 min later if necessary.

The current recommendation for pediatric dosing of naloxone is 0.1 mg/kg given IV [69]. Continuous IV injection of naloxone (0.4–0.5 mg/h for 2.5–4 days) in 2 patients (aged 3 days to 1 year) was also applied [70].

Decontamination is generally reserved for opioid agents taken orally. Opiates cause decreased gastric emptying and pylorospasm. This decrease in gastrointestinal motility suggests that there may be some benefit to gastrointestinal emptying several hours after ingestion. Gastric aspiration and lavage is affected in debulking large amounts of ingestant; it may also be beneficial with smaller amounts of ingestant due to delayed gastric motility in the obtuse patient. Endotracheal intubation should be performed prior to the placement of orogastric or nasogastric tubes, to protect against aspiration in comatose patients. Activated charcoal and cathartics (Magnesium citrate or sorbitol) should be administered after gastric emptying if bowel sounds are present. The initial dose of activated charcoal is 1.0 g/kg (50 g in an adult) by mouth or per nasogastric tube. Repetitive dosing of activated charcoal may be beneficial in patients who ingested large amounts of opiate or in an opium body packer with a ruptured pack.

Muscle rigidity, while possible after all narcotics, appears to be more common after administration of bolus doses of fentanyl or its congeners. Rigidity can be treated with depolarizing or non-depolarizing neuromuscular blocking agents while controlling the patient's ventilation [3].

Since the half-life of naloxone is short but the half-life of most opioids are long, the patients must not be discharged after recovery unless no signs of intoxication particularly CNS depression are found 24 h after cessation of naloxone therapy.

Drug Interactions

Opiates and opioids have wide range of pharmacological and toxicological interactions with many classes of drugs. The pharmacological interactions can be divided into pharmacokinetics and pharmacodynamics.

Pharmacokinetic Interactions

Food

Oral morphine in sustain-released form (Oramoph SR) and morphine sulfate in a continuous preparation (MST continus) taken by 24 healthy male volunteers in a 4 way crossover study revealed significant higher C_{max}, T_{max}, and AUCo-24 following high-fat breakfast than the fasting subjects [71]. In a randomized crossover study in 22 normal male and female subjects, it was revealed that oxycodon in sustain-released form had no significant interactions with food intake. However, both bioavailability and C_{max} were significantly altered by high-fat meal after taking immediate-release form of oxycodon [72]. It was shown that food has no effect on the pharmacokinetics of morphine following doses of immediate-release solution and the modified release preparations. However, the lack of bioequivalence between some of the formulations suggests that care should be taken by physicians in changes of modified release formulations [73]. Morphine sulfate and dextrometorphan combination (MorphiDex) in a single-dose double-blind study in patients suffered from post-operation pain, food reduced C_{max}, but not the extent of absorption [74]. In another study with a newly sustained-release form of tramadol in 24 healthy volunteers, food had no significant effects on the pharmacokinetics of the drug [75].

Drug Absorption and Bioavailability

Morphine and Metoclopramide

Metoclopramide increases the rate of absorption of oral morphine and exacerbates its sedative effects. A 10-mg dose of metoclorpramide markedly increased the extent and speed of sedation due to a 20-mg oral dose of morphine over a period of 3–4 h in 20 patients undergoing surgery. Peak serum morphine concentrations and the total absorption remained unaltered. Metoclopramide increases the rate of gastric emptying so that the rate of morphine absorption from the small intestine is increased. An alternative idea is that both drugs act additively on opiate receptors to increase sedation [76].

Codeine and Salicylate-Containing Herbs

Some authors have suggested that since salicylate-containing herbs can selectively precipitate some alkaloids, high doses of these herbs may impair the absorption of codeine [77].

Morphine and Tricyclic Antidepressants

The bioavailability and the degree of analgesia of oral morphine are increased by the concurrent use of clomipramine, desipramine, and possibly amitriptyline. Clomipramine or amitriptyline in daily doses of 20–50 mg increased the AUC of oral morphine by amounts ranging from 28% to 111% in 24 patients being treated for cancer pain. The half-life of morphine was also prolonged [78]. A previous study [79] found that desipramine but not amitryptamine increased and prolonged morphine analgesia, and a latter study by the same group [80] confirmed the value of desipramine. The reasons are not understood. The increased analgesia may be due to not only the increase of serum/morphine concentrations but possibly also to some alterations in the morphine receptors. Acute administration of clomipramine potentiates morphine analgesia in mice whereas chronic administration attenuates them [81].

Morphine and Trovafloxacine

Coadministration of trovafloxacine and morphine in 19 healthy volunteers reduced the bioavailability and C_{max} of trovafloxacine but the effects were not significant [82].

Codeine and Ibuprofen

Relative bioavailabilities of ibuprofen and codeine in 24 healthy volunteers revealed no significant interactions [83].

Methadone and Anti-HIV Drugs

Interaction between methadone and some HIV-related medications is known to occur, yet their characteristics cannot reliably be predicted based on current understandings of metabolic enzyme induction and inhibition, or through in vitro studies [84]. Nevertheless, it has been shown that methadone elevates Zidovudine's serum concentration, increasing the risk of side effects [85]. In 17 study subjects using drugs for HIV and stable methadone therapy, methadone reduced the AUC of didanosine by 63%, suggesting larger doses of didanosine are required for these patients [86].

Methadone and Anticonvulsants

Classic anticonvulsant drugs, such as phenytoin, carbamazepine, and phenobarbital, produce dramatic decreases in methadone levels, which may precipitate a

withdrawal syndrome; valproic acid and the new anticonvulsant drugs do not have these effects [87, 88].

Metabolism

The reported opioid interactions on drug metabolism are mostly in vitro or in experimental studies. The interactions may occur by induction or inhibition of drug metabolism.

Morphine and Alcohol

The respiratory depressant effect of morphine is significantly increased by alcohol. The use of morphine in patients who are intoxicated with alcohol is especially dangerous, and even small doses can be fatal when there is a high concentration in the blood [37]. Loss of tolerance, concomitant use of alcohol, and other CNS depressants, particularly morphine and its derivatives, clearly play a major role in fatality. However, age, gender, and other risk factors do not account for the strong age and gender patterns observed among victims of overdose. There is evidence that systemic diseases, particularly pulmonary and hepatic disorders, may be more prevalent in opiate users who are at greater risk of overdose. There is no effective role for opiate mediation in ethanol intake as well as any ethanol sweet-fluid intake interactions [89]. Both ethanol and opioids are metabolized in part by the hepatic Mixed Enzyme Oxidative System. When both drugs are used together, slower disposal rates and possibly higher toxicity may arise. Ethanol may affect some opiate receptors and possibly change the brain tissue's endogenous opiate peptide levels in some loci. Mixed alcohol and opiate abusers did poorly in standard alcohol abstinence treatment compared to matched alcoholics without opiate abuse histories [90].

Morphine and Rifampin

Rifampin significantly reduced the peak plasma morphine concentration and Area Under Curve (AUC) and the analgesic effect of morphine in 10 healthy volunteers on a double-blind placebo-controlled study. It has been found that Rifampin was found to reduce morphine's analgesic effects, probably due to the induction of its metabolism [91].

Morphine and Cimetidine

Respiratory depression, potentially fatal, occurred in patients receiving cimetidine with morphine or opium and methadone [92]. Decreased metabolism of morphine is the probable mechanism.

Methadone and Antidepressants

Important pharmacokinetic interactions may occur between methadone and antidepressant drugs. Desipramine plasma levels are increased by methadone. Furthermore, fluvoxamine (and fluoxetine to a less extent) may cause an important increase in serum methadone concentrations [93]. In patients unable to maintain effective methadone blood level throughout the dosing interval, fluvoxamine can help increase the methadone blood level and alleviate opiate withdrawal symptoms [94]. The inhibition of different clusters of the cytochrome P450 system is involved in these interactions.

Codeine and Quinidine

Patients who lack CYP2D6 or whose CYP2D6 is inhibited by quinidine will not benefit from codeine [95]. Quinidine-induced inhibition of codeine *O*-demethylation is ethnically dependent with the reduction being greater in Caucasians [96].

Methadone and Ciprofloxacine

Recent reports suggest a significant drug interaction between ciprofloxacin and methadone. Ciprofloxacine may inhibit cytochrome P450 3A4 up to 65%, thus elevating methadone levels significantly [97].

Propoxyphene and Carbamazepine

Since propoxyphene inhibits hepatic metabolism of carbamazepine, decreased clearance of carbamazepine may result in its increased serum concentration and toxicity [98].

Hydrocodone and Smoking

Nicotine is reported to have analgesic properties. Patients with chronic pain who smoke could, therefore, be expected to require less analgesia than nonsmokers because of the possible synergism of the two substances. However, contrary to this hypothesis, smokers had higher end of study pain scores and required more hydrocodone than nonsmokers but had significantly lower serum levels of hydrocodone than nonsmokers. The results of this study suggest that cigarette smoking adversely affects serum hydrocodone levels [99].

Elimination

Morphine and Oral Contraceptives

Clearance of morphine is approximately doubled by the concurrent use of oral contraceptives. The clearance of intravenous morphine (1 mg) was increased by 75%, oral morphine (10 mg) by 120% in 6 young women taking an oral contraceptive [100]. This implies that the dosage of morphine will need to be virtually doubled to achieve the same degree of analgesia. Urinary morphine concentration will then be greater in patients taking oral contraceptives.

Meperidine and Phenytoin

Meperidine systemic clearance rose from 1,017 ± 225 mL/min to 1,280 ± 130 mL/min during phenytoin dosing ($p < 0.01$) [101].

Morphine and 5-Fluro Uracil

The plasma clearance rate of 5-Fluoro Uracil (5FU) in mice is significantly reduced by concomitant use of morphine. The effects of morphine are due to reduced hepatic elimination of 5FU rather than to a decrease in its renal excretion [102].

Morphine and Gentamicin

Morphine administration has been shown to reduce glomerular filtration of gentamicin. This causes a reduction in gentamicin plasma clearance which results in a significant rise in gentamicin plasma levels [103].

Methadone and Urinary Acidifiers

Several studies have shown that patients with a high clearance rate of methadone also have a low urine pH (1–3). In a study, the administration of ammonium chloride and sodium carbonate over 3 days each resulted in a mean methadone elimination half-life of 19.5 h, compared with 42.1 h following sodium carbonate [104].

Fentanyl (or Alfentanil) and Propofol

Although clinically the hypnotic effect of propofol is enhanced by analgesic concentrations of μ-agonist opioids (e.g., fentanyl), the bispectral index does not

show this increased hypnotic effect [105]. It was shown that hemodynamic changes induced by propofol may have an important influence on the pharmacokinetics of alfentanil [106].

Pharmacodynamic Interaction

Sedatives-Hypnotics-Antipsychotics

Morphine and Barbiturates

Secobarbital increases the respiratory depressant effects of morphine, whereas diazepam appears not to interact in this way. In 30 normal subjects, it was found that quinalbarbitone and morphine depressed ventilation when given alone. However, a combination of quinalbarbitone and morphine resulted in a much greater and more prolonged depression. Other respiratory depressant drugs such as narcotics, opiate, analgesics can also have additive effects [107]. In one study, it was found that fentanyl and alfentanil pretreatment have also reduced the dose of thiopental required for anesthesia induction [108].

Morphine and Phenothiazines

Phenothiazines potentiate the depressant effects of morphine on the CNS, particularly with respect to respiration. Also, the simultaneous administration of morphine and phenothiazines can result in significant hypotension [37].

Morphine and Benzodiazepines

The depressant effects of morphine on respiration are significantly greater if the patient is simultaneously taking benzodiazepines [37]. Alprazolam mediated analgesic effects, most probably via a μ opiate mechanism of action [109].

Methadone and Psychoactive Agents

Psychoactive medication is frequently used in methadone maintenance treatment programs (MMP) to treat comorbid mental disorders (depression, anxiety, schizophrenia) in opiate addicts. Thus, several pharmacological interactions are possible. This problem becomes more relevant with the introduction of new CNS-drugs like SSRI, atypical antipsychotics, or new anticonvulsants. For instance, sertaline increases the plasma methadone concentration significantly in depressed patients on methadone

[110]. The most common interactions seen in practice are pharmacodynamic in nature, most often due to the cumulative effects of different drugs on the central nervous system (e.g., neuroleptics or benzodiazepine interactions). Several lines of evidence suggest that benzodiazepines and methadone may have synergistic interactions and that opiate sedation or respiratory depression could be increased. This is a serious problem, given the widespread use of benzodiazepines among MMP patients. Experimental but not clinical data support methadone and lithium interactions. Accordingly, caution is advised in the clinical use of methadone when other CNS-drugs are administered.

Meperidine and Phenothiazines

Although uncontrolled observations have supported concurrent administration of these agents to minimize narcotic dosage and control nausea and vomiting, serious side effects may outweigh the benefits. In a study, meperidine and chlorpromazine compared to meperidine and placebo resulted in significantly increased lethargy and hypotension [111].

CNS Stimulants

Dexamphetamine and methylphenidate increase the analgesic effects of morphine and reduce some of its side effects such as respiratory depression and sedation. It seems there would be advantages in using two drugs in combination. D-amphetamine potentiates the effects of di-acetyl morphine (heroin). Opiate abusers use amphetamines to increase the effects obtained from poor-quality heroin [112].

Hallucinating Agents

Opioids and Cannabinoids

Cannabinoids and opioids share the same pharmacological properties and to a lesser extent in drug reinforcement. Braida and co-workers demonstrated that cannabinoids produce a reward response in conditioned place preference tests and interconnection of opioid and cannabinoid systems [113]. Functional interaction between opiate and cannabinoid system exists at immune level that differs from the interaction present in the CNS [114]. SR141716A, a CB1 receptor antagonist, significantly reduced the intensity of naloxone-induced opiate withdrawal in tolerant rats. SR141716A could be of some interest in ameliorating opiate withdrawal syndrome [115]. Maternal exposure to delta-p tetra-hydro-cannabinol (THC) has the potential effects of motivational properties in female adult rats, as measured by an intravenous opiate self-administration paradigm [116].

Opioids and Cocaine

Enadolin, a selective and high efficacy κ agonist, and butorphanol, a mixed agonist with intermediate efficacy at both μ and κ receptors, failed to modify cocaine self-administration in humans [117].

Naloxone and Lysergic Acid Diethylamine (LSD)

Naloxone attenuated hallucinogenic effects of LSD and may subserve the development of tolerance to morphine-like drugs [118].

Endocrine Drugs

Thyrotropin-releasing hormone (TRH) and related compounds appear to (a) antagonize hypothermia, respiratory depression, locomotor depression, and catalepsy but not the analgesia induced by opiates; (b) inhibit the development of tolerance to the analgesic effects but not to the hypothermic effects of opiate; (c) inhibit the development of physical dependence of opiates as evidenced by the inhibition of development of certain withdrawal syndromes and; (d) suppress the abstinence syndrome in opiate dependent rodents.

TRH does not interact with the opiate receptors in the brain. Potential therapeutic application of TRH and its synthetic analogues can be used in counteracting some of the undesirable effects of opiates [119]. Possible common modes of action of ACTH opiate agonist and antagonists that are dependent on time of the day and stress intensity have been reviewed [120].

Muscle Relaxants

Patients recovering from relaxant anesthesia are especially vulnerable to the respiratory depressant effects of morphine. Respiratory acidosis, secondary to acute hypercapnia, can result in reactivation of the long-acting relaxant on the completion of anesthesia, resulting in further depression of respiration. The combination of muscle relaxant and morphine could result in a rapidly progressing respiratory crisis [37]. Morphine and $GABA_B$ agonists (e.g., baclofen) shared the same mechanism of action and thus in combination with morphine tends to induce higher analgesic response in mice [121].

Adrenergic Drugs

Agmatin (an endogenous polyamine metabolite formed by the carboxylation of L-arginine) potentiates antinociception of morphine via an alpha-2 adrenergic receptor–mediated mechanism. This combination may be an effective therapeutic

strategy for the medical treatment of pain [122]. Yohimbine (an alpha-2 antagonist) tends to limit opiate antinociception and the additive potential of μ and delta opioid agonists [123].

Clonidine (4 and 10 μg/kg) in cats had a differential degree of inhibition in the order of analgesia, much greater than hypotension, greater than bradycardia. Naloxone (0.4 and 1.0 mg/kg) failed essentially to antagonize these effects, suggesting the lack of involvement of the opiate receptors of endogenous opioids in these processes. Furthermore, pain suppression of clonidine appeared to be independent of vasodepression and cardioinhibition [124]. Clonidine did not affect the pain when administered with IV placebo. When administered with pentazocine, clonidine caused a statistically significant increase in pentazocine analgesia [125]. Clonidine induced dose- and time-dependent suprasensitivity to norepinephrine, similar to that produced by morphine. Thus, clonidine and morphine possess comparable properties on the antagonism of chronic morphine tolerance; and this maybe the therapeutic basis for clonidine's clinical application in the treatment of opiate addicts [126].

Heroin and Alcohol

There have been numerous reports of the enhancement of acute toxicity and fatal outcome of overdose of heroin by ethanol. Losses of tolerance and concomitant use of alcohol and other CNS depressants clearly play a major role in fatality; however, such risk factors do not account for the strong age and gender patterns observed consistently among victims of overdose. There is evidence that systemic disease may be more prevalent in users at greatest risk of overdose. It is suggested that pulmonary and hepatic dysfunction resulting from such disease may increase susceptibility to both fatal and nonfatal overdose [127]. In one study, at all ranges of free morphine concentrations, there was a greater percentage of heroin deaths when ethanol was present [128]. Toxicological evidence of infrequent heroin use was more common in decedents with blood ethanol concentration greater than 1 μg/mL than in those with lower concentrations [129]. The evidence is consistent with the hypothesis that heroin users who drink alcohol may require less heroin to overdose than those who do not drink (all other factors being equal) because of a pharmacological interaction [130].

Genotoxic Damage and Immunosuppression

Opiate addicts have higher chromosome damage and sister chromatid exchange frequencies. Opiates diminish DNA repair and reduce immunoresponsiveness as measured by T cell E-rosetting and other assays. These interactions of opiates with T lymphocytes may regulate metabolism and could thereby be responsible for the sensitivity of cells from opiate addicts to both genotoxic damage and immunological effects [131].

More drug interactions of some opioids are presented in Table 4.4.

Table 4.4 Drug interactions of some opioids

Object drug(s)	Precipitant drug(s)	Interaction	References
Morphine and other opioids	MAO inhibitors	Increased effects of morphine: anxiety, confusion, respiratory depression, coma, serotonin syndrome	[37, 135]
Morphine, Loperamide	Quinidine	Increased toxicity of opiates	[136, 137]
Morphine, Methadone	Hexoses	Reduction in potency ratio of objects drugs	[138]
Morphine	Fluoxetine	Fluoxetine attenuated morphine analgesia but not pentazocine	[139]
Narcotics	Maternal tobacco smoking	Fatal intrauterine growth retardation	[140]
Morphine	Ginseng	Ginseng inhibited the analgesic activity, tolerance to and dependence on morphine	[141]
Buprenorphine	Naloxone	Low abuse potential; opiate withdrawal symptoms	[142, 143]
Morphine, Cocaine	Buprenorphine	Buprenorphine significantly reduced both opiate and cocaine abuse	[144]
Yohimbine	Naltrexone	Altered sensitivity to Yohimbine	[145]
Pentazocine, Morphine	Amitriptyline	Respiratory depression may be increased by their concomitant use	[146, 147]
Codeine	Glutethimide	Specific concentrations of each drug in most cases were in the high therapeutic range, suggesting a possible toxic synergistic effect	[148]
Meperidine	Isoniazid	Isoniazid inhibits monoamine oxidase causing hypotensive episode or CNS depression	[149]
Fentanyl	Paroxetine (SSRI)	Serotonin syndrome	[150]
Tramadol	Cabergoline	Dopaminergic and serotonergic effects of cabergoline in combination with the tramadol; reuptake inhibition of serotonin and norepinephrine leads to severe hypertension	[151]
Methadone	Dextrometorphan	Methadone has been found to inhibit CYP2D6, indicating a potential for interaction with dextromethorphan which leads to delirium	[152]

Postmortem Examinations

The diagnosis of death due to opiates or opioids is based on the followings:

1. Examination of the scene where the body is found.
2. Investigation of the circumstances.
3. History obtained from friends and relations.
4. Autopsy examination.
5. Toxicological evidence.

Before attributing death due to narcotism purely on the basis of circumstantial evidence, it is essential to exclude other natural or unnatural causes of death such as spontaneous intracranial hemorrhage, occult subdural hemorrhage, or evidence of non-narcotic drugs.

Postmortem Appearances

The appearances could be divided into external and internal.

1. External: The smell of opium may be present. The face is deeply cyanosed, almost black. The finger nails are blue. The veins are engorged and distended in the neck. The postmortem lividity is intense, almost black, and is better seen in a fair-skinned body. The pupils may be contracted or dilated. There is froth at the mouth and nose, but neither so fine nor as copious as in drowning.
2. Internal: The stomach may show the presence of small, soft, brownish lumps of opium and the smell of drug may be perceived. It disappears with the onset of putrefaction. The internal organs especially the trachea, bronchi, lungs, and brain exhibit a marked degree of venous congestion. In addition, the trachea and bronchi are covered with froth and the lungs are edematous. The blood is usually dark and fluid.

Associated with edema of the lungs, the intense lividity of the face almost approaching to blackness should make one suspicious of opium poisoning as the cause of death. Such intense lividity is seldom seen in any other condition [132].

At autopsy of an individual who has died of an overdose of heroin, the lungs are heavy and show congestion, though the classic pulmonary edema mentioned in some of the other textbook is not always present. Microscopic examination of the lungs commonly reveals foreign-body granulomas with talc crystals and cotton fibers. Samples of the venous blood, urine, stomach and contents, liver, and in some circumstances, additional samples such as bile, cerebrospinal fluid and vitreous humor, kidney, and brain may be taken. When the drug has been injected, an ellipse of skin around the injection mark extending down through the subcutaneous tissue to the muscle should be excised, along with control area of skin from another non-injected site [133].

Toxicological Analyses

Various analytical methods for the estimation of morphine and its derivatives have been reported. The most reliable methods are gas chromatography–mass spectrometry and radioimmunoassay. Blood and urine as well as the other samples such as gastric contents and the organ tissue extracts may be analyzed. In order to identify a certain opiate or opioid, a highly specific method should be used to determine the parent drug as well as the metabolites. For instance, if both morphine and monoacetylmorphine are detected in the blood, then, the individual took heroin.

Plasma concentrations of some opiates such as methadone correlated well with the intake doses. Plasma methadone concentration appears to increase by 263 ng/mL for every milligram of methadone consumed per kilogram of body weight [134].

Interpretation of the Results

Interpretation of the results of toxicological analyses is very important both in clinical and forensic toxicology. History of drug use and abuse, overdose, clinical and postmortem findings should be considered for the evaluation and interpretation of the results.

As with all deaths from toxic substances, the interpretation of analytical results may present considerable difficulties. There might be a long delay between the intake of a drug and death, during which time the blood, urine, and even tissue levels may decline, or even disappear. Many drugs break down rapidly in the body, and their metabolites may be the only recognizable products of their administration. In some cases, data on lethal blood levels may be imperfectly known and great variations in personal susceptibility may make the range of concentrations found in a series of deaths so wide as to be rather unhelpful.

If a person dies rapidly after the first episode of taking a normal dose of a drug, because of some ill-understood personal idiosyncrasy, the quantitative analysis may not assist.

Where habituation and tolerance has developed, drug users may have concentrations in their body fluids and tissues far higher than lethal levels published for non-dependent. In general, the great usefulness of toxicological analysis is both qualitative and quantitative. The qualitative tests will show what drugs have been taken in the recent past; the length of time that drugs or their metabolites persist in different fluids and tissues varies widely.

The quantitative analysis can be useful, especially when the results reveal high levels – into the toxic or lethal ranges. These ranges are usually obtained anecdotally from surveys of large number of deaths but, as stated, can differ in terms of minimum and maximum values from different laboratories. Interaction of other drugs and alcohol or both, delayed death, and abnormal sensitivity are other problems that should be considered. Thus, the analysis is not the final arbiter of the cause of death, although it is a highly important component of the whole range of investigations [133].

References

1. Herz, A., *Opioids* Handbook of Experimental Pharmacology. Vol. 104. 1993, Berlin: Springer Verlag
2. Way, W.L., H.L. Fields, and M.A. Schumacher, *Opioid Analgesics & Antagonists*, in *Basic and Clinical Pharmacology*, B.G. Katzung, Editor. 2006, McGraw-Hill New York, NY. p. 489–510.
3. Akil, H., et al., *Endogenous opioids: overview and current issues.* Drug and Alcohol Dependence, 1998. **51**(1–2): p. 127–140.
4. Trescot, A.M., et al., *Opioid pharmacology.* Pain Physician, 2008. **11**(2 Suppl): p. S133-53.
5. Cone, E.J., et al., *Evidence of morphine metabolism to hydromorphone in pain patients chronically treated with morphine.* Journal of Analytical Toxicology, 2006. **30**(1): p. 1–5.
6. National Institute of Drug Abuse, 2000: Epidemiologic Trends in Drug Abuse Advance Report, December 2000 http://www.drugabuse.gov/CEWG/AdvancedRep/1200ADV/1200adv.html. Accessed February 05, 2009.
7. Shah, N.G., et al., *Unintentional drug overdose death trends in New Mexico, USA, 1990–2005: combinations of heroin, cocaine, prescription opioids and alcohol.* Addiction, 2008. **103**(1): p. 126–36.
8. *The NSDUH report: patterns and trends in nonmedical prescription pain reliever use: 2002 to 2005. Substance Abuse and Mental Health Services Administration Web site. http://www.oas.samhsa.gov/2 k7/pain/pain.pdf. Accessed February 27, 2008.* [cited].
9. *Drug Abuse Warning Network, 2005: national estimates of drug-related emergency department visits. Substance Abuse and Mental Health Services Administration Web site. http://dawninfo.samhsa.gov/files/DAWN-ED-2005-Web.pdf. Accessed February 05, 2009.* [cited].
10. Centers for Disease Control and Prevention. Unintentional poisoning deaths—United States, 1999–2004. MMWR Morb Mortal Wkly Rep. 2007;56(5):93–96. PUBMED
11. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf. 2006;15(9):618–627. FULL TEXT | ISI | PUBMED
12. Crowe, A.V., et al., *Substance abuse and the kidney.* The Quarterly Journal of Medicine, 2000. **93**(3): p. 147–152.
13. Hulse, G.K., et al., *The quantification of mortality resulting from the regular use of illicit opiates.* Addiction 1999. **94**(2): p. 221–229.
14. Marks, J., *Deaths from methadone and heroin.* Lancet, 1994. **343**(8903): p. 976.
15. Hendra, T.J., S.P. Gerrish, and A.R. Forrest, *Fatal methadone overdose.* British Medical Journal, 1996. **313**(7055): p. 481–482.
16. Nanji, A.A. and J.D. Filipenko, *Rhabdomyolysis and acute myoglobinuric renal failure associated with methadone intoxication.* Journal of Toxicology Clinical Toxicology, 1983. **20**(4): p. 353–360.
17. Friedman, R.A., et al., *Profound hearing loss associated with hydrocodone/acetaminophen abuse.* The American Journal of Otology, 2000. **21**(2): p. 188–191.
18. Tracqui, A., P. Kintz, and B. Ludes, *Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities.* Journal of Analytical Toxicology, 1998. **22**(6): p. 430–434.
19. McKeganey, N., *Should heroin be prescribed to heroin misusers? No.* Bmj, 2008. **336**(7635): p. 71.
20. Rehm, J. and B. Fischer, *Should heroin be prescribed to heroin misusers? Yes.* Bmj, 2008. **336**(7635): p. 70.
21. March, J.C., et al., *Controlled trial of prescribed heroin in the treatment of opioid addiction.* J Subst Abuse Treat, 2006. **31**(2): p. 203–11.
22. Thomas, S., R. Winecker, and J.P. Pestaner, *Unusual fentanyl patch administration.* Am J Forensic Med Pathol, 2008. **29**(2): p. 162–3.
23. Teske, J., et al., *Fatal outcome in a child after ingestion of a transdermal fentanyl patch.* Int J Legal Med, 2007. **121**(2): p. 147–51.
24. van Rijswijk, R. and C. van Guldener, *A delirious patient with opioid intoxication after chewing a fentanyl patch.* J Am Geriatr Soc, 2006. **54**(8): p. 1298–9.

25. Coon, T.P., et al., *Rectal insertion of fentanyl patches: a new route of toxicity.* Annals of Emergency Medicine, 2005. **46**(5): p. 473.
26. Woodall, K.L., T.L. Martin, and B.A. McLellan, *Oral abuse of fentanyl patches (Duragesic): seven case reports.* J Forensic Sci, 2008. **53**(1): p. 222–5.
27. Fodale, V., et al., *Killer fentanyl: is the fear justified?* Expert Opin Drug Saf, 2008. **7**(3): p. 213–7.
28. Haroz, R. and M.I. Greenberg, *New drugs of abuse in North America.* Clin Lab Med, 2006. **26**(1): p. 147–64, ix.
29. Schumann, H., et al., *Fentanyl epidemic in Chicago, Illinois and surrounding Cook County.* Clin Toxicol (Phila), 2008. **46**(6): p. 501–6.
30. Tjaderborn, M., et al., *Fatal unintentional intoxications with tramadol during 1995–2005.* Forensic Science International, 2007. **173**(2–3): p. 107–11.
31. National Institute of Drug, A. and H. National Institutes of, *Pain, opioids, and addiction: an urgent problem for doctors and patients.* Journal of Pain & Palliative Care Pharmacotherapy, 2007. **21**(4): p. 45–9.
32. Yaksh, T.L., *CNS mechanisms of pain and analgesia.* Cancer Surveys, 1988. **7**(1): p. 5–28.
33. Pattinson, K.T.S., *Opioids and the control of respiration.* British Journal of Anaesthesia, 2008. **100**(6): p. 747–58.
34. Martin, W.R., *Pharmacology of opioids.* Pharmacological Reviews, 1983. **35**(4): p. 283–323.
35. Lotsch, J., et al., *Fatal respiratory depression after multiple intravenous morphine injections.* Clinical Pharmacokinetics, 2006. **45**(11): p. 1051–60.
36. Melandri, R., et al., *Myocardial damage and rhabdomyolysis associated with prolonged hypoxic coma following opiate overdose.* Journal of Toxicology Clinical Toxicology, 1996. **34**(2): p. 199–203.
37. Dollery, C.M., *Therapeutic Drugs*. 1999, Edinburgh: Churchill Livingston. 231–233.
38. Cook, S.F., et al., *Gastrointestinal side effects in chronic opioid users: results from a population-based survey.* Alimentary Pharmacology & Therapeutics, 2008. **27**(12): p. 1224–32.
39. Lang, L., *The Food and Drug Administration approves methylnaltrexone bromide for opioid-induced constipation.* Gastroenterology, 2008. **135**(1): p. 6.
40. Portenoy, R.K., et al., *Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study.* Journal of Pain & Symptom Management, 2008. **35**(5): p. 458–68.
41. Webster, L., et al., *Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain.* Pain, 2008. **137**(2): p. 428–40.
42. Risdahl, J.M., et al., *Opiates and infection.* J Neuroimmunol, 1998. **83**(1–2): p. 4–18.
43. Martucci, C., A.E. Panerai, and P. Sacerdote, *Chronic fentanyl or buprenorphine infusion in the mouse: similar analgesic profile but different effects on immune responses.* Pain, 2004. **110**(1–2): p. 385–92.
44. Yardeni, I.Z., et al., *Relationship between fentanyl dosage and immune function in the postoperative period.* Journal of Opioid Management, 2008. **4**(1): p. 27–33.
45. Elliott, K., et al., *The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids.* Pain, 1994. **56**(1): p. 69–75.
46. Zhu, H. and G.A. Barr, *Opiate withdrawal during development: are NMDA receptors indispensable?* Trends in Pharmacological Sciences, 2001. **22**(8): p. 404–408.
47. Kolesnikov, Y.A., et al., *Blockade of tolerance to morphine but not to kappa opioids by a nitric oxide synthase inhibitor.* Proceedings of the National Academy of Sciences of the United States of America, 1993. **90**(11): p. 5162–5166.
48. Balali-Mood, M., *Opium body packing in Mashhad, Iran.* Journal of Toxicology Clinical Toxicology, 2000. **38**: p. 177–178.
49. Duberstein, J.L. and D.M. Kaufman, *A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema.* The American Journal of Medicine, 1971. **51**(6): p. 704–714.

50. Smith, D.A., et al., *Is admission after intravenous heroin overdose necessary?* Annals of Emergency Medicine, 1992. **21**(11): p. 1326–1330.
51. Maurer, P.M. and R.R. Bartkowski, *Drug interactions of clinical significance with opioid analgesics.* Drug Safety, 1993. **8**(1): p. 30–48.
52. Wang, M.L., et al., *Heroin lung: report of two cases.* Journal of the Formosan Medical Association = Taiwan yi zhi, 1994. **93**(2): p. 170–172.
53. Steinberg, A.D. and J.S. Karliner, *The clinical spectrum of heroin pulmonary edema.* Archives of Internal Medicine, 1968. **122**(2): p. 122–127.
54. Kjeldgaard, J.M., et al., *Methadone-induced pulmonary edema.* JAMA: the Journal of the American Medical Association, 1971. **218**(6): p. 882–883.
55. Persky, V.W. and L.R. Goldfrank, *Methadone overdoses in a New York City hospital.* Journal of the American College of Emergency Physicians, 1976. **5**(2): p. 111–113.
56. Lovejoy, F.H., A.A. Mitchell, and P. Goldman, *The management of propoxyphene poisoning.* The Journal of Pediatrics, 1974. **85**(1): p. 98–100.
57. Carson, D.J.L. and E.D. Carson, *Fatal dextropropoxyphene poisoning in Northern Ireland.* Lancet, 1977. **1**: p. 894–897.
58. Clark, R.F., E.M. Wei, and P.O. Anderson, *Meperidine: therapeutic use and toxicity.* The Journal of Emergency Medicine, 1995. **13**(6): p. 797–802.
59. Ng, S.K., et al., *Illicit drug use and the risk of new-onset seizures.* American Journal of Epidemiology, 1990. **132**(1): p. 47–57.
60. Mauro, V.F., M.F. Bonfiglio, and A.L. Spunt, *Meperidine-induced seizure in a patient without renal dysfunction or sickle cell anemia.* Clinical Pharmacy, 1986. **5**(10): p. 837–839.
61. Bonfiglio, M.F. and V.F. Mauro, *Naloxone in the treatment of meperidine induced seizures.* Drug Intelligence and Clinical Pharmacy, 1987. **2**: p. 174–175.
62. Nickander, R., S.E. Smits, and M.I. Steinberg, *Propoxyphene and norpropoxyphene: pharmacologic and toxic effects in animals.* The Journal of Pharmacology and Experimental Therapeutics, 1977. **200**(1): p. 245–253.
63. Holland, D.R. and M.I. Steinberg, *Electrophysiologic properties of propoxyphene and norpropoxyphene in canine cardiac conducting tissues in vitro and in vivo.* Toxicology and Applied Pharmacology, 1979. **47**(1): p. 123–133.
64. Kaplan, J.L. and J.A. Marx, *Effectiveness and safety of intravenous nalmefene for emergency department patients with suspected narcotic overdose: a pilot study.* Annals of Emergency Medicine, 1993. **22**(2): p. 187–190.
65. Glass, P.S., R.M. Jhaveri, and L.R. Smith, *Comparison of potency and duration of action of nalmefene and naloxone.* Anesthesia and Analgesia, 1994. **78**(3): p. 536–541.
66. Martin, W.R., *Naloxone.* Annals of Internal Medicine, 1976. **85**(6): p. 765–768.
67. Greenberg, M.I., *The use of endotracheal medication in cardiac emergencies.* Resuscitation, 1984. **12**(3): p. 155–165.
68. Maio, R.F., B. Gaukel, and B. Freeman, *Intralingual naloxone injection for narcotic-induced respiratory depression.* Annals of Emergency Medicine, 1987. **16**(5): p. 572–573.
69. Kauffman, R.E., W.J. Banner, and J.L. Blumer, *Naloxone dosage and route of administration for infants and children.* Pediatrics, 1990. **86**: p. 484–485.
70. Tenenbein, M., *Continuous naloxone infusion for opiate poisoning in infancy.* The Journal of Pediatrics, 1984. **105**(4): p. 645–648.
71. Drake, J., et al., *Effect of food on the comparative pharmacokinetics of modified-release morphine tablet formulations: Oramorph SR and MST Continus.* British Journal of Clinical Pharmacology, 1996. **41**(5): p. 417–420.
72. Benziger, D.P., et al., *Differential effects of food on the bioavailability of controlled-release oxycodone tablets and immediate-release oxycodone solution.* Journal of Pharmaceutical Sciences, 1996. **85**(4): p. 407–410.
73. Gourlay, G.K., *Sustained relief of chronic pain. Pharmacokinetics of sustained release morphine.* Clinical Pharmacokinetics, 1998. **35**(3): p. 173–190.
74. Caruso, F.S., *MorphiDex pharmacokinetic studies and single-dose analgesic efficacy studies in patients with postoperative pain.* Journal of Pain and Symptom Management, 2000. **19**(1 Suppl): p. S31-36.

75. Raber, M., et al., *Pharmacokinetic properties of tramadol sustained release capsules. 2nd communication: investigation of relative bioavailability and food interaction.* Arzneimittel-Forschung, 1999. **49**(7): p. 5588–5593.
76. Manara, A.R., et al., *The effect of metoclopramide on the absorption of oral controlled release morphine.* British Journal of Clinical Pharmacology, 1988. **25**(4): p. 518–521.
77. Brinker, F., *Interactions of pharmaceutical and botanical medicines.* Journal of Naturopathic Medicine, 1997. **7**: p. 14–20.
78. Ventafridda, V., et al., *Antidepressants increase bioavailability of morphine in cancer patients.* Lancet, 1987. **1**(8543): p. 1204.
79. Levine, J.D., et al., *Desipramine enhances opiate postoperative analgesia.* Pain, 1986. **27**(1): p. 45–49.
80. Gordon, N.C., et al., *Temporal factors in the enhancement of morphine analgesia by desipramine.* Pain, 1993. **53**(3): p. 273–276.
81. Fialip, J., et al., *Pharmacokinetic patterns of repeated administration of antidepressants in animals. II. Their relevance in a study of the influence of clomipramine on morphine analgesia in mice.* The Journal of Pharmacology and Experimental Therapeutics, 1989. **248**(2): p. 747–751.
82. Vincent, J., et al., *The pharmacokinetic effects of coadministration of morphine and trovafloxacin in healthy subjects.* American Journal of Surgery, 1988. **176**: p. 32 S-38 S.
83. Laneury, J.P., et al., *Comparative bioavailability study of codeine and ibuprofen after administration of the two products alone or in association to 24 healthy volunteers.* European Journal of Drug Metabolism and Pharmacokinetics, 1998. **23**(2): p. 185–189.
84. Gourepitch, M.N., G.H. Friedland, and J. Sinai, *Interactions between methadone and medications used to treat HIV infection: a review.* Mount Sinai Journal of Medicine, 2000. **67**: p. 429–436.
85. Schwartz, E.L., et al., *Pharmacokinetic interactions of zidovudine and methadone in intravenous drug-using patients with HIV infection.* Journal of Acquired Immune Deficiency Syndromes, 1992. **5**(6): p. 619–626.
86. Rainey, P.M., et al., *Interaction of methadone with didanosine and stavudine.* Journal of Acquired Immune Deficiency Syndromes, 2000. **24**(3): p. 241–248.
87. Tong, T.G., et al., *Phenytoin-induced methadone withdrawal.* Annals of Internal Medicine, 1981. **94**(3): p. 349–351.
88. Bell, J., et al., *The use of serum methadone levels in patients receiving methadone maintenance.* Clinical Pharmacology and Therapeutics, 1988. **43**(6): p. 623–629.
89. Goodwin, F.L., et al., *Effects of naltrexone on the intake of ethanol and flavored solutions in rats.* Alcohol, 2001. **25**(1): p. 9–19.
90. Cushman, P.J., *Alcohol and opioids: possible interactions of clinical importance.* Advances in Alcohol Substance Abuse, 1987. **6**: p. 33–46.
91. Fromm, M.F., et al., *Loss of analgesic effect of morphine due to coadministration of rifampin.* Pain, 1997. **72**(1–2): p. 261–267.
92. Sorkin, E.M. and D.L. Darvey, *Review of cimetidine drug interactions.* Drug Intelligence and Clinical Pharmacy, 1983. **17**(2): p. 110–120.
93. Bertschy, G., et al., *Probable metabolic interaction between methadone and fluvoxamine in addict patients.* Therapeutic Drug Monitoring, 1994. **16**(1): p. 42–45.
94. De Maria, P.A. and R.D. Serota, *A therapeutic use of methadone fluvoxamine drug interaction.* Journal of Addictive Diseases, 1999. **18**: p. 5–12.
95. Caraco, Y., J. Sheller, and A.J. Wood, *Pharmacogenetic determination of the effects of codeine and prediction of drug interactions.* The Journal of Pharmacology and Experimental Therapeutics, 1996. **278**(3): p. 1165–1174.
96. Caraco, Y., J. Sheller, and A.J. Wood, *Impact of ethnic origin and quinidine coadministration on codeine's disposition and pharmacodynamic effects.* The Journal of Pharmacology and Experimental Therapeutics, 1999. **290**(1): p. 413–422.
97. Herr, K., et al., *Methadone, ciprofloxacine and adverse drug reactions.* Lancet, 2000. **356**: p. 2069–2070.

98. Oles, K.S., W. Mirza, and J.K. Penry, *Catastrophic neurologic signs due to drug interaction: Tegretol and Darvon.* Surgical Neurology, 1989. **32**(2): p. 144–151.
99. Ackerman, W.E., 3 rd, et al., *Effect of cigarette smoking on serum hydrocodone levels in chronic pain patients.* Journal of the Arkansas Medical Society, 2007. **104**(1): p. 19–21.
100. Watson, K.J., et al., *The oral contraceptive pill increases morphine clearance but does not increase hepatic blood flow.* Gastroenterology, 1986. **90**: p. 1779.
101. Pond, S.M. and K.M. Kretschzmar, *Effect of phenytoin on meperidine clearance and normeperidine formation.* Clinical Pharmacology and Therapeutics, 1981. **30**(5): p. 680–686.
102. Li, Y., et al., *Opiate effects on 5-fluorouracil disposition in mice.* Cancer Chemotherapy and Pharmacology, 1997. **39**(3): p. 273–277.
103. Hurwitz, A., M. Garty, and Z. Ben-Zvi, *Morphine effects on gentamicin disposition and toxicity in mice.* Toxicology and Applied Pharmacology, 1988. **93**(3): p. 413–420.
104. Nilsson, M.I., et al., *Effect of urinary pH on the disposition of methadone in man.* European Journal of Clinical Pharmacology, 1982. **22**(4): p. 337–342.
105. Lysakowski, C., et al., *Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia.* British Journal of Anaesthesia, 2001. **86**(4): p. 523–527.
106. Mertens, M.J., et al., *Propofol alters the pharmacokinetics of alfentanil in healthy male volunteers.* Anesthesiology, 2001. **94**(6): p. 949–957.
107. Zsigmond, E.K. and K. Flynn, *Effect of secobarbital and morphine on arterial blood gases in healthy human volunteers.* Journal of Clinical Pharmacology, 1993. **33**(5): p. 453–457.
108. Dundee, J.W., et al., *Pretreatment with opioids. The effect on thiopentone induction requirements and on the onset of action of midazolam.* Anaesthesia, 1986. **41**(2): p. 159–161.
109. Pick, C.G., *Antinociceptive interaction between alprazolam and opioids.* Brain Research Bulletin, 1997. **42**(3): p. 239–243.
110. Hamilton, S.P., et al., *The effect of sertraline on methadone plasma levels in methadone-maintenance patients.* The American Journal on Addictions, 2000. **9**(1): p. 63–69.
111. Stambaugh, J.E.J. and I.W. Wainer, *Drug interaction: meperidine and chlorpromazine, a toxic combination.* Journal of Clinical Pharmacology, 1981. **21**: p. 140–146.
112. Gaiardi, M., et al., *Modulation of the stimulus effects of morphine by d-amphetamine.* Pharmacology, Biochemistry, and Behavior, 1998. **59**(1): p. 249–253.
113. Braida, D., et al., *Conditioned place preference induced by the cannabinoid agonist CP 55,940: interaction with the opioid system.* Neuroscience, 2001. **104**(4): p. 923–926.
114. Massi, P., et al., *Comparative characterization in the rat of the interaction between cannabinoids and opiates for their immunosuppressive and analgesic effects.* Journal of Neuroimmunology, 2001. **117**(1–2): p. 116–124.
115. Rubino, T., et al., *Long-term treatment with SR141716A, the CB1 receptor antagonist, influences morphine withdrawal syndrome.* Life Sciences, 2000. **66**(22): p. 2213–2219.
116. Ambrosio, E., et al., *The neurobiology of cannabinoid dependence: sex differences and potential interactions between cannabinoid and opioid systems.* Life Sciences, 1999. **65**(6–7): p. 687–694.
117. Walsh, S.L., et al., *Enadoline and butorphanol: evaluation of kappa-agonists on cocaine pharmacodynamics and cocaine self-administration in humans.* The Journal of Pharmacology and Experimental Therapeutics, 2001. **299**(1): p. 147–158.
118. Hadorn, D.C., J.A. Anistranski, and J.D. Connor, *Influence of naloxone on the effects of LSD in monkeys.* Neuropharmacology, 1984. **23**(11): p. 1297–1300.
119. Bhargava, H.N., D.J. Yousif, and G.A. Matwyshyn, *Interactions of thyrotropin releasing hormone, its metabolites and analogues with endogenous and exogenous opiates.* General Pharmacology, 1983. **14**(6): p. 565–570.
120. Galina, Z.H. and Z. Amit, *Interactions between ACTH, morphine, and naloxone and their effects on locomotor behavior.* Progress in Neuro-Psychopharmacology & Biological Psychiatry, 1985. **9**(5–6): p. 691–695.
121. Zarrindast, M.R. and M. Mahmoudi, *GABA mechanisms and antinociception in mice with ligated sciatic nerve.* Pharmacology & Toxicology, 2001. **89**(2): p. 79–84.

122. Yesilyurt, O. and I.T. Uzbay, *Agmatine potentiates the analgesic effect of morphine by an alpha(2)-adrenoceptor-mediated mechanism in mice.* Neuropsychopharmacology, 2001. **25**: p. 98–103.
123. Morales, L., C. Perez-Garcia, and L.F. Alguacil, *Effects of yohimbine on the antinociceptive and place conditioning effects of opioid agonists in rodents.* British Journal of Pharmacology, 2001. **133**(1): p. 172–178.
124. Chan, S.H., *Differential effects of clonidine on pain, arterial blood pressure, and heart rate in the cat: lack of interactions with naloxone.* Experimental Neurology, 1984. **84**(2): p. 338–346.
125. Gordon, N.C., P.H. Heller, and J.D. Levine, *Enhancement of pentazocine analgesia by clonidine.* Pain, 1992. **48**(2): p. 167–169.
126. Ramaswamy, S., et al., *Effect of clonidine on the chronic morphine tolerance and on the sensitivity of the smooth muscles in mice.* Life Sciences, 1983. **33**(12): p. 1167–1172.
127. Warner-Smith, M., et al., *Heroin overdose: causes and consequences.* Addiction, 2001. **96**(8): p. 1113–1125.
128. Levine, B., D. Green, and J.E. Smialek, *The role of ethanol in heroin deaths.* Journal of Forensic Sciences, 1995. **40**(5): p. 808–810.
129. Ruttenber, A.J., H.D. Kalter, and P. Santinga, *The role of ethanol abuse in the etiology of heroin-related death.* Journal of Forensic Sciences, 1990. **35**(4): p. 891–900.
130. Hickman, M., et al., *Does alcohol increase the risk of overdose death: the need for a translational approach [see comment].* Addiction, 2008. **103**(7): p. 1060–2.
131. Shafer, D.A., et al. *Biogenetic effects of opiates.* The International Journal of the Addictions, 1990. **25**(1A): p. 1–18.
132. Parkin, S., *Somniferous poisons*, in *Textbook of Medical Jurisprudence and Toxicology*, S. Parkin, Editor. 1990, Livingstone: Edinburgh. p. 834–846.
133. Knight, B., *Deaths from narcotic and hallucinogenic drugs*, in *Forensic Pathology*, B. Knight, Editor. 2004, Arnold: London. p. 577–584
134. Schonwald, S., *Opiates*, in *Medical Toxicology – A Synopsis and Study Guides*, S. Schonwald, Editor. 2001, Williams and Wilkins: London. p. 201–230
135. Gillman, P.K., *Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity.* British Journal of Anaesthesia, 2005. **95**(4): p. 434–41.
136. Thompson, S.J., K. Koszdin, and C.M. Bernards, *Opiate-induced analgesia is increased and prolonged in mice lacking P-glycoprotein.* Anesthesiology, 2000. **92**(5): p. 1392–1399.
137. Sadeque, A.J., et al., *Increased drug delivery to the brain by P-glycoprotein inhibition.* Clinical Pharmacology and Therapeutics, 2000. **68**(3): p. 231–237.
138. Brase, D.A., et al., *Antagonism of the morphine-induced locomotor activation of mice by fructose: comparison with other opiates and sugars, and sugar effects on brain morphine.* Life Sciences, 1991. **49**(10): p. 727–734.
139. Gordon, N.C., et al., *Interactions between fluoxetine and opiate analgesia for postoperative dental pain.* Pain, 1994. **58**(1): p. 85–88.
140. Sastry, B.V., *Placental toxicology: tobacco smoke, abused drugs, multiple chemical interactions, and placental function.* Reproduction, Fertility, and Development, 1991. **3**(4): p. 355–372.
141. Takahashi, M. and S. Tokuyama, *Pharmacological and physiological effects of ginseng on actions induced by opioids and psychostimulants.* Methods and Findings in Experimental and Clinical Pharmacology, 1998. **20**(1): p. 77–84.
142. Mendelson, J., et al., *Buprenorphine and naloxone interactions in opiate-dependent volunteers.* Clinical Pharmacology and Therapeutics, 1996. **60**(1): p. 105–114.
143. Mendelson, J., et al., *Buprenorphine and naloxone interactions in methadone maintenance patients.* Biological Psychiatry, 1997. **41**(11): p. 1095–1101.
144. Mello, N.K., et al., *Buprenorphine treatment of opiate and cocaine abuse: clinical and preclinical studies.* Harvard Review of Psychiatry, 1993. **1**(3): p. 168–183.
145. Rosen, M.I., T.R. Kosten, and M.J. Kreek, *The effects of naltrexone maintenance on the response to yohimbine in healthy volunteers.* Biological Psychiatry, 1999. **45**(12): p. 1636–1645.

146. Savarialho-Kerc, U., M.J. Mattila, and T. Seppala, *Parenteral pentazocine: effects on psychomotor skills and respirations with amitryptiline.* European Journal of Clinical Pharmacology, 1988. **35**: p. 483–489.
147. Kozer, E., et al., *The effect of amitriptyline, gabapentin, and carbamazepine on morphine-induced hypercarbia in rabbits.* Anesthesia & Analgesia, 2008. **107**(4): p. 1216–22.
148. Havier, R.G. and R. Lin, *Deaths as a result of a combination of codeine and glutethimide.* Journal of Forensic Sciences, 1985. **30**(2): p. 563–566.
149. Gannon, R., W. Pearsall, and R. Rowley, *Isoniazid, meperidine, and hypotension.* Annals of Internal Medicine, 1983. **99**(3): p. 415.
150. Rang, S.T., J. Field, and C. Irving, *Serotonin toxicity caused by an interaction between fentanyl and paroxetine.* Canadian Journal of Anaesthesia, 2008. **55**(8): p. 521–5.
151. Wang, L.P., A.N. Miles, and S. Schug, *Tramadol and severe hypertension during anesthesia.* Journal of Neurosurgical Anesthesiology, 2008. **20**(1): p. 69.
152. Lotrich, F.E., J. Rosen, and B.G. Pollock, *Dextromethorphan-induced delirium and possible methadone interaction.* American Journal Geriatric Pharmacotherapy, 2005. **3**(1): p. 17–20.

Chapter 5
Tricyclic Antidepressant Drug Interactions

Jeffrey P. Walterscheid and Terry J. Danielson

Abstract Depression is a common ailment in modern society, and drug intervention will continue to be a major mechanism in its control. Although selective serotonin reuptake inhibitors (SSRIs) have largely replaced TCAs in managing anxiety and dysphoria, TCAs still offer a cost-effective treatment for chronic pain therapy. Durable clinical responses are seen in those unresponsive to SSRI treatment, and many thousands of people have benefited from this class of drugs. However, their use does carry a risk of severe drug interactions and toxicities. This work provides a detailed background of the biological functions of TCAs, their clinical uses, toxicities, drug interactions, and tolerances based on pharmacogenetics. Some of the interactions may appear small in comparison to a broad range of therapeutic concentrations, but effects in a single patient can be dramatic. Therefore, this chapter should provide a basis for understanding and interpreting the toxic interactions of tricyclic antidepressants.

Keywords Tricyclic antidepressants • Metabolism • Interactions • Pharmacogenetics

Introduction

Depression is a mood disorder characterized as a range of feelings from extraordinary sadness, despair, and lethargy to intense anxiety, stress, and irritability. Apart from psychotherapy and environmental changes, drug therapy is the cornerstone of symptom management. Treatment of this disability typically involves the use of drugs such as monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants

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(TCAs), selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and psychostimulants. These drugs have multiple pharmacological and toxicological properties capable of producing severe side effects alone or in combination with other therapeutic agents.

The use of tricyclic antidepressants began during the 1950s, giving rise to the field of psychopharmacology. The first phenothiazine analog was an antihistaminic derivative that came to be known as chlorpromazine [1]. Its efficacy spurred the development of other derivatives, and led to the discovery of imipramine [2]. Initially, imipramine was evaluated as a treatment for psychotic disorders, but it actually exacerbated psychosis [3–5]. However, its antidepressant qualities were unsurpassed by other current antidepressants.

For many years, prior to the development of SSRIs, TCAs and MAOIs were the main drugs of choice having established their clinical efficacy among well-managed patients who were unresponsive to other therapies. In recent years, SSRIs have become a popular choice in the management of depressive illness because of the comparative infrequency and mildness of side effects during their use. However, some practitioners still prefer TCAs because of their lower cost, familiarity with pharmacological actions, and contextually beneficial side effects in managing chronic pain syndromes [6–8].

The most commonly prescribed tricyclic antidepressants include amitriptyline, desipramine, imipramine, nortriptyline, doxepin, and clomipramine. TCAs have a narrow therapeutic window, which increases their likelihood for toxicity. Recent surveys suggest that approximately 80% of fatal antidepressant intoxications involve TCAs [9–15]. Regardless of presentation, overdose by tricyclic antidepressants represents a serious medical crisis further magnified by the fact that the majority of self-poisonings occur while at home alone, without the benefit of supportive intervention [10, 13]. Even with the increased use of less toxic SSRIs, TCAs are frequently encountered in emergency rooms and postmortem toxicology.

Mechanism of Action

It is generally thought that tricyclic antidepressants work by inhibiting the neuronal reuptake of norepinephrine and serotonin neurotransmitters. Tricyclics are also competitive antagonists for muscarinic and histamine H1 receptors, while the dopamine system is nearly spared of their action [16]. Symptoms such as sedation, blurred vision, dry mouth, and urinary retention appear to be related to the antihistamine and antimuscarinic actions [17–19]. Hypotension is also closely related to antimuscarinic properties with changes in cardiac output due to alpha-adrenergic antagonism [17]. Despite their rapid absorption, depressive symptoms generally do not respond until at least 2–4 weeks of compliant therapy.

The chemical structures of five common TCAs, plus cyclobenzaprine and carbamazepine, are shown in Fig. 5.1. The latter compounds emphasize structural features that are important in retaining pharmacological activity. The C-5 double bond

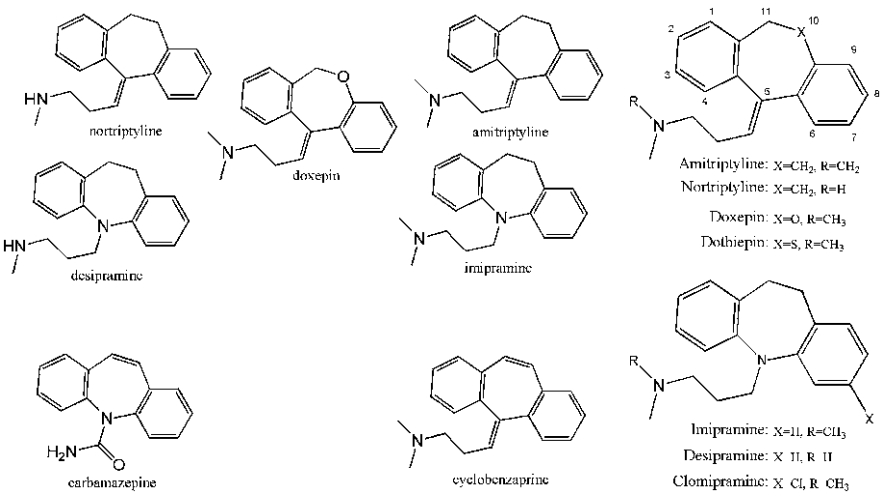

Fig. 5.1 Structural comparisons of the most common TCAs

in amitriptyline introduces a plane of symmetry which passes through C-5 and the C-10, C-11 bond of the molecule. Analogs or metabolites of amitriptyline become isomers through the introduction of C-10 hydroxylations, giving rise to *cis* or *Z* and *trans* or *E* with respect to the geometry of the ethylamino aliphatic chain. Subsequently, this type of isomerism exists with amitriptyline, nortriptyline, and doxepin, but is absent for all others because of unrestricted bond rotation. This distinction is important since *E* and *Z* isomers do contribute to treatment efficacy and can predict clinical outcome [20].

Other changes in the dibenzocycloheptane ring and side chain can dramatically alter the pharmacological properties of a TCA analog. Useful antidepressant activity is lost after dehydrogenation of the C-10, C-11 ethyl bridge. This alteration differentiates the identity between cyclobenzaprine and amitriptyline, where cyclobenzaprine is clinically more useful as a centrally acting muscle relaxant. In comparison, carbamazepine contains the C-10, C-11 unsaturation, but modifications at the C-5 side chain abolish both antidepressant and anticholinergic activities [21].

Pharmacokinetics

Absorption and Distribution

Tricyclic antidepressants are rapidly absorbed in the gastrointestinal tract and undergo first-pass metabolism in the liver. They are rather lipophilic and highly protein-bound, leading to large volumes of distribution (Table 5.1):

Table 5.1 Pharmacokinetic properties of tricyclic antidepressants. TCAs tend to have a relatively long half-life, large volume of distribution, strongly bound to plasma proteins, and high pKa due to basic nitrogen functional groups

Drug	$T_{1/2}$ (h)	Vd (L/kg)	Fb	pK_a
Amitriptyline	8–51	6–10	0.94	9.4
Nortriptyline	15–90	20–57	0.95	9.7
Protriptyline	54–92	15–31	0.92	8.2
Imipramine	6–20	20–40	0.80–0.95	9.5
Desipramine	12–54	22–59	0.70–0.90	9.5
Trimipramine	16–39	17–48	0.95	7.7
Amoxapine	8–33	–	0.90	–
Doxepin	8–25	9–33	0.76	8.0
Clomipramine	12–36	17	0.96	9.5
Cyclobenzaprine	24–72	–	0.97	8.5

Data compiled from Baselt [22]

Metabolism

TCAs are extensively metabolized by at least five CYP450 isoforms into *N*-desmethyl and 2- or 10-hydroxylated derivatives. These enzymes are the well-known CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 subtypes [23–31]. Ghahramani et al. studied amitriptyline metabolism in human liver microsomes over a concentration range from 1 to 500 μM (250–12,500 ng/mL) and showed that the *N*-demethylation of amitriptyline primarily involved CYP3A4, CYP2C9, and CYP2D6 [24]. However, studies with imipramine at more clinically relevant levels near 500 ng/mL showed that CYP2C19 was the major participant in generating desipramine. CYP2D6, with a minor contribution from CYP2C19, was the major catalyst of 2-hydroxylation [26].

Figure 5.2 illustrates the common metabolic transformations encountered by imipramine and amitriptyline. Similar reactions are observed with each of the other TCAs [32]. As a group, TCAs are subjected to *N*-demethylation and hydroxylation reactions to become mono-*N*-desmethyl homologues. These demethylated homologues accumulate in plasma and tissues, yet retain potent pharmacological properties of the parent drug. In fact, the mono-*N*-demethylated metabolites of amitriptyline and imipramine are known as nortriptyline and desipramine, which are marketed in their own right as antidepressant drugs [32].

Hydroxylation followed by conjugation represents the principal metabolic route for elimination of TCAs. In addition, the 10-hydroxy metabolites of TCAs and their desalkyl homologues appear to contribute to treatment efficacy. For example, clinicians have observed a perceptible antidepressant response among patients treated with *E*-10-hydroxynortriptyline [33], but a superior clinical outcome was measured in patients favoring higher plasma levels of amitriptyline and *Z*-10-hydroxy metabolites in comparison to patients favoring formation of nortriptyline and *E*-10-hydroxy metabolites [20].

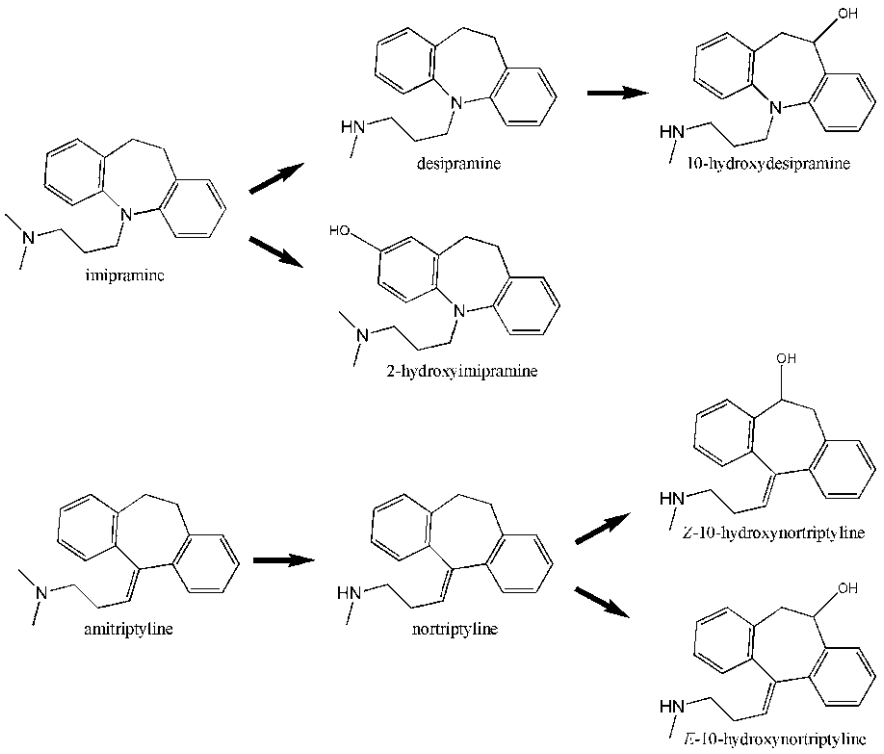

Fig. 5.2 Imipramine, amitriptyline, and their active metabolites

Elimination

Less than 1% of a typical TCA dose is recovered in the urine as unchanged drug [34–37]. However, TCAs have long elimination half-lives that often exceed 24 h, up to 51 h in the case of amitriptyline [38]. In an overdose, altered pharmacokinetics may prolong elimination and increase toxic effects, likely due to the anticholinergic effects of delayed gastric emptying. Additionally, the acidosis that results from respiratory depression and hypotension reduces protein binding, which can result in higher serum levels of active free drug. There is little evidence that hydroxylated metabolites accumulate in blood or tissue, so their overall contribution to toxicity may be minor. Although hydroxylated TCA metabolites appear to possess toxic properties, they are eliminated from the body more rapidly than the non-hydroxylated TCA [39].

Toxicity

Tricyclic antidepressants differ in their relative effects on serotonin, norepinephrine, and acetylcholine. Many of the observed side effects are related to antimuscarinic activity, which manifests as dry mouth, blurred vision, constipation, urinary retention, hyperthermia, orthostatic hypotension, and tachycardia. The most serious adverse effects of TCAs are due to central nervous system impairment, seizures, and cardiovascular instability [40]. Suppressed mental status is generally caused by antihistamine and anticholinergic activities, while life-threatening cardiovascular complications result from fast sodium channel blockade. Profound hypotension can also occur, which is primarily attributed to vasodilatation caused by alpha-adrenergic antagonism [41]. Other studies also indicate that central nervous system symptoms can occur as the sole manifestation of TCA overdose [42]. In a small number of cases, involvement of other organs has also been observed [43].

Antidepressant treatment efficacy is greatest when the combined serum levels of amitriptyline and its metabolite nortriptyline range between 100 and 200 ng/mL [44]. Other studies suggest that levels of imipramine near 180 ng/mL [45] or in a range between 200 and 300 ng/mL were consistent with a good clinical response [46, 47]. In contrast, combined levels of parent TCAs plus their major active metabolites at concentrations greater than 500 ng/mL have been associated with clinical signs of overdose and toxicity [41]. Furthermore, combined levels approaching 1,000 ng/mL have been associated with severe toxicity [48–51]. These findings suggest there is only a three- to four-fold difference between therapeutic and toxic amounts in blood.

There are many factors that influence the treatment and outcome of a TCA overdose. From treating symptoms to managing emerging conditions, the following studies are indicated in a TCA overdose with emphasis on the latter three in a postmortem examination:

- Arterial blood gas (ABG): TCA toxicity usually results in mixed acidosis due to respiratory depression and hypotension, which results in increased lactate production. Acidemia decreases protein binding and increases plasma levels of free drug. Therefore, treatment with sodium bicarbonate is part of the primary therapy [52].
- Electrocardiography (ECG): The most common ECG finding in TCA intoxication is sinus tachycardia. Other ECG changes include prolongation of the PR, QRS, and QT intervals, atrioventricular blocks, ventricular extrasystole, and Brugada pattern ST elevations evident of calcium channel blockade [53].
- Renal function: TCA metabolites are renally eliminated after hepatic metabolism. Elevated creatinine and urea nitrogen levels indicate impaired renal function. Since many of these metabolites retain pharmacological activity, reduced excretion may prolong or exacerbate intoxication.
- Electrolytes: Hypokalemia frequently occurs because of increased catecholamine receptor stimulation secondary to norepinephrine reuptake inhibition.

- Urine drug screen (UDS): It is always a good idea to check serum acetaminophen levels along with other potential co-ingestants such as ethanol, aspirin, and other prescribed or illicit drugs that can explain the clinical presentation.
- TCA level: TCA levels are not likely to be helpful in the immediate treatment of an overdose, since levels do not necessarily correlate with toxic effects. This can be attributed to the large volume of distribution TCAs, where tissue levels are often much higher than serum levels of free drug. In addition, quetiapine has been shown to cause false-positive readings by immunoassay [54].

Central Nervous System Toxicity

One of the hallmarks of TCA toxicity is altered mental status. These symptoms can range from confusion, agitation, delirium, and hallucinations, to drowsiness, seizures, and coma following a serious TCA overdose. The culmination of hypoventilation and coma can lead to respiratory arrest without intervention. Comas usually resolve within 24 h, but only with airway support provided by endotracheal intubation. In the event that a coma does not reverse itself within that time frame, other etiologies should be investigated to rule out head trauma or the ingestion of other toxins.

Seizures can be associated with increased mortality and have been witnessed to occur immediately before cardiac arrest. Seizures secondary to TCA toxicity are generally self-limiting, but should be treated to counteract the acidosis produced by vigorous muscle contractions and hypoxia from impaired ventilation. Myoclonic jerking may precede or mimic seizure activity. Myoclonus is a relatively benign muscle contraction of the extremities that can be mistaken for seizure activity. One of the distinguishing factors about myoclonus is that the patient rarely loses consciousness.

Cardiotoxicity

Although their use as antidepressants may be declining, TCAs are increasingly being applied as alternative analgesics in a variety of pain management settings [55–60]. Dosages in these applications are less than doses required for antidepressant actions and generally do not result in significant cardiac effects [61]. However, a TCA overdose is a serious condition that is becoming progressively more common. Serious arrhythmias and intracardiac blocks have been reported on therapeutic doses [62, 63].

As mentioned earlier, sodium bicarbonate therapy is a key treatment for TCA-induced conduction disturbances, ventricular arrhythmias, and hypotension. Restoration of physiological pH appears to uncouple TCA toxicity from myocardial

sodium channels, and the increased extracellular sodium concentration improves the gradient across the channel [64]. Supportive measures are all that is generally needed for mild poisoning. Moderate and severe overdoses will require respiratory support, anticonvulsants, physostigmine, beta-blockers, cardioversion, or even pacing may be necessary [65].

Tricyclic antidepressant toxicity is often characterized by a prolonged QT interval (cardiac depolarization–repolarization) associated with sodium/potassium ion channel blockade [66–68]. Other substances acting on these channels might be expected to enhance this aspect of TCA toxicity [63, 69]. QT prolongation is a relatively common consequence of therapy with psychotropic drugs, and single or combined use may have a deleterious effect on cardiac conductance [63, 70, 71]. Many of these drugs can occur simultaneously in fatal poisonings, possibly at concentrations not generally regarded as lethal.

There is a close association between a prolonged QT interval, the development of more severe arrhythmias, and sudden cardiac death. For example, introduction of dromperidol resulted in torsades de pointes in a patient previously treated with cyclobenzaprine and fluoxetine who was already displaying a prolonged QT interval [72]. In a second case, QTc prolongation developed in a patient being treated with levofloxacin, imipramine, and fluoxetine [73].

It is generally considered that widening of the QRS complex is associated with the development of seizures and arrhythmias, whereas patients with a QRS of less than 100 ms are unlikely to develop seizures and arrhythmias. A recent meta-analysis of prognostic indicators to predict seizures, arrhythmias, and death in TCA overdose found that the sensitivity and specificity of serum TCA concentration to predict ventricular arrhythmias were 0.78 (95% confidence interval [CI], 0.56–0.9) and 0.57 (95% CI, 0.46–0.67), respectively. The sensitivity and specificity of cyclic antidepressant concentration to predict death were 0.76 (95% CI, 0.49–0.91) and 0.6 (95% CI, 0.47–0.72), respectively [74]. In the context of TCA poisoning, QRS widening is not an accurate indicator of these risks [75].

The potential role of hydroxylated TCA metabolites in cardiac toxicity has also been studied in animals. In these experiments, 2-hydroxyimipramine produced a significantly greater incidence of life-threatening arrhythmias than imipramine itself [76]. In comparison, E-10-hydroxynortriptyline produced fewer cardiac arrhythmias than nortriptyline or Z-10-hydroxynortriptyline [77].

Discontinuation Syndrome

Those who receive selective serotonin reuptake inhibitor antidepressants (SSRIs) and dual-action antidepressants (DAAs) for their symptoms of depression are at risk for a well-documented withdrawal syndrome if they abruptly stop their medication [78]. This withdrawal syndrome may produce significant effects that may impair a person's ability to drive, putting at risk both the driver and others on the road [79]. In a situation of the antidepressant withdrawal syndrome, the impairment is due to

the absence of drugs in the patient, producing the paradox of a potentially impaired driver because of an absence of the influence of a drug.

The withdrawal syndrome from tricyclic antidepressants is primarily a cholinergic syndrome with symptoms such as nausea, vomiting, anorexia, diarrhea, rhinorrhea (runny nose), diaphoresis (excessive sweating), myalgias (muscle pain), increased anxiety, agitation, and sleep disturbances [80]. In contrast, the withdrawal syndrome from the SSRIs and DAAs is primarily a serotonergic syndrome, with symptoms such as dizziness, lethargy, impaired concentration, electric-like shock sensations, impaired coordination, blurred vision, and sleep disturbances.

There are a number of symptoms of the withdrawal syndrome that could potentially cause a patient to operate a motor vehicle in a manner that might be interpreted as operating under the influence of alcohol or drugs. These symptoms include visual disturbances, dizziness/vertigo, impaired coordination, tremors, confusion, impaired concentration, and nystagmus that cause difficulty with tracking and memory impairment [81]. These clinical effects might produce an altered driving pattern, including weaving, variable speed, and erratic lane changes, which might be interpreted as driving while intoxicated.

Drug Interactions

Tricyclic antidepressants are highly metabolized by several cytochrome P450 hepatic enzymes. As mentioned before in the section on metabolism, the two principal enzymes involved in TCA modifications are CYP2D6 and CYP2C19. Drugs that inhibit these enzymes may decrease TCA metabolism, thus prolonging parent concentrations and their accompanying toxicities. TCAs also magnify the effects of alcohol, barbiturates, and other CNS depressants. The observed toxicity can also be enhanced by any other drugs that contribute to antimuscarinic properties and their unpleasant clinical side effects.

Anticoagulants

Although there are no known interactions between common anticoagulants such as argatroban, ticlopidine, prasugrel, clopidogrel, warfarin, and TCAs [82], the potential for interactions does exist. One example of this possibility is ticlopidine, which is a potent inhibitor of CYP2D6 and CYP2C19 [83–86]. As of yet, there is no evidence of an interaction between a ticlopidine and a TCA. However, known interactions between ticlopidine and the anticonvulsant phenytoin may serve as examples. Phenytoin is metabolized predominantly by CYP2C9 and CYP2C19 isoforms. When combined with ticlopidine, phenytoin concentrations were seen to reach dangerously elevated levels. In addition, since inhibition by ticlopidine may be mechanism based, which permanently inactivates the metabolizing enzyme, inhibition may be long term [84, 85].

Antibiotics, Antifungals, Antivirals

In vivo studies have shown that terbinafine is an inhibitor of the CYP450 2D6 isozyme. Coadministration of terbinafine with drugs that are primarily metabolized by the CYP450 2D6 isozyme (e.g., TCAs, selective serotonin reuptake inhibitors, beta-blockers, and monoamine oxidase inhibitors Type B) should be done with careful monitoring and may require dose reductions. In a study to assess the effects of terbinafine on desipramine in healthy volunteers characterized as normal metabolizers, the administration of terbinafine resulted in a twofold increase in C_{max} and a fivefold increase in AUC. In this study, these effects were shown to persist at the last observation at 4 weeks after discontinuation of terbinafine [87].

Fluconazole is known to cause long QT syndrome and has interactions with amitriptyline [88–91]. Quinoline antibiotics such as ciprofloxacin, ofloxacin, moxifloxacin, gemifloxacin, levofloxacin, and norfloxacin are inhibitors of CYP1A2 and CYP2D6, which moderately contribute to TCA metabolism. Therefore, it is possible to witness a clinically significant rise in TCA levels when used in combination.

Antiviral therapy for the management of herpes zoster outbreaks usually relies on chronic application of acyclovir, valacyclovir, or famciclovir. These compounds do not seem to interfere with tricyclic antidepressants, and are safe to use in combination. In addition, TCAs offer some collateral benefits by alleviating the pain associated with postherpetic neuralgia [92, 93].

Anticonvulsants

The incidence of other prescription drug effects on the metabolism of amitriptyline and nortriptyline has been assessed through the analysis of drug levels on several thousands of patients [94]. These studies revealed that patients also treated with carbamazepine have a 60% reduction in the amounts of parent and demethylated TCA in comparison to patients treated with TCA alone [95–97]. These effects by carbamazepine on TCA metabolism appear to be mediated through induction of CYP1A2 and CYP3A4 enzymes [31, 98]. By most standards, the blood concentrations of parent TCA plus demethylated metabolites in these patients might be seen as subtherapeutic, although the clinical response may be increased.

These contradictory observations of lowered levels and increased clinical efficacy appear related to changes in the amount of drug available for pharmacological action. Under normal circumstances, greater than 95% of a TCA is bound to plasma protein and the pharmacological response is related to the smaller 5% unbound fraction. Some evidence suggests that carbamazepine acts to reduce binding of the TCA to plasma protein and thereby increases the amount of free drug available for pharmacological effect. Attempts to adjust the TCA dosage to obtain amounts in blood within a “therapeutic window” may not be necessary or even prudent.

Other compounds, such as gabapentin and pregabalin, are safe choices since they do not have overlapping receptor targets or interfering metabolism pathways.

The coadministration of these agents with a TCA is encouraged, particularly in treating the neuropathic pain associated with cancer chemotherapy. In this manner, pain management can be addressed while limiting the TCA dose and its unpleasant anticholinergic effects [99].

As mentioned before, phenytoin is contraindicated in combination with TCAs since they interfere with CYP2C19-catalyzed phenytoin hydroxylation. Likewise, phenytoin interferes with CYP2C19 hydroxylation of TCAs, which promotes a longer serum half-life. As proven by in vitro studies with human liver microsomes expressing chosen P450 enzymes, amitriptyline and imipramine strongly and competitively inhibit this reaction, while nortriptyline and desipramine give the least effect [100]. Since phenytoin also blocks sodium channels and may exacerbate or cause dysrhythmias in a patient with TCA poisoning, it is not recommended for seizure control.

Alcohol

Amitriptyline and ethanol have clinically important interactions, since ethanol blocks the antidepressant action of tricyclic antidepressants but increases their sedative effects. Ethanol can double the amount of unbound amitriptyline, yet simultaneously reduce hepatic clearance [101]. These pharmacodynamic interactions increase the toxicity of the combination and enhance the deleterious effects on motor skills. This often manifests as increased mean postural sway and reduced short-term memory. Ethanol has also been shown to increase the cardiotoxic effects of imipramine and amitriptyline [102].

Opiates

Clinical depression is more common among methadone maintenance patients than in the general population [103]. Amitriptyline is frequently encountered in these patients either as a therapeutic agent or as a recreational drug of abuse [104]. Levomethadyl acetate has been associated with a prolonged QT interval and torsades de pointes [105], where methadone appears to inhibit the cardiac potassium channel IKr [106, 107]. In these patients, exposure to a tricyclic antidepressant has been associated with an increased risk of an accidental overdose death [108]. Therefore, practitioners suggest that routine cardiac monitoring is necessary in methadone maintenance programs.

Neuroleptics

Recent studies support the common belief that cardiovascular mortality is greater among psychiatric patients receiving neuroleptics than in the general population

[109, 110]. Other evidence suggests that the risk cardiotoxicity may be greater with thioridazine than other neuroleptics [111] and that cardiac effects such as delayed ventricular repolarization are dose related and due predominantly to unmetabolized thioridazine [112].

In a rodent model, treatment with imipramine or amitriptyline increased the blood plasma levels of thioridazine and its metabolites 20- and 30-fold, respectively [113]. These authors noted that the TCA/thioridazine concentration ratio was important in determining the final result of the TCA/neuroleptic interaction. This is consistent with the observations in psychiatric patients that the effect of thioridazine or amitriptyline metabolism varied with the antidepressant/neuroleptic dose ratio. When the ratio favored amitriptyline, thioridazine metabolism was inhibited. When the ratio favored thioridazine, amitriptyline metabolism was inhibited.

SSRIs, SNRIs

Crewe et al. reported that several of the SSRI antidepressant drugs inhibited CYP2D6-catalyzed metabolism [114]. They observed that paroxetine had the greatest inhibitory effect while fluvoxamine contributed the least. Fluoxetine and sertraline had intermediate activities. They also observed that *N*-desmethylfluoxetine was a potent inhibitor, while metabolites of paroxetine caused negligible inhibition [115, 116]. Since *N*-desmethylfluoxetine is a potent inhibitor of CYP2D6 activity and persists in blood, inhibition of TCA hydroxylation in clinical settings may be more significant after fluoxetine than any other SSRI.

Combined treatments with a TCA and fluoxetine have also been examined in refractory depression. In patients treated with 50 mg/day amitriptyline and 20 mg/day fluoxetine for extended periods, the steady-state concentration of amitriptyline in blood was increased approximately two-fold and that of nortriptyline nine-fold, relative to patients treated with amitriptyline alone [117]. By comparison, 20 mg/day paroxetine increased amitriptyline and imipramine by only 50% and doubled the concentrations of nortriptyline and desipramine [118]. However, fatalities have been associated with combined fluoxetine/amitriptyline and paroxetine/imipramine combination therapies [119, 120].

The effects of the SSRI on the pharmacokinetics of the demethylated TCAs desipramine and nortriptyline have also been examined in clinical settings. For example, 20 mg/day fluoxetine or 50 mg/day sertraline was coadministered with 50 mg/day desipramine [121]. After 3 weeks of combined treatment, fluoxetine increased the levels of desipramine by four-fold while sertraline increased levels by only 31%. Inhibitory effects of paroxetine and sertraline on desipramine pharmacokinetics have also been compared [122]. Each of these reports again supports the original assignment of relative inhibitory actions decreasing in the order: fluoxetine > paroxetine > sertraline. Citalopram and venlafaxine either do not appear to inhibit CYP450 metabolism or have only very modest clinical impacts [123, 124].

The results of these mixed antidepressant studies are consistent with the presence of demethylation and hydroxylation metabolic pathways, which are utilized in TCA metabolism. Olesen and Linnet have estimated that 90% of nortriptyline metabolism is dependent on CYP2D6 hydroxylation activity [28]. Subsequently, a higher affinity SSRI explains how these drug interactions inhibit TCA hydroxylations as the rate-determining step in the overall elimination process. Therefore, inhibition of TCA hydroxylation by SSRI results in accumulation of the parent TCA and its *N*-desmethylated metabolite.

The interaction between TCAs and the predominant demethylating enzyme, CYP2C19, is less studied because highly potent and selective inhibitors are currently unavailable. However, the SSRI drug fluvoxamine is a potent inhibitor of CYP1A2 and also a moderately potent inhibitor of CYP2C19 [28]. Since desipramine metabolism by CYP1A2 is slight, fluvoxamine may act as a relatively specific inhibitor of metabolism by the CYP2C19 enzyme.

Genetic Polymorphism and TCA Metabolism

A review of the literature suggests that individuals vary in their abilities to metabolize TCAs due to genetic variations. This phenomenon can result in the amounts of active antidepressant in blood to vary beyond the concentration ranges associated with the clinical antidepressant responses, without metabolic inhibition of coadministered drugs. Individuals with differences in the distribution of CYP2C19 and CYP2D6 also play important roles in determining their ability to metabolize TCAs and their susceptibility in accumulating toxic concentrations [125, 126]. This unambiguous demonstration of the involvement of a CYP450 enzyme in the metabolism of TCAs sparked a new path in understanding drug interactions and the contribution of genetic differences in responses to TCAs.

These revelations raised the question: Are genetic polymorphisms and CYP450 interactions with other drugs significant factors in the toxicology of TCAs? Patient phenotype has been seen to play an important role in determining the pharmacokinetic interactions between TCAs and other drugs that interfere with CYP450-catalyzed metabolism. The interaction between TCAs and SSRIs is greatest in individuals from the “ultra-rapid metabolizer” (UM) and “extensive metabolizer” (EM) phenotypes where the CYP2D6 gene may be duplicated or multi-duplicated [127, 128], while TCA metabolism by patients from the “intermediate metabolizer” (IM) or “poor metabolizer” (PM) phenotypes is largely unaffected [129]. The lack of an inhibitory effect in PM subjects is due to a lack of CYP2D6 enzyme activity, which illustrates that TCAs are metabolized through alternative routes in these subjects.

A clinical application has been proposed for the interaction between the TCA and SSRI [130]. Clinical experience has shown that patients in the CYP2D6 UM phenotype may require larger doses of a TCA to maintain therapeutically useful concentrations in plasma. In clinical trials, treatment with 10 mg/day paroxetine

produced an apparent conversion from UM to EM status, where four out of five subjects achieved therapeutic levels of nortriptyline. After a higher dose of paroxetine of 20 mg/day, two subjects converted to PM status. This conversion to PM status illustrates the variability in responses to inhibitors such as paroxetine and further supports the implementation of therapeutic drug monitoring.

The "thioridazine effect" on TCA metabolism exhibited a complex dose dependency and was greatest after low doses of TCA and high doses of the neuroleptic. Treatments with thioridazine have been shown to convert CYP2D6 EM phenotype patients to the PM phenotype [131, 132]. In one instance, coadministration of thioridazine in a pediatric patient was seen to push blood concentrations of imipramine into a toxic range [133].

The frequency of PM follows strong ethnic lines [134, 135]. In a group of unrelated German volunteers, Sachse et al. reported three main alleles, CYP2D6*1 (EM), CYP2D6*2 (IM), and CYP2D6*4 (PM). Frequencies of these alleles were 0.36, 0.32, and 0.21, respectively [136]. Approximately 7% of the population were in the PM genotype, while 0.5% had multiple copies of the CYP2D6*1 allele (UM). In other studies, 5.5% of Dutch volunteers were poor metabolizers [137], while only 1–2% of subjects tested in Turkey and East and South Africa were of the PM phenotype [138, 139]. Less than 1% of a group of 216 black Tanzanians were PM but 9% exhibited allele duplication consistent with UM status [140]. Asian populations also have a low CYP2D6 PM frequency but, because of a high incidence of defective alleles of intermediate efficiency, the CYP2D6 metabolic capability of the Asian EM phenotype is somewhat lower than in other parts of the world.

These observations suggest a Northern European bias toward the CYP2D6 PM phenotype which may explain the metabolism of TCAs in some patients. For example, 8% of a group of Swedish Caucasians were found to have reduced abilities to hydroxylate the CYP2D6-sensitive drugs debrisoquine and desipramine [141]. In the Danish population, there is a reported instance of a PM phenotype Danish woman who developed toxic serum levels after successive treatments with 100 mg/day of nortriptyline. After adjusting the dosage to 25 mg/day, the woman's depression disappeared without any notable side effects [126].

The effects of CYP2D6 and CYP2C19 phenotype on TCA metabolism have been examined in several clinical studies involving Chinese or Japanese subjects because of the higher frequency of the CYP2D6*10 and CYP2C19 PM phenotypes in the Asian population. The CP2D6*10 (IM) allele occurs in approximately 34% of the Asian population, which encodes for an enzyme with reduced metabolic activity. In one study, the pharmacokinetics of nortriptyline and 10-hydroxynortriptyline were compared among subjects homozygous for CYP2D6*1 and CYP2D6*10 or heterozygous for these two alleles as CYP2D6*1*10 [142]. The study showed that the CYP2D6*10 homozygous subjects had impaired nortriptyline metabolism, resulting in a prolonged plasma half-life. Two additional studies examined the impact of CYP2D6 genotype on nortriptyline and desipramine metabolism, which showed a two-fold reduction in the rate of hydroxylation in those with one or two defective alleles [143, 144].

Examination of the effects of CYP2C19 PM status on the metabolism of the TCA is less common. In three studies, subjects homozygous for defective

CYP2C19 alleles had approximately double the plasma concentrations of imipramine or clomipramine as did the members of the homozygous EM phenotype [145, 146].

Postmortem TCA Evaluations

It is clear that individual patients are more or less responsive to the beneficial and toxic effects of TCAs. Amounts of TCA in plasma from living patients can cover a rather broad range greater than the clinical to toxic range in any individual patient. In postmortem cases, amounts of a TCA in blood occur in a broad range and are often several times higher than normally seen in living or even severely intoxicated people [147–149].

Pounder and Jones studied this phenomenon of postmortem redistribution and observed diffusion of drugs along a concentration gradient out of solid organs and into the blood [150]. The highest levels were seen in pulmonary arteries and veins, while concentrations were at their lowest in peripheral vessels. They reported that amounts of doxepin or clomipramine in postmortem blood collected from different sites ranged from 3.6 to 12.5 mg/L and from 4.0 to 21.5 mg/L, respectively.

The consequence of postmortem redistribution is that reference data is rendered less useful unless a record of the site of collection is available. It is therefore common practice to assay the TCA in blood collected from different peripheral vascular sites, the stomach contents, and the liver, in order to receive enough data for a correct interpretation. Sudden cardiac deaths due to simultaneous exposure to a TCA and a second cardiotoxic agent are not easily recognized because the drug levels may be below the accepted lethal levels. Nevertheless, this scenario is entirely possible and should be considered in cases where the drugs are present and other causes cannot be identified.

Conclusion

In recent years, less toxic SSRIs have largely replaced TCAs in managing anxiety and depression. Tricyclic antidepressant drug intervention is still widely used in controlling depression and as a cost-effective treatment for chronic pain therapy. Durable clinical responses are seen in those unresponsive to SSRI treatment, and many thousands of people have benefited from this class of drugs. However, their use does carry a risk of severe drug interactions and toxicities. This work examined a detailed background of the biological functions of TCAs, their clinical uses, toxicities, drug interactions, and tolerances based on pharmacogenetics. Some of the interactions may appear small in comparison to a broad range of therapeutic concentrations, but effects in a single patient can be dramatic. Therefore, this chapter provides a basis for understanding and interpreting the toxic interactions of tricyclic antidepressants.

References

1. Flugel, F. 1954. [Experiences with chlorpromazine in the psychiatric and neurological clinic.]. *Langenbecks Arch Klin Chir Ver Dtsch Z Chir* 279:767–772.
2. Azima, H., and R. H. Vispo. 1958. Imipramine; a potent new anti-depressant compound. *Am J Psychiatry* 115:245–246.
3. Bastecky, J., and A. Janik. 1963. [Mania-Like Syndrome after Tofranil.]. *Bratisl Lek Listy* 2:602–609.
4. Cahill, C. A. 1961. Post-thyroidectomy psychosis treated with imipramine. *Am J Psychiatry* 117:837–838.
5. Gol'Denberg, M. A. 1962. [Induction of "psychopathological" syndromes in animals related to tofranil poisoning.]. *Zh Nevropatol Psikhiatr Im S S Korsakova* 62:1799–1805.
6. Jann, M. W., and J. H. Slade. 2007. Antidepressant agents for the treatment of chronic pain and depression. *Pharmacotherapy* 27:1571–1587.
7. Muller, N., R. Schennach, M. Riedel, and H. J. Moller. 2008. Duloxetine in the treatment of major psychiatric and neuropathic disorders. *Expert Rev Neurother* 8:527–536.
8. Sindrup, S. H., M. Otto, N. B. Finnerup, and T. S. Jensen. 2005. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol* 96:399–409.
9. Battersby, M. W., J. J. O'Mahoney, A. R. Beckwith, and J. L. Hunt. 1996. Antidepressant deaths by overdose. *Aust N Z J Psychiatry* 30:223–228.
10. Buckley, N. A., I. M. Whyte, A. H. Dawson, P. R. McManus, and N. W. Ferguson. 1995. Self-poisoning in Newcastle, 1987–1992. *Med J Aust* 162:190–193.
11. Ghazi-Khansari, M., and S. Oreizi. 1995. A prospective study of fatal outcomes of poisoning in Tehran. *Vet Hum Toxicol* 37:449–452.
12. Jick, S. S., A. D. Dean, and H. Jick. 1995. Antidepressants and suicide. *Bmj* 310:215–218.
13. Jonasson, B., U. Jonasson, and T. Saldeen. 2000. Among fatal poisonings dextropropoxyphene predominates in younger people, antidepressants in the middle aged and sedatives in the elderly. *J Forensic Sci* 45:7–10.
14. Obafunwa, J. O., and A. Busuttil. 1994. Deaths from substance overdose in the Lothian and Borders region of Scotland (1983–1991). *Hum Exp Toxicol* 13:401–406.
15. Ohberg, A., E. Vuori, T. Klaukka, and J. Lonnqvist. 1998. Antidepressants and suicide mortality. *J Affect Disord* 50:225–233.
16. Biederman, J., and T. Spencer. 1999. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. *Biol Psychiatry* 46:1234–1242.
17. Cusack, B., A. Nelson, and E. Richelson. 1994. Binding of antidepressants to human brain receptors: focus on newer generation compounds. *Psychopharmacology (Berl)* 114:559–565.
18. Green, J. P., and S. Maayani. 1977. Tricyclic antidepressant drugs block histamine H2 receptor in brain. *Nature* 269:163–165.
19. Tsai, B. S., and T. O. Yellin. 1984. Differences in the interaction of histamine H2 receptor antagonists and tricyclic antidepressants with adenylate cyclase from guinea pig gastric mucosa. *Biochem Pharmacol* 33:3621–3625.
20. Shimoda, K., S. Yasuda, S. Morita, M. Shibasaki, T. Someya, L. Bertilsson, and S. Takahashi. 1997. Significance of monitoring plasma levels of amitriptyline, and its hydroxylated and desmethylated metabolites in prediction of the clinical outcome of depressive state. *Psychiatry Clin Neurosci* 51:35–41.
21. Kobayashi, H., Y. Hasegawa, and H. Ono. 1996. Cyclobenzaprine, a centrally acting muscle relaxant, acts on descending serotonergic systems. *Eur J Pharmacol* 311:29–35.
22. R.C. Baselt. 2000. Disposition of toxic drugs and chemicals in man, 5th ed. *Chemical Toxicology Institute*, Foster City, CA
23. Coutts, R. T., M. V. Bach, and G. B. Baker. 1997. Metabolism of amitriptyline with CYP2D6 expressed in a human cell line. *Xenobiotica* 27:33–47.
24. Ghahramani, P., S. W. Ellis, M. S. Lennard, L. E. Ramsay, and G. T. Tucker. 1997. Cytochromes P450 mediating the N-demethylation of amitriptyline. *Br J Clin Pharmacol* 43:137–144.

25. Haritos, V. S., H. Ghabrial, J. T. Ahokas, and M. S. Ching. 2000. Role of cytochrome P450 2D6 (CYP2D6) in the stereospecific metabolism of E- and Z-doxepin. *Pharmacogenetics* 10:591–603.
26. Koyama, E., K. Chiba, M. Tani, and T. Ishizaki. 1997. Reappraisal of human CYP isoforms involved in imipramine N-demethylation and 2-hydroxylation: a study using microsomes obtained from putative extensive and poor metabolizers of S-mephenytoin and eleven recombinant human CYPs. *J Pharmacol Exp Ther* 281:1199–1210.
27. Lemoine, A., J. C. Gautier, D. Azoulay, L. Kiffel, C. Belloc, F. P. Guengerich, P. Maurel, P. Beaune, and J. P. Leroux. 1993. Major pathway of imipramine metabolism is catalyzed by cytochromes P-450 1A2 and P-450 3A4 in human liver. *Mol Pharmacol* 43:827–832.
28. Olesen, O. V., and K. Linnet. 1997. Hydroxylation and demethylation of the tricyclic antidepressant nortriptyline by cDNA-expressed human cytochrome P-450 isozymes. *Drug Metab Dispos* 25:740–744.
29. Venkatakrishnan, K., D. J. Greenblatt, L. L. von Moltke, J. Schmider, J. S. Harmatz, and R. I. Shader. 1998. Five distinct human cytochromes mediate amitriptyline N-demethylation in vitro: dominance of CYP 2C19 and 3A4. *J Clin Pharmacol* 38:112–121.
30. Venkatakrishnan, K., J. Schmider, J. S. Harmatz, B. L. Ehrenberg, L. L. von Moltke, J. A. Graf, P. Mertzanis, K. E. Corbett, M. C. Rodriguez, R. I. Shader, and D. J. Greenblatt. 2001. Relative contribution of CYP3A to amitriptyline clearance in humans: in vitro and in vivo studies. *J Clin Pharmacol* 41:1043–1054.
31. Venkatakrishnan, K., L. L. von Moltke, and D. J. Greenblatt. 1999. Nortriptyline E-10-hydroxylation in vitro is mediated by human CYP2D6 (high affinity) and CYP3A4 (low affinity): implications for interactions with enzyme-inducing drugs. *J Clin Pharmacol* 39:567–577.
32. Baselt, R. C., and R. H. Cravey. 1995. Disposition of toxic drugs and chemicals in man. *Chemical Technology Institute*.
33. Nordin, C., L. Bertilsson, M. L. Dahl, B. Resul, G. Toresson, and F. Sjoqvist. 1991. Treatment of depression with E-10-hydroxynortriptyline--a pilot study on biochemical effects and pharmacokinetics. *Psychopharmacology (Berl)* 103:287–290.
34. Crammer, J. L., B. Scott, and B. Rolfe. 1969. Metabolism of 14C-imipramine. II. Urinary metabolites in man. *Psychopharmacologia* 15:207–225.
35. Diamond, S. 1965. Human Metabolization of Amitriptyline Tagged with Carbon-14. *Curr Ther Res Clin Exp* 7:170–175.
36. Dusci, L. J., and L. P. Hackett. 1971. Gas chromatographic determination of doxepin in human urine following therapeutic doses. *J Chromatogr* 61:231–236.
37. Kawahara, K., T. Awaji, K. Uda, Y. Sakai, and Y. Hashimoto. 1986. Urinary excretion of conjugates of dothiepin and northiaden (mono-N-demethyl-dothiepin) after an oral dose of dothiepin to humans. *Eur J Drug Metab Pharmacokinet* 11:29–32.
38. Ziegler, V. E., J. T. Biggs, A. B. Ardekani, and S. H. Rosen. 1978. Contribution to the pharmacokinetics of amitriptyline. *J Clin Pharmacol* 18:462–467.
39. Dahl-Puustinen, M. L., T. L. Perry, Jr., E. Dumont, C. von Bahr, C. Nordin, and L. Bertilsson. 1989. Stereoselective disposition of racemic E-10-hydroxynortriptyline in human beings. *Clin Pharmacol Ther* 45:650–656.
40. Kerr, G. W., A. C. McGuffie, and S. Wilkie. 2001. Tricyclic antidepressant overdose: a review. *Emerg Med J* 18:236–241.
41. Shannon, M., J. Merola, and F. H. Lovejoy, Jr. 1988. Hypotension in severe tricyclic antidepressant overdose. *Am J Emerg Med* 6:439–442.
42. Roberge, R. J., and E. P. Krenzelok. 2001. Prolonged coma and loss of brainstem reflexes following amitriptyline overdose. *Vet Hum Toxicol* 43:42–44.
43. Pezzilli, R., R. Melandri, B. Barakat, P. L. Broccoli, and F. Miglio. 1998. Pancreatic involvement associated with tricyclic overdose. *Ital J Gastroenterol Hepatol* 30:418–420.
44. Breyer-Pfaff, U., H. Giedke, H. J. Gaertner, and K. Nill. 1989. Validation of a therapeutic plasma level range in amitriptyline treatment of depression. *J Clin Psychopharmacol* 9:116–121.

45. Perel, J. M., J. Mendlewicz, M. Shostak, S. J. Kantor, and A. H. Glassman. 1976. Plasma levels of imipramine in depression. Environmental and genetic factors. *Neuropsychobiology* 2:193–202.
46. Eilers, R. 1995. Therapeutic drug monitoring for the treatment of psychiatric disorders. Clinical use and cost effectiveness. *Clin Pharmacokinet* 29:442–450.
47. Preskorn, S. H., M. J. Burke, and G. A. Fast. 1993. Therapeutic drug monitoring. Principles and practice. *Psychiatr Clin North Am* 16:611–645.
48. Biggs, J. T., D. G. Spiker, J. M. Petit, and V. E. Ziegler. 1977. Tricyclic antidepressant overdose: incidence of symptoms. *Jama* 238:135–138.
49. Caravati, E. M., and P. J. Bossart. 1991. Demographic and electrocardiographic factors associated with severe tricyclic antidepressant toxicity. *J Toxicol Clin Toxicol* 29:31–43.
50. Haddad, L. M. 1992. Managing tricyclic antidepressant overdose. *Am Fam Physician* 46:153–159.
51. Spiker, D. G., A. N. Weiss, S. S. Chang, J. F. Ruwitch, Jr., and J. T. Biggs. 1975. Tricyclic antidepressant overdose: clinical presentation and plasma levels. *Clin Pharmacol Ther* 18:539–546.
52. Eizadi-Mood, N., N. Moein, and M. Saghaei. 2005. Evaluation of relationship between arterial and venous blood gas values in the patients with tricyclic antidepressant poisoning. *Clin Toxicol (Phila)* 43:357–360.
53. Chan, H. Y., Y. C. Chan, and F. L. Lau. 2008. Reversal of Brugada electrocardiographic pattern with sodium bicarbonate solution after amitriptyline overdose. *Clin Toxicol (Phila)* 46: 892–896.
54. Hendrickson, R. G., and A. P. Morocco. 2003. Quetiapine cross-reactivity among three tricyclic antidepressant immunoassays. *J Toxicol Clin Toxicol* 41:105–108.
55. Nishishinya, B., G. Urrutia, B. Walitt, A. Rodriguez, X. Bonfill, C. Alegre, and G. Darko. 2008. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. *Rheumatology (Oxford)* 47:1741–1746.
56. Ohn, M. T., D. Gupta, and B. J. Burton. 2009. Amitriptyline for pain control in scleritis may help to avoid excessive steroid use in selected cases: a case report. *Cases J* 2:8148.
57. Saarto, T., and P. J. Wiffen. 2007. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*:CD005454.
58. Sansone, R. A., and L. A. Sansone. 2008. Pain, pain, go away: antidepressants and pain management. *Psychiatry (Edgmont)* 5:16–19.
59. Uceyler, N., W. Hauser, and C. Sommer. 2008. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. *Arthritis Rheum* 59:1279–1298.
60. Zin, C. S., L. M. Nissen, M. T. Smith, J. P. O'Callaghan, and B. J. Moore. 2008. An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. *CNS Drugs* 22:417–442.
61. da Cunha, R. J., Jr., L. Barrucand, and N. Vercosa. 2009. A study on electrocardiographic changes secondary to the use of tricyclic antidepressants in patients with chronic pain. *Rev Bras Anestesiol* 59:50–55, 46–50.
62. Allen LaPointe, N. M., L. H. Curtis, K. A. Chan, J. M. Kramer, J. E. Lafata, J. H. Gurwitz, M. A. Raebel, and R. Platt. 2006. Frequency of high-risk use of QT-prolonging medications. *Pharmacoepidemiol Drug Saf* 15:361–368.
63. Pacher, P., and V. Kecskemeti. 2004. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? *Curr Pharm Des* 10:2463–2475.
64. McCabe, J. L., D. J. Cobaugh, J. J. Menegazzi, and J. Fata. 1998. Experimental tricyclic antidepressant toxicity: a randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. *Ann Emerg Med* 32:329–333.
65. Rose, J. B. 1977. Tricyclic antidepressant toxicity. *Clin Toxicol* 11:391–402.
66. Punke, M. A., and P. Friederich. 2007. Amitriptyline is a potent blocker of human Kv1.1 and Kv7.2/7.3 channels. *Anesth Analg* 104:1256–1264, tables of contents.
67. Sasyniuk, B. I., V. Jhamandas, and M. Valois. 1986. Experimental amitriptyline intoxication: treatment of cardiac toxicity with sodium bicarbonate. *Ann Emerg Med* 15:1052–1059.

68. Vieweg, W. V., and M. A. Wood. 2004. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. *Psychosomatics* 45:371–377.
69. Dennis, A., L. Wang, X. Wan, and E. Ficker. 2007. hERG channel trafficking: novel targets in drug-induced long QT syndrome. *Biochem Soc Trans* 35:1060–1063.
70. Alvarez, P. A., and J. Pahissa. 2009. QT Alterations in Psychopharmacology: Proven Candidates and Suspects. *Curr Drug Saf*.
71. Gongadze, N., T. Kezeli, and N. Antelava. 2007. Prolong QT interval and "torsades de pointes" associated with different group of drugs. *Georgian Med News*:45–49.
72. Michalets, E. L., L. K. Smith, and E. D. Van Tassel. 1998. Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother* 32:761–765.
73. Nykamp, D. L., C. L. Blackmon, P. E. Schmidt, and A. G. Roberson. 2005. QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. *Ann Pharmacother* 39:543–546.
74. Bailey, B., N. A. Buckley, and D. K. Amre. 2004. A meta-analysis of prognostic indicators to predict seizures, arrhythmias or death after tricyclic antidepressant overdose. *J Toxicol Clin Toxicol* 42:877–888.
75. Foulke, G. E., and T. E. Albertson. 1987. QRS interval in tricyclic antidepressant overdosage: inaccuracy as a toxicity indicator in emergency settings. *Ann Emerg Med* 16:160–163.
76. Pollock, B. G., and J. M. Perel. 1992. Imipramine and 2-hydroxyimipramine: comparative cardiotoxicity and pharmacokinetics in swine. *Psychopharmacology (Berl)* 109:57–62.
77. Pollock, B. G., G. Everett, and J. M. Perel. 1992. Comparative cardiotoxicity of nortriptyline and its isomeric 10-hydroxymetabolites. *Neuropsychopharmacology* 6:1–10.
78. Perahia, D. G., D. K. Kajdasz, D. Desaiah, and P. M. Haddad. 2005. Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder. *J Affect Disord* 89:207–212.
79. Shelton, R. C. 2001. Steps Following Attainment of Remission: Discontinuation of Antidepressant Therapy. *Prim Care Companion J Clin Psychiatry* 3:168–174.
80. Dilsaver, S. C. 1994. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Saf* 10:103–114.
81. Tint, A., P. M. Haddad, and I. M. Anderson. 2008. The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. *J Psychopharmacol* 22:330–332.
82. Opatrny, L., J. A. Delaney, and S. Suissa. 2008. Gastro-intestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look. *Br J Clin Pharmacol* 66:76–81.
83. Donahue, S. R., D. A. Flockhart, D. R. Abernethy, and J. W. Ko. 1997. Ticlopidine inhibition of phenytoin metabolism mediated by potent inhibition of CYP2C19. *Clin Pharmacol Ther* 62:572–577.
84. Ha-Duong, N. T., S. Dijols, A. C. Macherey, J. A. Goldstein, P. M. Dansette, and D. Mansuy. 2001. Ticlopidine as a selective mechanism-based inhibitor of human cytochrome P450 2C19. *Biochemistry* 40:12112–12122.
85. Ko, J. W., Z. Desta, N. V. Soukhova, T. Tracy, and D. A. Flockhart. 2000. In vitro inhibition of the cytochrome P450 (CYP450) system by the antiplatelet drug ticlopidine: potent effect on CYP2C19 and CYP2D6. *Br J Clin Pharmacol* 49:343–351.
86. Lopez-Ariztegui, N., M. Ochoa, M. J. Sanchez-Migallon, C. Nevado, and M. Martin. 1998. [Acute phenytoin poisoning secondary to an interaction with ticlopidine]. *Rev Neurol* 26:1017–1018.
87. Madani, S., D. Barilla, J. Cramer, Y. Wang, and C. Paul. 2002. Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. *J Clin Pharmacol* 42:1211–1218.
88. Dorsey, S. T., and L. A. Biblo. 2000. Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. *Am J Emerg Med* 18:227–229.
89. Esch, J. J., and M. J. Kantoch. 2008. Torsades de Pointes ventricular tachycardia in a pediatric patient treated with fluconazole. *Pediatr Cardiol* 29:210–213.

90. Hrovatin, E., F. Zardo, M. Brieda, E. Dametto, R. Piazza, F. Antonini-Canterin, M. Cassin, N. Meneguzzo, E. Viel, C. Lestuzzi, G. Di Gennaro, and G. L. Nicolosi. 2004. [Long QT and torsade de pointes in a patient with acquired human immunodeficiency virus infection in multitherapy with drugs affecting cytochrome P450]. *Ital Heart J Suppl* 5:735–740.
91. Tatetsu, H., N. Asou, M. Nakamura, N. Hanaoka, F. Matsuno, K. Horikawa, and H. Mitsuya. 2006. Torsades de pointes upon fluconazole administration in a patient with acute myeloblastic leukemia. *Am J Hematol* 81:366–369.
92. Pavan-Langston, D. 2008. Herpes zoster antivirals and pain management. *Ophthalmology* 115:S13-20.
93. Sra, K. K., and S. K. Tyring. 2004. Treatment of postherpetic neuralgia. *Skin Therapy Lett* 9:1–4.
94. Jerling, M., L. Bertilsson, and F. Sjoqvist. 1994. The use of therapeutic drug monitoring data to document kinetic drug interactions: an example with amitriptyline and nortriptyline. *Ther Drug Monit* 16:1–12.
95. Leinonen, E., P. Lillsunde, V. Laukkanen, and P. Ylitalo. 1991. Effects of carbamazepine on serum antidepressant concentrations in psychiatric patients. *J Clin Psychopharmacol* 11:313–318.
96. Spina, E., F. Pisani, and E. Perucca. 1996. Clinically significant pharmacokinetic drug interactions with carbamazepine. An update. *Clin Pharmacokinet* 31:198–214.
97. Szymura-Oleksiak, J., E. Wyska, and A. Wasieczko. 2001. Pharmacokinetic interaction between imipramine and carbamazepine in patients with major depression. *Psychopharmacology (Berl)* 154:38–42.
98. Parker, A. C., P. Pritchard, T. Preston, and I. Choonara. 1998. Induction of CYP1A2 activity by carbamazepine in children using the caffeine breath test. *Br J Clin Pharmacol* 45:176–178.
99. Uhm, J. H., and W. K. Yung. 1999. Neurologic Complications of Cancer Therapy. *Curr Treat Options Neurol* 1:428–437.
100. Shin, J. G., J. Y. Park, M. J. Kim, J. H. Shon, Y. R. Yoon, I. J. Cha, S. S. Lee, S. W. Oh, S. W. Kim, and D. A. Flockhart. 2002. Inhibitory effects of tricyclic antidepressants (TCAs) on human cytochrome P450 enzymes in vitro: mechanism of drug interaction between TCAs and phenytoin. *Drug Metab Dispos* 30:1102–1107.
101. Dorian, P., E. M. Sellers, K. L. Reed, J. J. Warsh, C. Hamilton, H. L. Kaplan, and T. Fan. 1983. Amitriptyline and ethanol: pharmacokinetic and pharmacodynamic interaction. *Eur J Clin Pharmacol* 25:325–331.
102. Stromberg, C., A. Suokas, T. Seppala, and M. Kupari. 1991. Echocardiographic and psychometric effects of amitriptyline or imipramine plus alcohol. *Eur J Clin Pharmacol* 40:349–354.
103. Peles, E., S. Schreiber, Y. Naumovsky, and M. Adelson. 2007. Depression in methadone maintenance treatment patients: rate and risk factors. *J Affect Disord* 99:213–220.
104. Peles, E., S. Schreiber, and M. Adelson. 2008. Tricyclic antidepressants abuse, with or without benzodiazepines abuse, in former heroin addicts currently in methadone maintenance treatment (MMT). *Eur Neuropsychopharmacol* 18:188–193.
105. Deamer, R. L., D. R. Wilson, D. S. Clark, and J. G. Prichard. 2001. Torsades de pointes associated with high dose levomethadyl acetate (ORLAAM). *J Addict Dis* 20:7–14.
106. Krantz, M. J., I. B. Kutinsky, A. D. Robertson, and P. S. Mehler. 2003. Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy* 23:802–805.
107. Lin, C., T. Somberg, J. Molnar, and J. Somberg. 2009. The effects of chiral isolates of methadone on the cardiac potassium channel IKr. *Cardiology* 113:59–65.
108. Chan, G. M., M. Stajic, E. K. Marker, R. S. Hoffman, and L. S. Nelson. 2006. Testing positive for methadone and either a tricyclic antidepressant or a benzodiazepine is associated with an accidental overdose death: analysis of medical examiner data. *Acad Emerg Med* 13:543–547.
109. Gury, C., O. Canceil, and P. Iaria. 2000. [Antipsychotic drugs and cardiovascular safety: current studies of prolonged QT interval and risk of ventricular arrhythmia]. *Encephale* 26:62–72.
110. Ray, W. A., S. Meredith, P. B. Thapa, K. G. Meador, K. Hall, and K. T. Murray. 2001. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 58:1161–1167.

111. Buckley, N. A., I. M. Whyte, and A. H. Dawson. 1995. Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. *J Toxicol Clin Toxicol* 33:199–204.
112. Hartigan-Go, K., D. N. Bateman, G. Nyberg, E. Martensson, and S. H. Thomas. 1996. Concentration-related pharmacodynamic effects of thioridazine and its metabolites in humans. *Clin Pharmacol Ther* 60:543–553.
113. Daniel, W. A., M. Syrek, A. Haduch, and J. Wojcikowski. 2000. Pharmacokinetics and metabolism of thioridazine during co-administration of tricyclic antidepressants. *Br J Pharmacol* 131:287–295.
114. Crewe, H. K., M. S. Lennard, G. T. Tucker, F. R. Woods, and R. E. Haddock. 1992. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Clin Pharmacol* 34:262–265.
115. Alfaro, C. L., Y. W. Lam, J. Simpson, and L. Ereshefsky. 2000. CYP2D6 inhibition by fluoxetine, paroxetine, sertraline, and venlafaxine in a crossover study: intraindividual variability and plasma concentration correlations. *J Clin Pharmacol* 40:58–66.
116. Amchin, J., L. Ereshefsky, W. Zarycranski, K. Taylor, D. Albano, and P. M. Klockowski. 2001. Effect of venlafaxine versus fluoxetine on metabolism of dextromethorphan, a CYP2D6 probe. *J Clin Pharmacol* 41:443–451.
117. el-Yazigi, A., K. Chaleby, A. Gad, and D. A. Raines. 1995. Steady-state kinetics of fluoxetine and amitriptyline in patients treated with a combination of these drugs as compared with those treated with amitriptyline alone. *J Clin Pharmacol* 35:17–21.
118. Leucht, S., H. J. Hackl, W. Steimer, D. Angersbach, and R. Zimmer. 2000. Effect of adjunctive paroxetine on serum levels and side-effects of tricyclic antidepressants in depressive inpatients. *Psychopharmacology (Berl)* 147:378–383.
119. Preskorn, S. H., and B. Baker. 1997. Fatality associated with combined fluoxetine-amitriptyline therapy. *Jama* 277:1682.
120. Vermeulen, T. 1998. Distribution of paroxetine in three postmortem cases. *J Anal Toxicol* 22:541–544.
121. Preskorn, S. H., J. Alderman, M. Chung, W. Harrison, M. Messig, and S. Harris. 1994. Pharmacokinetics of desipramine coadministered with sertraline or fluoxetine. *J Clin Psychopharmacol* 14:90–98.
122. Alderman, J., S. H. Preskorn, D. J. Greenblatt, W. Harrison, D. Penenberg, J. Allison, and M. Chung. 1997. Desipramine pharmacokinetics when coadministered with paroxetine or sertraline in extensive metabolizers. *J Clin Psychopharmacol* 17:284–291.
123. Albers, L. J., C. Reist, R. L. Vu, K. Fujimoto, V. Ozdemir, D. Helmeste, R. Poland, and S. W. Tang. 2000. Effect of venlafaxine on imipramine metabolism. *Psychiatry Res* 96:235–243.
124. Brosen, K., and C. A. Naranjo. 2001. Review of pharmacokinetic and pharmacodynamic interaction studies with citalopram. *Eur Neuropsychopharmacol* 11:275–283.
125. Dahl, M. L., L. Bertilsson, and C. Nordin. 1996. Steady-state plasma levels of nortriptyline and its 10-hydroxy metabolite: relationship to the CYP2D6 genotype. *Psychopharmacology (Berl)* 123:315–319.
126. Petersen, P., and K. Brosen. 1991. [Severe nortriptyline poisoning in poor metabolizers of the sparteine type]. *Ugeskr Laeger* 153:443–444.
127. Daly, A. K., M. Armstrong, S. C. Monkman, M. E. Idle, and J. R. Idle. 1991. Genetic and metabolic criteria for the assignment of debrisoquine 4-hydroxylation (cytochrome P4502D6) phenotypes. *Pharmacogenetics* 1:33–41.
128. Eichelbaum, M., and B. Evert. 1996. Influence of pharmacogenetics on drug disposition and response. *Clin Exp Pharmacol Physiol* 23:983–985.
129. Brosen, K., J. G. Hansen, K. K. Nielsen, S. H. Sindrup, and L. F. Gram. 1993. Inhibition by paroxetine of desipramine metabolism in extensive but not in poor metabolizers of sparteine. *Eur J Clin Pharmacol* 44:349–355.
130. Laine, K., G. Tybring, S. Hartter, K. Andersson, J. O. Svensson, J. Widen, and L. Bertilsson. 2001. Inhibition of cytochrome P4502D6 activity with paroxetine normalizes the ultrarapid metabolizer phenotype as measured by nortriptyline pharmacokinetics and the debrisoquin test. *Clin Pharmacol Ther* 70:327–335.

131. A, L. L., R. Berecz, A. de la Rubia, P. Fernandez-Salguero, and P. Dorado. 2001. Effect of thioridazine dosage on the debrisoquine hydroxylation phenotype in psychiatric patients with different CYP2D6 genotypes. *Ther Drug Monit* 23:616–620.
132. Baumann, P., J. W. Meyer, M. Amey, D. Baettig, C. Bryois, M. Jonzier-Perey, L. Koeb, C. Monney, and B. Woggon. 1992. Dextromethorphan and mephenytoin phenotyping of patients treated with thioridazine or amitriptyline. *Ther Drug Monit* 14:1–8.
133. Maynard, G. L., and P. Soni. 1996. Thioridazine interferences with imipramine metabolism and measurement. *Ther Drug Monit* 18:729–731.
134. Ingelman-Sundberg, M., M. Oscarson, and R. A. McLellan. 1999. Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. *Trends Pharmacol Sci* 20:342–349.
135. Meyer, U. A., and U. M. Zanger. 1997. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol* 37:269–296.
136. Sachse, C., J. Brockmoller, S. Bauer, and I. Roots. 1997. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet* 60:284–295.
137. Tamminga, W. J., J. Wemer, B. Oosterhuis, R. A. de Zeeuw, L. F. de Leij, and J. H. Jonkman. 2001. The prevalence of CYP2D6 and CYP2C19 genotypes in a population of healthy Dutch volunteers. *Eur J Clin Pharmacol* 57:717–722.
138. Aynacioglu, A. S., C. Sachse, A. Bozkurt, S. Kortunay, M. Nacak, T. Schroder, S. O. Kayaalp, I. Roots, and J. Brockmoller. 1999. Low frequency of defective alleles of cytochrome P450 enzymes 2C19 and 2D6 in the Turkish population. *Clin Pharmacol Ther* 66:185–192.
139. Dandara, C., C. M. Masimirembwa, A. Magimba, J. Sayi, S. Kaaya, D. K. Sommers, J. R. Snyman, and J. A. Hasler. 2001. Genetic polymorphism of CYP2D6 and CYP2C19 in east- and southern African populations including psychiatric patients. *Eur J Clin Pharmacol* 57:11–17.
140. Bathum, L., E. Skjelbo, T. K. Mutabingwa, H. Madsen, M. Horder, and K. Brosen. 1999. Phenotypes and genotypes for CYP2D6 and CYP2C19 in a black Tanzanian population. *Br J Clin Pharmacol* 48:395–401.
141. Yue, Q. Y., Z. H. Zhong, G. Tybring, P. Dalen, M. L. Dahl, L. Bertilsson, and F. Sjoqvist. 1998. Pharmacokinetics of nortriptyline and its 10-hydroxy metabolite in Chinese subjects of different CYP2D6 genotypes. *Clin Pharmacol Ther* 64:384–390.
142. Horai, Y., M. Nakano, T. Ishizaki, K. Ishikawa, H. H. Zhou, B. I. Zhou, C. L. Liao, and L. M. Zhang. 1989. Metoprolol and mephenytoin oxidation polymorphisms in Far Eastern Oriental subjects: Japanese versus mainland Chinese. *Clin Pharmacol Ther* 46:198–207.
143. Morita, S., K. Shimoda, T. Someya, Y. Yoshimura, K. Kamijima, and N. Kato. 2000. Steady-state plasma levels of nortriptyline and its hydroxylated metabolites in Japanese patients: impact of CYP2D6 genotype on the hydroxylation of nortriptyline. *J Clin Psychopharmacol* 20:141–149.
144. Shimoda, K., S. Morita, G. Hirokane, A. Yokono, T. Someya, and S. Takahashi. 2000. Metabolism of desipramine in Japanese psychiatric patients: the impact of CYP2D6 genotype on the hydroxylation of desipramine. *Pharmacol Toxicol* 86:245–249.
145. Dahl, M. L., L. Iselius, C. Alm, J. O. Svensson, D. Lee, I. Johansson, M. Ingelman-Sundberg, and F. Sjoqvist. 1993. Polymorphic 2-hydroxylation of desipramine. A population and family study. *Eur J Clin Pharmacol* 44:445–450.
146. Skjelbo, E., K. Brosen, J. Hallas, and L. F. Gram. 1991. The mephenytoin oxidation polymorphism is partially responsible for the N-demethylation of imipramine. *Clin Pharmacol Ther* 49:18–23.
147. Chaturvedi, A. K., J. T. Hidding, N. G. Rao, J. C. Smith, 2nd, and S. J. Bredehoeft. 1987. Two tricyclic antidepressant poisonings: levels of amitriptyline, nortriptyline and desipramine in post-mortem biological samples. *Forensic Sci Int* 33:93–101.
148. Musshoff, F., W. Grellner, and B. Madea. 1999. [Toxicologic findings in suicide with doxepin and paroxetine]. *Arch Kriminol* 204:28–32.
149. Rohrig, T. P., and R. W. Prouty. 1989. A nortriptyline death with unusually high tissue concentrations. *J Anal Toxicol* 13:303–304.
150. Pounder, D. J., and G. R. Jones. 1990. Post-mortem drug redistribution--a toxicological nightmare. *Forensic Sci Int* 45:253–263.

Chapter 6
Selective Serotonin Reuptake Inhibitors

Mojdeh Mozayani

Abstract Antidepressant drugs have been referred to by the labels first-, second-, and third-generation. These terms are nonspecific, although generally the selective serotonin reuptake inhibitors (SSRIs) fall into the second-generation group. The tricyclics (TCAs like amitriptyline, clomipramine, imipramine, and doxepin) are considered to be first-generation, while some of the newer drugs that have mixed modes of action are considered to be third-generation antidepressants (e.g., amoxapine, mirtazapine, bupropion, nefazodone, venlafaxine). This chapter will deal only with the second-generation antidepressants, i.e., citalopram, fluoxetine, fluvoxamine, sertraline, and paroxetine.

Selective serotonin reuptake inhibitors (SSRIs) are one of the newer classes of antidepressants. Since their introduction in the United States, they have been greatly used and accepted in the psychiatric field to treat a number of conditions including major depressive disorder (MDD), obsessive-compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder, posttraumatic stress disorder (PTSD), and social anxiety disorder (SAD) [1] due to their efficacy and the reduced occurrence of undesirable side effects [2–4].

SSRIs act by inhibiting neuronal uptake of serotonin (5HT). Selective serotonin reuptake inhibitors are generally shown to be as effective and overall better tolerated than tricyclic antidepressants (TCAs) in treatment of depression [3, 4]. SSRIs are also used in treating other psychiatric disorders such as panic disorder [5, 6], obsessive-compulsive disorder, and social anxiety disorder [7–9].

Depression is among the most common illnesses in the United States [10]. However, it is underdiagnosed and undertreated in this country [11]. In recent years, there has been a significant increase in number of patients who received outpatient treatment for depression [12]. Selective serotonin reuptake inhibitors are widely used in the treatment of psychiatric disorders [7–9, 13]; therefore, understanding

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drug interactions involving this class of agents is very important. In this chapter, SSRIs' mechanism of action, pharmacokinetics, drug and herbal interactions, and adverse reactions are described.

Keywords SSRI • Selective serotonin reuptake inhibitors • Serotonin syndrome • Drug interactions

Mechanism of Action

Selective serotonin reuptake inhibitors, as indicated by their name, block the CNS neuronal uptake of serotonin (5HT), which is related to their antidepressant action [14]. SSRIs selectively inhibit the reuptake of serotonin; however, they also have a different degree of effect on blocking the reuptake of norepinephrine and dopamine [14, 15]. Paroxetine is the most potent SSRI available [1]. However, it has less selectivity for the serotonin site than fluvoxamine or sertraline [15].Citalopram is the most selective SSRI in the market [15]. Sertraline is both the second most potent and second most selective SSRI [15].

Pharmacokinetics

In order to better understand the drug interactions involving SSRIs, it is essential to understand their pharmacokinetic properties.

Absorption

SSRIs are in general well absorbed from the gastrointestinal tract, but they undergo hepatic first-pass metabolism to a varying degree. This reduces the amount of intact drug that reaches the systemic circulation [15].

Fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram are well absorbed [16–19]. Food does not alter their absorption significantly [20]. All SSRIs with the exception of citalopram undergo extensive hepatic first-pass metabolism [16–19].

Distribution

SSRIs have a relatively large volume of distribution (V_d) due to their lipophilic properties. Their large V_d indicates extensive accumulation in tissues [16]. Fluoxetine, paroxetine, and sertraline are highly protein bound, especially to alpha-1 acid glycoprotein. Citalopram and fluvoxamine do not bind as extensively to plasma proteins [16]. Fluoxetine's V_d is about 20–45 L/kg. It reaches steady state in about 1–22 months [16]. Fluvoxamine's steady state is reached within 10 days. Its V_d is

5 L/kg [21]. Paroxetine's V_d is 20 L/kg. It reaches its steady state between 7 and 14 days [19, 22]. Sertraline's time to reach steady state ranges between 5 and 7 days. Its V_d is 20 L/kg [15, 23]. Citalopram reaches steady state in 6–15 days [24, 25]. Its volume of distribution is 12–15 L/kg [24, 26].

Metabolism and Elimination

Metabolism is the main route of elimination for all selective serotonin reuptake inhibitors [15]. SSRIs are mainly hepatically metabolized and renally excreted [25]. Fluoxetine is metabolized extensively by CYP2D6 to its active metabolite (norfluoxetine) and other metabolites [27]. It is reported that half-lives ($t_{½}$) of fluoxetine and its metabolite norfluoxetine range from 1 to 5 days for fluoxetine and 7–20 days for its active metabolite [28, 29]. Fluvoxamine is metabolized by CYP1A2 and CYP2D6 [30]. Its metabolites are inactive [18]. Fluvoxamine's $t_{½}$ is between 8 and 28 h [21]. Paroxetine is also metabolized to clinically inactive metabolites by CYP2D6 [31, 32]. Its $t_{½}$ is variable depending on the subject, dosage, and duration of administration [17]. Its terminal half-life is about 1 day [17, 19]. Metabolism is also the main route of elimination for sertraline. Its main active metabolite, desmethylsertraline, is obtained by demethylation of sertraline by CYP3A4 [33]. This metabolite has a half-life three times longer than sertraline (60–100 h) [23, 34]. Sertraline has a longer $t_{½}$ in elderly and female volunteers (32.1–36.7 h) than young male volunteers (22.4 h) [23]. Citalopram is metabolized by CYP2C19 and CYP3A4 to several metabolites, including two pharmacologically active metabolites: desmethylcitalopram and didesmethylcitalopram [26, 35]. The half-life for citalopram ranges from 35 to 58.5 h depending on the study [24, 25]. Although its active metabolites have half-lives that are two to three times longer, their activity is not clinically important due to their low potency [15, 24]. Refer to Table 6.1 for a summary of metabolites.

Cytochrome P-450 System

Selective serotonin reuptake inhibitors are extensively metabolized as discussed previously. Cytochrome P-450 isoenzymes play a major role in their metabolism and hence their interactions with other drugs [16, 36]. In order to better understand the drug interactions involving SSRIs, it is essential to understand this system [37]. Cytochrome P-450 is comprised of many enzymes, but most drugs are metabolized by only three enzymes in this system: CYP1A2, CYP2D6, and CYP3A4. SSRIs' inhibitory effects on these enzymes play a major role in most of their drug interactions [38]. Fluoxetine, its metabolite norfluoxetine, and paroxetine are potent inhibitors of CYP2D6 enzymes, and therefore inhibit the metabolism of many tricyclic antidepressants and antipsychotic drugs [38–40]. Fluoxetine and fluvoxamine also inhibit CYP2C19 to a lesser extent [29, 40]. Fluvoxamine is a strong inhibitor of CYP1A2 and has a high propensity to interact with other drugs [18, 38–40]. Sertraline has a moderate inhibitory effect on CYP2D6 [39]. Citalopram does not

Table 6.1 SSRIs and their active metabolites

SSRIs	Active metabolites	Clinically significant
Fluoxetine	Norfluoxetine	Yes
Fluvoxamine	–	–
Paroxetine	–	–
Sertraline	Desmethylsertraline	No
Citalopram	Desmethylcitalopram, Didesmethylcitalopram	No

Table 6.2 SSRIs and CYP450 enzymes

SSRIs	Metabolized by	CYP450 enzyme inhibited
Fluoxetine	CYP2D6	CYP2C19, CYP2D6[a]
Norfluoxetine	–	CYP2D6[a]
Fluvoxamine	CYP1A2, CYP2D6	CYP2C19, CYP1A2[a], CYP3A4[c]
Paroxetine	CYP2D6	CYP2D6[a], CYP2C19[a]
Sertraline	CYP3A4	CYP2D6[b]
Citalopram	CYP2C19, CYP3A4	CYP2D6[c]
Desmethylcitalopram	–	CYP2D6[b]

Degree of inhibition: [a]Potent, [b]Moderate, [c]Weak

seem to have many pharmacokinetic drug interactions, since it is a weak inhibitor of CYP2D6 [40, 41]. Table 6.2 summarizes the actions of these enzymes.

Drug–Drug Interactions

Drug interactions are classified into two major groups: pharmacodynamic interactions and pharmacokinetic interactions. Pharmacodynamic interactions are described as a change in the pharmacologic effect of the target drug produced by the activity of another drug at the same receptor or a different site with the same activity. In other words, mechanism of action of one drug amplifies or diminishes the mechanism of action of another drug [42]. Pharmacokinetic interactions involve any alteration in absorption, distribution, metabolism, or elimination of the target drug caused by coadministration of another medication.

Pharmacodynamic Interactions

Serotonin syndrome is a major pharmacodynamic interaction that occurs when SSRIs are administered concomitantly with other drugs including monoamine oxidase inhibitors [43], lithium, other SSRIs, dextromethorphan, meperidine, l-tryptophan, sumatriptan, risperidone, methylphenidate, and methylenedioxymethamphetamine (MDMA, or Ecstasy) [42, 44–49]. Serotonin syndrome has been suggested to occur

in some elderly patients taking SSRIs and opioid analgesics [50]. In the case of dextromethorphan, recent research has suggested that extremely high serum levels of dextromethorphan coupled with therapeutic levels of the SSRI are required to induce serotonin syndrome [51]. A patient on an established regimen of paroxetine who underwent surgery in which fentanyl was used during anesthesia developed serotonin toxicity [52]. Serotonin syndrome has also been reported with fentanyl in combination with citalopram [53]. However, other mechanisms such as defects in monoamine metabolism, hepatic and pulmonary insufficiency may also contribute in developing this condition [54].

Serotonin syndrome is described as serotonergic hyperstimulation. Any drug or drug combination that increases serotonin neurotransmission can cause serotonin syndrome [42]. Serotonin syndrome is an acute condition that is characterized by changes in mental status, restlessness, dyskinesia, clonus and myoclonus, autonomic dysfunction such as mydriasis, hyperthermia, shivering, diaphoresis, and diarrhea [42, 44, 55, 56].

Neuroleptic malignant syndrome is described as an idiosyncratic response of patients to mostly neuroleptic agents with a high ability to block D2 receptors [42]. Serotonin syndrome and neuroleptic malignant syndrome are very similar in signs and symptoms. It is difficult to differentiate between these two syndromes, but in general, patients with neuroleptic malignant syndrome present with higher fever and more muscle rigidity. On the other hand, patients with serotonin syndrome have more gastrointestinal dysfunction and myoclonus [57]. Symptoms in neuroleptic malignant syndrome appear more gradual and resolve more slowly [55]. Both syndromes are treated by discontinuing the offending agent and supportive care [55, 57]. Caution is advised if initiating drug therapy in these two syndromes. Some patients with serotonin syndrome may require drug therapy with antiserotonergic agents such as cyproheptadine, methysergide, and propranolol [42]. These agents may not be effective in treating neuroleptic malignant syndrome. Dopamine agonists that are used to treat this syndrome may exacerbate serotonin syndrome [55].

Serotonin syndrome is usually mild and resolves quickly when the serotonergic drugs are discontinued and supportive care is provided. However, there have been numerous cases of fatalities due to this syndrome caused mostly by intentional drug overdose or combining different serotonergic drugs [58–62].

When taken in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs), SSRIs can increase the chance of upper gastrointestinal hemorrhage [63–67].

Rhabdomyolysis has been reported from the combination of SSRIs and irinotecan [68].

Pharmacokinetic Interactions

Oral absorption can be affected by the presence of certain drugs that can change gastrointestinal motility or pH. Food can also change a drug's absorption. In the case of SSRIs, interactions involving absorption are not clinically significant [69].

Table 6.3 CYP450 enzymes and some common drugs

Enzyme	Examples of metabolized drugs
CYP1A2	TCAs (amitriptyline, imipramine), clozapine, propranolol, theophylline, R-warfarin
CYP2C19	Citalopram, imipramine, barbiturates, propranolol
CYP2D6	Antiarrhythmics (propafenone, flecainide), β-blockers (propranolol, metoprolol, timolol), opiates, SSRIs (fluoxetine, paroxetine), TCAs, venlafaxine
CYP3A3/4	Acetaminophen, codeine, dextromethorphan
CYP2C9/10	Phenytoin, S-warfarin, tolbutamide

Drug distribution is influenced by such factors as blood flow, the drug's lipophilicity, and its protein-binding ability. Only the unbound drug (free fraction) is able to act on a receptor site. Although SSRIs are highly protein bound, their interaction involving protein binding is clinically minor [69].

Interactions involving metabolism and the enzymes which facilitate this process are the most studied. There is also individual variability in metabolizing drugs. For example, it is a well-established fact that there are individuals who do not synthesize the enzyme CYP2D6, leading to poor metabolism of the drugs metabolized by this enzyme. As indicated in Table 6.2, SSRIs inhibit some of the most important CYP450 enzymes involved in other drugs' metabolism, thus leading to increased levels of those drugs. There are a great number of drugs that are metabolized by these enzymes. A few examples are given in Table 6.3 [70].

On the other hand, since SSRIs are also metabolized by these same enzymes, their metabolism can be affected by inhibitors and inducers of these enzymes. Drugs such as sulfonylureas, barbiturates, phenytoin, carbamazepine, rifampin, and primidone are CYP enzyme inducers which cause an increase in metabolism of the drugs whose main route of metabolism is by CYP450 system enzymes, including SSRIs. Enzyme inhibitors such as cimetidine, erythromycin, isoniazid, verapamil, and propoxyphene can lead to an increase in plasma levels of affected drugs. Table 6.4 summarizes a number of drug–drug interactions mediated by metabolic enzymes. It should be emphasized that this table does not include all the drug interactions involving SSRIs. However, it indicates the importance of understanding pharmacokinetic drug interactions involving this class of drugs.

Drug-Natural Product Interaction

There are not many clinical trials on the interaction of SSRIs' with herbal products. It is suggested that if a natural product has an effect on CYP450 isoenzymes, it potentially can interact with drugs metabolized by these enzymes. However, this is not a reliable predictor for drug–natural product interaction [90]. Some examples of known drug–natural product interaction are described below.

Fluvoxamine significantly increases melatonin (sleep aid) levels by reducing its metabolism due to inhibition of CYP1A2 and CYP2C9 [90]. Ayahuasca is an

Table 6.4 SSRIs' drug-drug interactions

Precipitant drug	Object drug	Effect
Paroxetine	Codeine	Loss of efficacy [70]
Paroxetine	Risperidone	Increased plasma levels [71]
Fluoxetine	Phentermine	Increased plasma levels [72]
Fluoxetine, norfluoxetine, fluvoxamine, paroxetine, sertraline	Phenytoin	Increased plasma levels [73, 74]
Fluvoxamine	Methadone	Increased plasma levels [75]
Sertraline	Alprazolam	No effect [76, 77]
Fluoxetine, fluvoxamine, paroxetine	Benzodiazepines	Increased plasma levels [70]
SSRIs	TCAs	Increased plasma levels [78]
Rifampin	Sertraline	Decreased plasma levels [79]
Fluoxetine, paroxetine, fluvoxamine	Propafenone	Increased plasma levels [80]
Fluoxetine, fluvoxamine	Warfarin	Increased risk of bleeding [81]
Citalopram	Carbamazepine	No effect [82]
Fluoxetine, fluvoxamine	Carbamazepine	Increased plasma levels [14]
Fluoxetine	Methadone	Increased/decreased plasma levels [75, 83]
Paroxetine	Lithium	No effect [84, 85]
Paroxetine	Metoprolol	Increased plasma levels [86]
Risperidone	Fluoxetine	Increased plasma levels [87]
Citalopram	Propafenone	Increased plasma levels [88]
Paroxetine	Tamoxifen	Reduced plasma levels [89]

Amazonian psychoactive beverage that contains potent monoamine oxidase inhibiting alkaloids (harmala alkaloids). It may induce serotonin syndrome if given with SSRIs [91]. St John's wort (*Hypericum perforatum*) is used to treat mild to moderate depression. It may cause mild serotonin syndrome when given with SSRIs [92].

Adverse Reactions

Selective serotonin reuptake inhibitors are generally well tolerated [93, 94]. However, they are associated with a few adverse effects. The most commonly reported adverse reactions to SSRIs are nausea, anorexia, diarrhea, insomnia, nervousness, headache, anxiety, dry mouth, constipation, hypotension, and fatigue [95, 96]. Cases of hyponatremia caused by SSRIs have also been reported, particularly in the elderly and in females [14, 97–99]. Mydriasis has been reported with paroxetine, sertraline, and citalopram [96, 100]. SSRIs are also implicated in extrapyramidal side effects and akathisia [101]. Although SSRIs are relatively safe in large doses, they have been associated with seizures in overdose situations [102]. Abnormal bleeding poses a slight risk in patients taking SSRIs [64, 103–106]. Serotonin syndrome has also been reported in individuals who are taking *only* therapeutic doses of paroxetine [107].

Conclusions

Selective serotonin reuptake inhibitors have become the first line of therapy in treatment of depression. They are also used in other areas of psychiatry such as obsessive-compulsive disorder (OCD) and panic disorder. In general, SSRIs are considered to be well tolerated and safe. Therapeutic drug monitoring (TDM) is not commonly performed with SSRIs since there is no clear relationship between drug plasma concentrations and clinical response [108]. However, TDM may be useful in patients with poor compliance. It is also suggested that TDM of SSRIs can be a factor in overall cost reduction [109]. SSRIs are involved in many drug–drug interactions due to their interactions with CYP enzymes. Therefore, when dealing with SSRIs, it is essential for the clinician to have a thorough knowledge of the drugs' interaction with CYP enzymes and its metabolism. Although these interactions are usually undesirable, but there have been instances in which clinicians have taken advantage of them to successfully treat resistant cases [110].

References

1. Marks DM, Park MH, Ham BJ, Han C, Patkar AA, Masand PS, Pae CU, Paroxetine: safety and tolerability issues, Expert Opin Drug Saf. 2008 Nov;7(6):783–94.
2. Leonard B and Tollfeson, G. Focus on SSRIs: broadening the spectrum of clinical use. J. Clin. Psychiatry. 55: 459–466 (1994).
3. Menting JE, Honig A, Verhey FR, Hartmans M, Rozendaal N, de Vet HC, van Praag HM. Selective serotonin reuptake inhibitors (SSRIs) in the treatment of elderly depressed patients: a qualitative analysis of the literature on their efficacy and side effects. Int Clin Psychopharmacol. 11 (3): 165–75 (Sep 1996).
4. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord. 58(1): 19–36 (Apr 2000).
5. Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin reuptake inhibitors for panic disorder. Am J Psychiatry 158(12): 1989–92 (Dec 2001).
6. Rapaport M H, Wolkow R, Rubin A, Hackett E, Pollack M, Ota K Y. Sertraline treatment of panic disorder: results of a long-term study. Acta Psychiatrica Scandinavica. 104 (4): 289–298 (Oct 2001).
7. Tollefson GD, Rampey AH Jr, Potvin JH, Jenike MA, Rush AJ, kominguez RA, Koran LM, Shear MK, Goodman W, Genduso LA. A multicenter investigation of fixed dose fluoxetine in the treatment of obsessive compulsive disorder. Arch Gen Psychiatry 51(7): 559–67 (Jul 1994).
8. Wagstaff AJ, Cheer SM, Matheson AJ, Ormond D, Goa KL. Paroxetine: an update of its use in psychiatric disorder in adults. Drugs 62(4): 655–703 (2002).
9. Montgomery SA, Kasper S, Stein DJ, Bang Hededgaard K, Lemming OM. Citalopram 20 mg, 40 mg, and 60 mg are all effective and well tolerated compared with placebo in obsessive compulsive disorder. Int Clin Psychopharmacol 16(2):75–86 (Mar 2001).
10. Fichter MM, Narrow WE, Roper MT, et al. Prevalence of Mental illness in Germany and the United States: comparison of the Upper Bavarian Study and the Epidemiologic Catchment Area Program. J Nerv Ment Dis. 184: 598–606 (1996).
11. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the under treatment of depression. JAMA. 277: 333–340 (1997).

12. Olfson M, Marcus S C. Druss B, Elinson L, Tanielian T, Pincus H A. National trends in the outpatient treatment of depression. JAMA. 287(2): 203–209 (2002).
13. Gregor KJ, Way K, Young CH, James SP. Concomitant use of selective serotonin reuptake inhibitors with other cytochrome P450 2D6 or 3A4 metabolized medications: how often does it really happen? J Affect Disord. 46(1): 59–67 (Oct 1997).
14. Drug facts and comparison Jan 2000.
15. Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther. 85(1): 11–28 (Jan 2000).
16. Catterson M, Preskorn SH. Pharmacokinetics of selective serotonin reuptake inhibitors: clinical relevance. Pharmacology & Toxicology. 78 (4): 203-208 (Apr 1996).
17. Van Harten J. Clinical pharmacokinetics of selective serotonin reuptake inhibitors. Clin Pharmacokinet. 24: 203–220 (1993).
18. De Vane C L, Gill H S. Clinical pharmacokinetics of fluvoxamine: applications to dosage regimen design. J Clin Psychiatry. 58 (5):7–14 (1997).
19. Kaye C M, Haddock R E, Langley P F, Mellows G, Tasker T C G, Zussman B D, Greb W H. A review of the metabolism of paroxetine in man. Acta Psychiatr Scand. 80 (350): 60-75(1989).
20. DeVane CL. Pharmacokinetics of the newer antidepressants: clinical relevance. Amer J Med. 97 (6A): 13S-23S (1994).
21. DeVries M H, Raghoebar M, Mathlener I S, van Harten J. Single and multiple oral dose fluvoxamine kinetics in young and elderly subjects. Therap Drug Monit. 14: 493–498 (1992).
22. Lundmark J, Scheel Thomsen I, Fjord-Larsen T, Manniche PM, Mengel H, Moller-Nielsen EM, Pauser H, Walinder J. Paroxetine: pharmacokinetic and antidepressant effect in the elderly. Acta Psychiatr Scand. 350: 76–80 (1989).
23. Ronfeld R A, Tremaine L M, Wilner K D. Pharmacokinetics of sertraline and N-demethyl metabolite in elderly and young male and female volunteers. Clin Pharmacokinet. 32(suppl.1): 22–30 (1997).
24. Kragh-Sorensen P, Overo K F, Peterson O L, Jensen K, Parnas W. the kinetics of citalopram: single and multiple dose studies in man. Acta Pharmacol toxicol. 48(1): 53–60 (1981).
25. Gutierrez M, Abramowitz W. Steady-state pharmacokinetics of citalopram in young and elderly subjects. Pharmacotherapy. 20(12): 1441–1447 (2000).
26. Milne R J, Goa K L. Citalopram. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs. 41(3): 450–477 (March 1991).
27. Fjordside L, Jeppsen U, Eap CB, Powell K, Baumann P, Brosen K. The streoselective metabolism of fluoxetine in poor and extensive metabolisers of sparteine. Pharmacogentics. 9:55–60 (1999).
28. Gram L F. Fluoxetine. N Engl J Med. 331: 1354–1361 (1994).
29. Harvey, A T, Preskorn S H. Fluoxetine pharmacokinetics and effect on CYP2C19 in young and elderly volunteers. J Clin Psychopharmacol. 21(2): 161–166 (Apr 2001).
30. Carrillo JA, Dahl ML, Svensson J O, Alm C, Rodriguez I, Bertillsson L. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. Clin Pharmacol Ther. 60: 183–190 (1996).
31. Bloomer J C, Woods F R, Haddock R E, Lennard M S, Tucker G T. The role of cytochrome P-450D6 in the metabolism of paroxetine by human liver microsomes. Br J Clin Pharmacol. 33: 521–523 (1992).
32. Tang SW, Helmeste D, Paroxetine, Expert Opin Pharmacother. 2008 Apr;9(5):787–94.
33. Preskorn S H. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. Clin Pharmacokinet. 32 (suppl.1): 1–21 (1997).
34. Murdoch D, Mc Tavish D. Sertraline. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. Drugs. 44 (4): 604–624 (October 1992).
35. Rochat B, Amey M, Gillet M, Meyer U A, Baumann P. Identification of three cytochrome P-450 isozymes involved in N-demethylation of citalopram enantiomers in human liver microsomes. Pharmacogentics. 7: 1–10 (1997).

36. Mandrioli R, Forti GC, Raggi MA, Fluoxetine metabolism and pharmacological interactions: the role of cytochrome p450, Curr Drug Metab, 2006 Feb;7(2):127–33.
37. Spina E, Scordo MG, D'Arrigo C, Metabolic drug interactions with new psychotropic agents, Fundam Clin Pharmacol, 2003 Oct;17(5):517–38.
38. Richelson E. Pharmacology of antidepressants. Mayo Clinic Proceedings. 76(5):511-527(May 2001).
39. Brosen K. The pharmacogenetics of the selective serotonin reuptake inhibitors. Clin Investig. 71: 1002–1009 (1993).
40. Jeppesen U, Gram L F, Vistisen K, Loft S, Poulsen H E, Brosen K. Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. Eur J Clin Pharmacol. 51: 73–78 (1996).
41. Gram L F, Hansen M G, Sindrup S H, Brosen K, Poulsen J H, Aaes-Jorgensen T, and Overo K F. Citalopram: interaction studies with levomepromazine, imipramine, and lithium. Ther Drug Monit. 15: 18–24 (1993).
42. Lane R, Baldwin D. Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. J Clin Psychopharmacol. 17 (3): 208–221 (1997).
43. Clark DB, Andrus MR, Byrd DC, Drug interactions between linezolid and selective serotonin reuptake inhibitors: case report involving sertraline and review of the literature, Pharmacotherapy. 2006 Feb;26(2):269–76.
44. Hamilton S, Malone K. Serotonin syndrome during treatment with paroxetine and risperidone. J Clin Psychopharmacol. 20(1): 103–105 (Feb 2000).
45. Voirol P, Hodel P F, Zullino D, Baumann P. Serotonin syndrome after small doses of citalopram or sertraline. J Clin Psychopharmacol. 20(6): 713–714 (Dec 2000).
46. Ishii M, Tatsuzawa Y, Yoshino A, Nomura S, Serotonin syndrome induced by augmentation of SSRI with methylphenidate, Psychiatry Clin Neurosci. 2008 Apr;62(2):246.
47. Evans RW, The FDA alert on serotonin syndrome with combined use of SSRIs or SNRIs and Triptans: an analysis of the 29 case reports, MedGenMed. 2007 Sep 5;9(3):48.
48. Copeland J, Dillon P, Gascoigne M, Ecstasy and the concomitant use of pharmaceuticals, Addict Behav. 2006 Feb;31(2):367–70.
49. Karki SD, Masood GR, Combination risperidone and SSRI-induced serotonin Syndrome, Ann Pharmacother. 2003 Mar;37(3):388–91.
50. Gnanadesigan N, Espinoza RT, Smith R, Israel M, Reuben DB, Interaction of serotonergic antidepressants and opioid analgesics: Is serotonin syndrome going undetected?, J Am Med Dir Assoc. 2005 Jul-Aug;6(4):265–9.
51. Schwartz AR, Pizon AF, Brooks DE, Dextromethorphan-induced serotonin syndrome, Clin Toxicol (Phila). 2008 Sep;46(8):771–3.
52. Rang ST, Field J, Irving C, Serotonin toxicity caused by an interaction between fentanyl and paroxetine, Can J Anaesth. 2008 Aug;55(8):521–5.
53. Gordon L, Giraud E, Ganière JP, Armand F, Bouju-Albert A, de la Cotte N, Mangion C, Le Bris H, Serotonin syndrome caused by interaction between citalopram and fentanyl, J Appl Microbiol. 2007 Apr;102(4):1167–76.
54. Brown T M, Skop B P, Mareth T R. Pathophysiology and management of the serotonin syndrome. Ann Pharmacother. 30: 527–533 (1996).
55. Mills K C. Serotonin syndrome. Am Fam Physician. 52(5): 1475–82 (Oct 1995).
56. Weitzel C, Jiwanlal S. The darker side of SSRIs. RN. 64(8): 43–48 (Aug 2001).
57. Carbone J R. The neuroleptic malignant and serotonin syndromes. Emerg Med Clin North Am. 18(2):317–25 (May 2000).
58. Dams R, Benijts T H, Lambert W E, Van Bocxlaer J F, Van Varenbergh D, Van Peteghem C, De Leenheer A P. A fatal case of serotonin syndrome after combined moclobemide-citalopram intoxication. J Anal Toxicol. 25(2): 147–51 (Mar 2001).
59. Hernandez A F, Montero M N, Pla A, Villaneuva E. Fatal moclobemide overdose or death caused by serotonin syndrome? J Forensic Sci. 40(1): 128–30 (Jan 1995).
60. Rogde S, Hillberg T, Teige B. Fatal combined intoxication with new antidepressants. Human cases and an experimental study of postmortem moclobemide redistribution. Forensic Sci Int. 100(1–2): 109–16 (Mar 1999).

61. Goeringer K E, Raymon L, Christian G D, Logan B K. Postmortem forensic toxicology of selective serotonin reuptake inhibitors: a review of pharmacology and report of 168 cases. J Forensic Sci. 45(3): 633–48 (May 2000).
62. Keltner N, Harris C P. Serotonin syndrome: a case of fatal SSRI/MAOI interaction. Perspect Psychiatr Care. 30(4): 26–31 (1995).
63. Loke YK, Trivedi AN, Singh S, Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs, Aliment Pharmacol Ther. 2008 Jan 1;27(1):31–40.
64. Reeves RR, Wise PM, Cox SK, SSRIs & the risk of abnormal bleeding, J Psychosoc Nurs Ment Health Serv. 2007 Apr;45(4):15–21.
65. Helin-Salmivaara A, Huttunen T, Grönroos JM, Klaukka T, Huupponen R, Risk of serious upper gastrointestinal events with concurrent use of NSAIDs and SSRIs: a case-control study in the general population, Eur J Clin Pharmacol. 2007 Apr;63(4):403–8.
66. Mort JR, Aparasu RR, Baer RK, Interaction between selective serotonin reuptake inhibitors and nonsteroidal antiinflammatory drugs: review of the literature, Pharmacotherapy. 2006 Sep;26(9):1307–13.
67. Zullino DF, Khazaal Y, Increased risk of gastrointestinal adverse effects under SSRI/NSAID combination may be due to pharmacokinetic interactions, Br J Clin Pharmacol. 2005 Jan;59(1):118–9.
68. Richards S, Umbreit JN, Fanucchi MP, Giblin J, Khuri F,Selective serotonin reuptake inhibitor-induced rhabdomyolysis associated with irinotecan, South Med J. 2003 Oct;96(10):1031–3.
69. DeVane C L, Nemroff C B. 2000 guide to psychotropic drug interactions. Primary Psych. 7(10): 40–68 (2000).
70. Preskorn SH. Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors, 1st ed., Professional Communications Inc., Caddo, OK, 1996.
71. Spina E, Avenoso A, Facciol G, Scordo M, Anciono M, Madia A. Plasma concentrations of risperidone and 9-hydroxyrisperidone during combined treatment with paroxetine. Ther Drug Monit. 23(3): 223–227 (June 2001).
72. Bostwick J, Brown T. A toxic reaction from combining fluoxetine and phentermine. J Clin Psychopharmacol. 16(2): 189–190. Letter (Apr 1996).
73. Mamiya K, Kojima K, Yukawa E, Higuchi S, Ieiri I, Ninomiya H, Tashiro N. Phenytoin intoxication induced by fluvoxamine. Ther Drug Monit. 23(1): 75–77 (Feb 2001).
74. Nelson M H, Birnbauma A K, Remmel R P. Inhibition of phenytoin hydroxylation in human liver microsomes by several selective serotonin reuptake inhibitors. Epilepsy Res. 44(1): 71–82 (Apr 2001).
75. Eap C, Bertschy G, Powell K, Baumann P. Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. J Clin Psychopharmacol. 17(2): 113–117 (Apr 1997).
76. Preskorn S, Greenblatt D, Harvey A. Lack of effect of sertraline on the pharmacokinetics of alprazolam. J Clin Psychopharmacol. 20(5): 585–586. Letter. (Oct 2000).
77. Hassan P, Sproule B, Naranjo C, Hermann N. Dose-response evaluation of the interaction between sertraline and alprazolam in vivo. J Clin Psychopharmacol. 20(2): 150–158 (Apr 2000).
78. Taylor D. Selective serotonin reuptake inhibitors and tricyclic antidepressants in combination. Interactions and therapeutic uses. Br J Psychiatry. 167 (5): 575–80 (Nov 1995).
79. Markowitz J, DeVane C L. Rifampin induced selective serotonin reuptake inhibitor withdrawal syndrome in a patient treated with sertraline. J Clin Psychopharmacol. 20(1): 109–110. Letter. (Feb 2000).
80. Hemeryck A, De Vriendt C, Belapaire F M. Effect of selective serotonin reuptake inhibitors on the oxidative metabolism of propafenone: in vitro studies using human liver microsomes. J Clin Psychopharmacol. 20(4): 428–434 (Aug 2000).
81. Sayal K, Duncan-McConnell D A, McConnell H W. Taylor D. Psychotropic interactions with warfarin. Acta Psychiatr Scand. 102(4): 250–255 (Oct 2000).
82. Moller S E, Larsen F, Khan A, Rolan P E. Lack of effect of citalopram on the steady state pharmacokinetics of carbamazepine in healthy male subjects. J Clin Psychopharmacol. 21(5): 493–499 (Oct 2001).

83. Bertschy G, Eap C B, Powell K, Baumann P. Fluoxetine addition to methadone in addicts: pharmacokinetic aspects. Ther Drug Monit. 18(5): 570–572 (Oct 1996).
84. Bauer M, Zaninelli R, Muller-Oerlinghausen B, Meister W. Paroxetine and amitriptyline augmentation of lithium in the treatment of major depression: a double-blind study. J Clin Psychopharmacol. 19(2): 164–171 (Apr 1999).
85. Fagiolini A, Buysse D J, Frank E, Houck P, Luther J F, Kupfer D J. Tolerability of combined treatment with lithium and paroxetine in patients with bipolar disorder and depression. J Clin Psychopharmacol. 21(5): 474–478 (Oct 2001).
86. Hemeryck A, Lefebvre R, De Vriendt C E, Belpaire F M. Paroxetine effects metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. Clin Pharmacol Ther. 67(3): 283–291 (Mar 2000).
87. Dhir A, Kulkarni SK, Risperidone, an atypical antipsychotic enhances the antidepressant-like effect of venlafaxine or fluoxetine: possible involvement of alpha-2 adrenergic receptors., Neurosci Lett. 2008 Nov 7;445(1):83–8.
88. Garcia A, Adverse effects of propafenone after long-term therapy with the addition of citalopram, Am J Geriatr Pharmacother. 2008 Jun;6(2):96–9.
89. Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, Hayes DF, Desta Z, Flockhart DA, Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine, J Natl Cancer Inst, 2003 Dec 3;95(23):1758–64.
90. Scott G N, Elmer G W. Update on natural product- drug interactions. Am J Health Syst Pharm. 59(4): 339–347 (Feb 2002).
91. Callaway J C, Grob C S. Ayahuasca preparations and serotonin reuptake inhibitors: a potential combination for severe adverse interactions. J Psychoactive Drugs. 30(4): 367–9 (1998).
92. Izzo A A, Ernst E. Interactions between herbal medicines and prescribed drugs: a systemic review. Drugs. 61(15): 2163–2175 (2001).
93. Montgomery S A, Judge R. Treatment of depression with associated anxiety: comparisons of tricyclic and selective serotonin reuptake inhibitors. Acta Psychiatr Scand. 101 (403): 9–16 (2000).
94. Emslie G J, Walkup J T, Pliszka S R, Ernst M. Nontricyclic antidepressants: current trends in children and adolescents. J Am Acad Child Adolesc Psychiatry. 38(5): 517–528 (May 1999).
95. Trindade E, Menon D, Topfer L A, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ. 159: 1245–52 (1998).
96. Huska MT, Catalano G, Catalano MC, Serotonin syndrome associated with the use of escitalopram, CNS Spectr. 2007 Apr;12(4):270–4.
97. Corrington K A, Gatlin C, Fields K. A case of SSRI-induced hyponatremia. J Am Board Fam Pract. 15(1):63–65 (2002).
98. Fitzgerald MA, Hyponatremia associated with SSRI use in a 65-year-old Woman, Nurse Pract. 2008 Feb;33(2):11–2.
99. Wright SK, Schroeter S, Hyponatremia as a complication of selective serotonin reuptake inhibitors, J Am Acad Nurse Pract. 2008 Jan;20(1):47–51.
100. McKoy G K, Ed, American Hospital Formulary Service Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 1954 &1966 (1999).
101. Lane R M. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. J Psychopharmacol. 12(2): 192–214 (1998).
102. Alldredge B K. Seizure risk associated with psychotropic drugs: clinical and pharmacokinetic considerations. Neurology. 53(5): S68-S75 (1999).
103. Serebruany VL, Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? Am J Med. 2006 Feb;119(2):113–6.
104. Weinrieb RM, Auriacombe M, Lynch KG, Lewis JD, Selective serotonin re-uptake inhibitors and the risk of bleeding, Expert Opin Drug Saf. 2005 Mar;4(2):337–44.
105. Weinrieb RM, Auriacombe M, Lynch KG, Chang KM, Lewis JD, A critical review of selective serotonin reuptake inhibitor-associated bleeding: balancing the risk of treating hepatitis C-infected patients, J Clin Psychiatry. 2003 Dec;64(12):1502–10.

106. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study, Dalton SO, Johansen C, Mellemkjaer L, Nørgård B, Sørensen HT, Olsen JH, Arch Intern Med. 2003 Jan 13;163(1):59–64.
107. Paruchuri P, Godkar D, Anandacoomarswamy D, Sheth K, Niranjan S, Rare case of serotonin syndrome with therapeutic doses of paroxetine, Am J Ther. 2006 Nov-Dec;13(6):550–2.
108. Rasmussen B, Brosen K. Is therapeutic drug monitoring a case for optimizing clinical outcome and avoiding interactions of the selective serotonin reuptake inhibitors? Ther Drug Monit. 22(2): 143–154 (2000).
109. Lundmark J, Bengtsson F, Nordin C, Reis M, Walinder J. Therapeutic drug monitoring of selective serotonin reuptake inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients. Acta Psychiatr Scand. 101(5): 354–359 (2000).
110. Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, Jozier-Perey M. A double blind, placebo – controlled study of citalopram with and without lithium in the treatment of therapy – resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol. 16(4): 307–314 (1996).

Chapter 7
Antipsychotic Drugs and Interactions: Implications for Criminal and Civil Litigation

Michael Welner and Lewis Opler

Abstract Antipsychotics can be classified into two general types: *traditional antipsychotics* (also referred to as first-generation antipsychotics or FGAs and as standard neuroleptics) and *atypical antipsychotics* (also referred to as second-generation antipsychotics or SGAs).

Both traditional and atypical antipsychotics treat positive psychosis symptoms such as hallucinations and delusions by blocking dopamine neurotransmitter receptors [1]. The traditional antipsychotics, however, all cause extrapyramidal motor side effects (EPS), including acute dystonias, drug-induced parkinsonism, and akathisia [1].

Clozapine, the first atypical antipsychotic, was synthesized by scientists attempting to develop a new tricyclic antidepressant. Instead, clozapine turned out to treat positive psychosis symptoms, but, without causing EPS, leading to its being referred to as an *atypical antipsychotic.*

Keywords Traditional antipsychotics • Atypical antipsychotics • Second-generation antipsychotics • First-generation antipsychotics

Both traditional and atypical antipsychotics treat positive psychosis symptoms such as hallucinations and delusions by blocking dopamine neurotransmitter receptors [1]. The traditional antipsychotics, however, all cause extrapyramidal motor side effects (EPS), including acute dystonias, drug-induced parkinsonism, and akathisia [1].

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Table 7.1 Atypical antipsychotics and some of the typical antipsychotics available in the United States, along with their brand names

Name	Generic name	Chemical type	Atypical/traditional
Abilify	Aripiprazole	Quinolone	Atypical
Clozaril	Clozapine	Dibenzodiazepines	Atypical
Geodon	Ziprasidone	Benzisothiazole	Atypical
Haldol	Haloperidol	Butyrophenones	Traditional
Invega	Paliperidone	Benzisoxazole	Atypical
Loxitane	Loxapine	Dibenzoxazepine	Traditional
Moban	Molindone	Dihydroindole	Traditional
Navane	Thiothixene	Thioxanthene	Traditional
Orap	Pimozide	Diphenylbutylpiperidine	Traditional
Prolixin	Fluphenazine	Phenothiazine	Traditional
Risperdal	Risperidone	Benzisoxazole	Atypical
Seroquel	Quetiapine Fumarate	Dibenzothiazepine	Atypical
Thorazine	Chlorpromazine	Phenothiazine	Traditional
Zyprexa	Olanzapine	Thienobenzodiazepine	Atypical

*Physicians' Desk Reference [3]

Clozapine, the first atypical antipsychotic, was synthesized by scientists attempting to develop a new tricyclic antidepressant. Instead, clozapine turned out to treat positive psychosis symptoms, but, without causing EPS, and leading to its being referred to as an *atypical antipsychotic.*

This serendipitous discovery that clozapine had antipsychotic efficacy without causing EPS led to the development of five additional *atypical antipsychotics,* all of which treat psychosis [2], without causing clinically significant EPS, either by affecting other neurotransmitter systems in addition to dopamine, or, in the case of aripiprazole, by being a partial dopamine receptor agonist (activator) (Table 7.1).

Interactions involving antipsychotics:

1. Make side effects of the antipsychotics more pronounced
2. Render the antipsychotics less effective
3. Affect the metabolism of other medicines (referred to as pharmacokinetic drug–drug interactions), and either increase or decrease their effects and side effects depending upon whether they block or induce metabolism

Both older and more recently developed varieties of antipsychotics are known for their manifold side effects on numerous organ systems. Interactions have forensic significance when efficacy and/or side effects are heightened by the co-prescription of medicines that affect antipsychotic metabolism.

Drug interactions involving antipsychotics warrant particular scrutiny in the elderly, the brain-damaged, those on other psychotropics, and those with a history of special sensitivity to antipsychotics.

Given the severe conditions for which antipsychotic prescribing is reserved, interactions also have forensic relevance when an antipsychotic is no longer effective because of the medicines prescribed along with it. In these cases, the greatest

forensic significance of the drug interaction is the relapse of the root illness, rather than drug's side effects.

Before we explore how these interactions manifest themselves in criminal and civil case scenarios, an appreciation for the neurochemistry involved is necessary.

Key Neurochemistry of Antipsychotics

Antipsychotics are able to exert their effects by influencing how specific chemicals, known as neurotransmitters, move through the brain. Messages pass through the nervous system, from cell to cell, by these chemical neurotransmitters [4]. Psychosis and other psychiatric maladies occur when the delicate equilibrium of each of these microscopic neurochemical transmitters is disrupted. The chemical imbalance causes chain reactions that result in the development of symptoms or outwardly visible behaviors.

Antipsychotics impact a number of neurotransmitters and regulatory systems in the body. Like other psychotropics, antipsychotics exert their effects on receptors of these neurotransmitters, receptors that normally catch and relay the transmitting neurochemical that has been released by the nerve cell nearby.

In addition to directly blocking dopamine transmission at D2 receptors, antipsychotics have antihistaminic and anti-adrenergic effects [4]. All traditional antipsychotics, particularly those that are classified as low potency such as chlorpromazine, have anticholinergic effects due to blockade of the muscarinic class of receptors [5]. The effects of such neurotransmitter blockade depend not only on the neurotransmitter, but where in the brain that neurotransmitter is active, as well as what role it plays.

Atypical antipsychotic drugs earn their name, in part, because they do not cause effects on movement to the extent that the traditional antipsychotic drugs do. While each of the atypical antipsychotics impacts a distinct profile of neurotransmitters, five of the atypical class block dopamine D2 receptors as well as serotonin 2A receptors [6], while one (aripiprazole) is a partial dopamine agonist and therefore interferes with dopamine transmission in brain areas where it is overactive while promoting dopamine transmission in brain areas where it is too low.

Dopamine: The Benefits and Movement Problems Caused by Its Blockade

Dopamine has been the foundation of antipsychotic treatment. Traditional antipsychotics' influence on the different centers of dopamine activity has directly and indirectly accounted for side effects of forensic significance.

Psychotic illnesses and certain drug intoxications, such as cocaine and amphetamines, arise from altered dopamine transmission. Traditional antipsychotics decrease or eliminate psychotic symptoms like hallucinations and delusions, and organize confused thinking, regardless of their origin. These medicines block

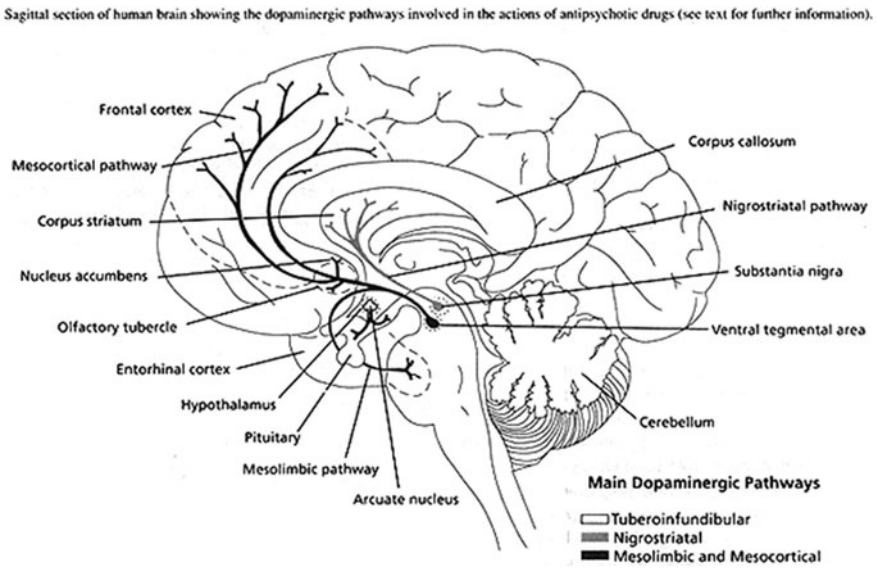

Fig. 7.1 Primary dopaminergic pathways

dopamine transmission at D2 receptors in the mesolimbic nerve pathways that lead to the nucleus accumbens in the limbic system of the brain (Fig. 7.1) [4].

Dopamine activity is associated with numerous vital human functions. Therefore, regrettably dopamine blocking in other areas of the brain results in unwanted consequences as well.

Parkinsonism, dystonia, akathisia, tardive dyskinesia, and tardive dystonia stem, through a variety of mechanisms, from the capacity of antipsychotics to block dopamine transmission in the brain [7]. Dopamine activity in the brain substantia nigra is necessary for unrestricted movement. Potent blockade of dopamine transmission from the substantia nigra at D2 receptors is therefore associated with severely slowed movements, a resting tremor, loss of the ability to instinctively maintain upright posture (postural reflex), and trouble in initiating movement [7, 8].

These symptoms mimic the movement disorders of Parkinson's disease, in which the degeneration of dopamine-transmitting nerve cells leads to symptoms [9]. Because the nerve cells of those receiving antipsychotic treatment are not deteriorating – it is merely the transmission of dopamine that is blocked – the symptoms of dopamine blocker–induced parkinsonian-type symptoms are reversible.

Parkinsonism may result in more dangerous consequences, particularly when problems with regulating postural reflexes manifest. A person so affected, when pushed, has trouble regaining footing; falls can result, and in the elderly or those with advanced osteoporosis, spills may cause hip fractures [10]. Compounding the significance of this risk is the greater sensitivity of the elderly to parkinsonian effects from traditional antipsychotics [11].

While logically, one might assume that reversing these symptoms should be accomplished with a medicine that promotes dopamine transmission to overcome a dopamine blockade, remember that dopamine transmission in mesolimbic nerve pathways would aggravate the symptoms of psychosis that start this mess in the first place. Clinicians thus rely upon the important relationship between acetylcholine and dopamine to remedy some movement problems, specifically the parkinsonian symptoms.

Dopamine released in the substantia nigra blocks acetylcholine transmission [4]. Therefore, dopamine-blocking drugs prevent the suppression of acetylcholine. Anticholinergics such as benztropine and trihexyphenidyl reduce the dopamine-blocking effects on the substantia nigra without affecting dopamine blocking that treats psychosis [12]. Anticholinergics are also instrumental at providing an immediate reversal of symptoms of dystonia [13].

Dystonia involves the relatively abrupt onset of severe and extended spasm of a muscle group. Typically, muscles of the back, neck, eyes, or tongue are involved [9]. But when muscles of the larynx spasm, a person can suffocate [14]. Fortunately, over 90% of dystonic reactions occur within 2 weeks of starting treatment [15]. Furthermore, anticholinergics quickly reverse these effects [16]. However, a dystonic reaction in the wrong setting can still inspire fear, humiliation, and an unwillingness to continue with treatment.

Unlike parkinsonian effects, dystonia has not been definitively localized as originating in the substantia nigra. However, its dramatic reversal by anticholinergics is further evidence of an elegant balance between dopamine blockage and the potency of acetylcholine transmission.

Dopamine blockade at D2 receptors in other movement centers in the brain is not so easily reversed by anticholinergics. Other dopamine-induced movement disorders are thought to result from phenomena that have less to do with acetylcholine, and more with other numerous effects of the traditional antipsychotics.

Antipsychotics and Akathisia

Akathisia, unlike dystonia and parkinsonism, begins to develop – often insidiously – weeks after the antipsychotic treatment begins [17]. The subjective sense of restlessness, akathisia, is exquisitely uncomfortable [18]. Visitors to psychiatric wards who encounter patients pacing the hallways are likely witnessing a person's response to akathisia.

Primarily high-potency traditional antipsychotics are associated with the development of akathisia. These include haloperidol, fluphenazine, trifluoperazine, and thiothixene [19]. Risperidone, an atypical antipsychotic, also causes akathisia in some of the patients taking that medicine. Pimozide is a high-potency traditional antipsychotic, but is typically prescribed at very low doses for its clinical effect. This is in part due to its potential at higher doses to prolong the Qt interval on electrocardiograms (ECGs), thereby increasing the risk of arrhythmia.

Because atypical antipsychotics do not frequently cause akathisia, many presume that the dopamine-blocking qualities of traditional antipsychotics account for this movement disorder. However, drugs that promote dopamine transmission, or anticholinergics that reverse dopamine-blocking effects leading to parkinsonism, do not relieve akathisia.

The delay in onset of akathisia suggests that traditional antipsychotics' causative influence is indirect – the antipsychotics initiate a chain reaction that can culminate in akathisia.

Further shrouding the neurochemical understanding of akathisia is its treatment; β-blockers and benzodiazepines, which improve akathisia, act in a general manner on both the central and peripheral nervous systems [20]. Therefore, unlike the anticholinergics, for example, the mystery of why akathisia can be improved by broadly acting drugs conceals the neurochemical and neuroanatomic mechanisms responsible for akathisia in the first place.

While prescribing fluphenazine and haloperidol, their potential to cause akathisia and other high-potency side effects such as tardive dyskinesia must also be taken into account. These two antipsychotics are often prescribed in oil-based depot forms that are injected into fatty areas of the buttocks or rear shoulder, and released steadily into the bloodstream over a period of 2–4 weeks [21].

Since the onset of akathisia is more common weeks after a medicine has begun, and since those patients on depot medicines have the prospect of slowly metabolizing antipsychotics accumulating in their system, these patients are at higher risk for developing akathisia. Since patients taking depot haloperidol or fluphenazine are managed as outpatients, their akathisia may go undetected, relative to the discomfort of someone on a hospital ward who is under intermittent observation all day, every day.

An additional dilemma associated with akathisia is that patients often find it difficult to express the source of their discomfort or restlessness. Families or physicians may note a sense of increasing distress, and may mistakenly – and sometimes understandably – attribute that disquiet to psychosis, from undertreatment or noncompliance with the antipsychotic. If the psychiatrist's reaction is to then increase the dose of the dopamine-blocking antipsychotic, the akathisia only gets. By the time the basis for the patient's discomfort is identified, the mounting discomfort may cause the patient to refuse further treatment.

Civil and Criminal Law and Implications of Akathisia

Those who experience akathisia feel a driven pressure to keep moving, and the effects are enough to have been occasionally associated with suicide [22].

The clinician must distinguish akathisia's internal discomfort from the outward expression of discomfort through hostility and assaultiveness. Theoretically, one might imagine a scenario in which someone is so uncomfortable from his akathisia that he might strike out at another. However, resolving this idea requires factoring in a person's inherent baseline predisposition to assaulting others.

The notion of someone's violence arising exclusively from akathisia in a person who is not otherwise violent is unsubstantiated in the clinical literature. As such, this notion would likely not achieve *Daubert* standards for having been systematically studied and confirmed as a cause–effect relationship between akathisia and violence.

Tardive Dyskinesia

Tardive dyskinesia baffled clinicians for decades. This involuntary and disfiguring twisting movement of muscles of the face, tongue, hands, or feet [9] was found in people who had been treated with traditional antipsychotics, particularly those who had been treated with those drugs for an extended period [23]. Complicating tardive dyskinesia was its sometimes irreversible course [8]; many who stop traditional antipsychotics, hoping the tardive dyskinesia would somehow improve, note no change. Some even experience a worsening of symptoms that improve only when their medicines are restored [23].

Traditional antipsychotics have all been known to frequently cause tardive dyskinesia, [7] as often as 20% for those who have taken these medicines as long as 4 years [4]. Less commonly, the antipsychotics cause tardive dystonia, an involuntary tightening of muscle groups, usually of the head and neck [8]. The pronounced impact of irreversible tardive dyskinesia and dystonia on appearance and body image has civil liability implications. Disfigurement can be as grievous as surgical errors in the head and neck or other sensitive body areas.

Atypical antipsychotics of the newer generation are far less likely to cause tardive dyskinesia [24]. Of course, once these medicines have been in use for many years, we may learn otherwise. Clozapine, the original atypical antipsychotic, is the only antipsychotic that has been shown to treat tardive dyskinesia.

Current neuropsychiatric perspective primarily endorses the idea that dopamine receptor hypersensitivity is responsible for tardive dyskinesia [4]. This idea, while otherwise completely consistent with our understanding of neurotransmitters and psychotropic drugs' impact on the sensitivity of neuroreceptors, does not successfully account for Vitamin E's therapeutic effects. Other possible causes of tardive dyskinesia include damage to the gamma-amino-butyric acid or GABA tract; in Huntington's chorea, there is an actual loss of GABA fibers leading to what are referred to as "box car ventricles." The choreoathetoid (twisting, writhing) movement disorder of Huntington's chorea and that of tardive dyskinesia is indistinguishable.

Dopamine Blockade and Interactions

The parkinsonian side effects of traditional antipsychotics are enhanced by the coadministration of the mood stabilizer lithium [25]. Lithium added to traditional antipsychotics also increases the risk for tardive dyskinesia and akathisia [25]. Still, the

combination of traditional antipsychotics with lithium is safe and essential for many individuals whose health would collapse otherwise from persistent psychosis.

The risk of parkinsonism, and of akathisia, is also heightened when fluphenazine is taken by those who chew betel nut. Betel nut, chewed as a recreational drug in many countries, is a mild stimulant, also known as *areca catechu* [26].

Dopamine Blockade: Cognitive Side Effects of Note

The frontal cortex of the brain includes some of the most sophisticated intellectual and cognitive qualities that distinguish man as the most able of the animal kingdom. Dopamine transmission occurs in the frontal lobe as well [27]. Blockade of dopamine transmission through mesocortical nerve pathways to the frontal lobe is therefore accompanied by substantial intellectual impairment [28]. Closer study has specified these problems as attention, memory, planning, problem solving, and effortful cognitive processing [29].

The dopamine-blocking effects of traditional antipsychotics on the frontal cortex may be difficult to readily detect, especially in diagnosis on the schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizoid personality). Each of these conditions is associated with a baseline of low initiative, simple thinking, passivity, emotional withdrawal, anhedonia, lack of spontaneity, poor attention, and/or more impoverished expression, or negative symptoms [30]. Perhaps these qualities reflect that dopamine activity in the frontal lobe is diminished to begin with, even before the patient takes medicines [4].

For this reason, medication side effects on the frontal lobe, particularly because they are subtle to begin with, commonly go unnoticed. Further complicating the aforementioned overlap is the resemblance of these symptoms to depression, and to a lack of stimulation resulting from the abandonment of many with this condition.

The standard for care in psychiatry has not achieved the attentiveness to schizophrenia that mandates neurocognitive testing of those being medicated with dopamine blockers in order to ensure that cognitive effects independent of the disease process can be accounted for. However, as our sensitivity to the functional rights of our patients improves, this seems to be an appropriate objective – certainly in line with informed consent.

Antipsychotics, Cognition, and Implications for Criminal Law

Impaired cognition can be especially relevant in the appraisal of a defendant's ability to render a knowing and intelligent confession. Cognitive impairment may impact a defendant's competency, or his criminal responsibility.

The limited cognitive flexibility of those with schizophrenia and the subduing qualities of dopamine blockade do not include a suspension of morality.

Antipsychotic-induced cognitive changes, pertinent to the above issues, pale in importance to the cognitive processes of the underlying disease. It is not the dopamine blockade that impacts mental competency for specific tasks within the course of a criminal case, but the underlying condition may be relevant, especially if the legal issues are nuanced and the deficits are pronounced.

Cognitive problems associated with some traditional antipsychotics have been attributed to the anticholinergic properties of the given medicines, in addition to effects on dopamine transmission in the cortex [1]. Memory and mental clarity can be affected in this way [31]. Chlorpromazine and thioridazine each possess high intrinsic anticholinergic activity, in addition to being more highly sedating than most other antipsychotics [21]. Higher doses of antipsychotics cause increased sedation, at which point all cognitive domains are affected [21].

In the unusual circumstance of anticholinergic toxicity, confusion may be implicated in crime, particularly a disorganized event. An acute change in mental status, such as would be seen in a delirium associated with anticholinergic drug toxicity, would give reason to question competency to waive Miranda. The fast reversibility of this drug effect, however, renders this an unlikely consequence in cases of questioned trial or sentence competency.

Antipsychotics, Cognition, and Implications for Civil Law

Impaired cognition associated with the effects of traditional antipsychotics may be responsible for motor vehicle or heavy equipment accidents that kill or injure the patient or someone else. In other instances, work proficiency may be affected, resulting in the loss of a job.

The cognitive deficits identified with traditional antipsychotics do not readily affect decision-making for parenting, contracts, and other simple transactions. The cognitive effects of the underlying condition are of more likely pertinence to problems people experience in these matters. However, presuming parental, contract, and other incompetence on the basis of even an advanced presentation of schizophrenia – without a specific assessment relating to capacity – is unfair and professionally irresponsible.

Atypical antipsychotics may impact cognition as well; these effects are more directly related to the sedating qualities of the medicines, however, than anticholinergic properties [1].Clearly, however, there are cognitive advantages to the atypical antipsychotics, which we will review and explain below.

Other Dopamine-Blockade Side Effects of Note

Dopamine transmission from the hypothalamus to the anterior pituitary is also blocked by traditional antipsychotics [4]. This blockade causes an increase in circulating prolactin levels. Indirectly, therefore, dopamine blockade results, through this

mechanism, in unexpected breast secretions, or galactorrhea, menstrual interruption, and amenorrhea [4].

Sexual dysfunction occurs in a number of individuals taking dopamine-blocking antipsychotics [28]. Whether elevated prolactin levels – or direct effects of dopamine blockade on the sexual arousal cycle – are responsible, has not yet been determined. Nevertheless, atypical antipsychotics, which (with the exception of risperidone) do not cause a significant rise in prolactin levels, have and have not been shown to be associated with sexuality effects [32].

Closer attention to the sexual arousal cycle is necessary in order to sort out the potential troubles that both traditional and atypical antipsychotics can cause. After discussing neurotransmitters other than dopamine, we will focus on sexuality later in the chapter, as well as the civil forensic implications.

Acetylcholine Blockade Through Anti-Muscarinic Effects

In addition to the cognitive side effects noted above, anticholinergic effects also include dry mouth, blurred vision, constipation, and urinary retention [33].

Independent of cognitive effects, visual problems can affect work performance, as well as equipment and motor vehicle operation. Furthermore, visual impairment may result in misdiagnosis of other eye conditions, prompting unnecessary treatment.

Chlorpromazine, thioridazine, perphenazine, and molindone are most frequently associated with causing blurred vision [28]. However, those who are especially sensitive to the anticholinergic properties of traditional antipsychotics may experience vision effects as well.

Older individuals, particularly men with benign prostatic hypertrophy, are going to be more sensitive to the urinary side effects of anticholinergics. Protracted effects can contribute to serious kidney problems, because urine is not passing through the excretory channels. Risk is heightened when the patient has only sporadic outpatient follow-up.

While a desire to avoid the parkinsonian, dystonic, and akathisia effects associated with high-potency neuroleptics might favor low-potency antipsychotics, anticholinergic side effects offset any apparent advantage. Some patients simply are too affected by the anticholinergic and other effects of the low-potency drugs, which are far more pronounced than they are in high-potency antipsychotic drugs.

Antihistaminic Effects and Weight Gain

Traditional antipsychotics also have been associated with blocking histamine and adrenergic receptors. Antihistaminic effects are responsible for sedation and weight gain. The weight gain, unfortunately, may persist even with careful dieting and exercise.

All traditional and atypical antipsychotics have antihistaminic effects (with the reported exception of the atypical antipsychotic ziprasidone and the traditional antipsychotic molindone) and are associated with substantial weight gain [34]. This side effect has important implications for the management of heart disease, diabetes, and high blood pressure, as well as other conditions that are aggravated by obesity.

This is more than merely an "eating hot dogs causes cancer" point. If someone can trace the origin of weight gain or diabetes to prescription of an antipsychotic, then scrutiny of the basis for the physician's conceding those health risks must be warranted. This is part of the standard dialogue of today's doctor-patient care, particularly because medication alternatives are available.

Sugar Metabolism

Traditional and atypical antipsychotics, especially clozapine and olanzapine, impair glucose metabolism [35] (though risperidone has proven in the period of its use to be less associated with this side effect) [36]. For those with diabetes, or who develop type 2 diabetes, the progression of this pernicious condition has a major impact on quality of life in many functional domains.

New-onset diabetes from atypical antipsychotics [37] does not merely introduce long-term risks of stroke, heart disease, and end-organ damage. A number of cases of sudden death from diabetic ketoacidosis have been attributed to atypical antipsychotics [37].

Given the Achilles' heel of the advanced treatments, regularly monitoring sugar metabolic functions is therefore a responsibility of prescribing psychiatrists.

Atypical Antipsychotics: Different Areas of the Brain, Different Effects

Serotonin inhibits dopamine release. Blockade of serotonin 2A receptors, therefore, allows dopamine transmission to occur [4]. Atypical antipsychotics (with the exception of aripiprazole) have both serotonin S2 and dopamine D2 receptor–blocking properties [4]. With the potential for both dopamine stimulation as well as blockade, and the side effects of blockade, the answer to the riddle of atypical antipsychotics rests in the neuroanatomy.

In the nigrostriatal area, atypical antipsychotics (with the exception of risperidone) block a far lower percentage of D2 receptors than traditional antipsychotics. The degree of blockade remains below the threshold to produce parkinsonian effects [4]. In the case of risperidone, while nigrostriatal D2 receptors are blocked, this is counteracted by potent S2 blockade.

Dopamine blockade causes prolactin release; serotonin blockade limits prolactin release [4]. Effects on prolactin levels differ between antipsychotics, suggesting other neurochemical or neuroanatomical forces are also pertinent.

In the mesolimbic pathway, where dopamine transmission influences psychotic symptoms, dopamine blockade predominates over the effects of serotonin 2A blockade [4]. Therefore, atypical antipsychotics are able to successfully exert their clinical effects without the baggage of dopamine blockade in untargeted areas of the brain.

As for the mesocortical pathway, serotonin 2A blockade activity predominates in the atypical antipsychotics, so dopamine transmission in the frontal lobes is ultimately enhanced [4]. This accounts for improvements in initiative, expression, interest, and a variety of other frontal lobe functions in those with schizophrenia spectrum disorders.

The availability of atypical antipsychotics, with their favorable effects on cognition, increases the viability of malpractice liability for the effects of traditional antipsychotics. No longer can the effects of traditional antipsychotics be readily explained away by the severity of the illness, and the "lesser of two evils" argument.

As social and occupational reintegration of the chronic mentally ill assumes greater importance in mental health care, the expectations of the chronic mentally ill will be felt in liability demands and request for workplace and parental accommodations because of the cognitive enhancing potential of the atypical antipsychotics relative to the traditional antipsychotics.

α-Adrenergic Effects

Anti-adrenergic effects, which act at α1 receptors, are implicated in sedation, as well as sudden drops of blood pressure upon rising from a laying or sitting position (orthostatic hypotension) [38].

The traditional antipsychotics, particularly chlorpromazine and thioridazine, may cause precipitous drops in blood pressure through α-adrenergic blockade [39]. These medicines have been implicated as well in sudden death [40]. Effects on blood pressure, specifically in the case of chlorpromazine and thioridazine, may be amplified by the antihypertensives propranolol and pindolol; the latter β-blockers have been shown to increase the blood levels of both of those antipsychotics [41], and add to the hypotensive effects of the antipsychotics. Other antihypertensives such as ACE inhibitors and clonidine, which have no effect on the amount of antipsychotic in the bloodstream [42], also increase the hypotensive effects of antipsychotics via pharmacodynamic mechanisms (i.e., synergy of mechanisms of action, but not involving changes in blood levels of drugs).

While novel antipsychotics are otherwise appreciated for their less pronounced effects on blood pressure, clozapine, the atypical antipsychotic, has nevertheless been frequently associated with precipitous drop of blood pressure [43].

Clozapine has also been reported to cause inflammation of the heart muscle (myocarditis) and degeneration of the heart muscle (cardiomyopathy) [44]. Furthermore, alcohol and benzodiazepines increase orthostatic hypotension when taken along with olanzapine [45]. Therefore, clinicians should regard advantages of newer antipsychotic medicines in less absolute terms, so as to avoid overlooking the need to monitor patients for dizziness and to educate them to recognize signs of such circulatory problems.

Sudden Death and Cardiac Conductance

Sudden death from antipsychotics does not result typically from hypotension, but from arrhythmias [46]. The effects at this writing appear to begin with antipsychotic-induced blockade of potassium channels, through which electrical signals flow through the heart to make it beat in an orderly manner [47]. The resulting disturbance, in the rare instances in which it progresses to ventricular arrhythmia, would cause sudden death.

Pharmaceutical marketing campaigns have highlighted the association of thioridazine especially, with torsades de pointes, a disturbance featuring prolonged cardiac rhythm conduction [48]. Theoretically, torsades de pointes may be responsible for some sudden deaths attributed to antipsychotics, if heart rhythm conduction is slowed to a severe degree. However, because antipsychotics and diagnoses of torsades de pointes has no more than rarely been demonstrated in practice [49], the current discussion in the medical literature may prove to be overestimated in its importance to later forensic questions.

Given that the rare phenomenon of sudden death is real, the need to minimize the risk of torsades de pointes is necessary. Attention to combinations of medicines and their relative risk is therefore essential. Antipsychotics that may introduce risk in patients who are on other medicines that affect cardiac conduction also include droperidol [50]. This medicine, used more frequently in preoperative settings, or in emergency rooms, has been assigned a special warning by the FDA, for reasons similar to the noticeably more risky thioridazine [49].

Neuroleptic Malignant Syndrome (NMS)

This very uncommon, but emergent condition may spontaneously arise in those who have been prescribed antipsychotics, particularly the traditional variety [51]. NMS is characterized by a collapse of the body's regulatory system – blood pressure, temperature, and pulse – followed by catastrophic muscle breakdown all over the body. If not treated, NMS results in death from respiratory failure

(due to breakdown of muscles in the respiratory apparatus), or kidney failure (due to sludging of proteins from muscles being broken down) [52].

It is not so simple to explain NMS as attributable to dopamine blockade. The primary treatment of NMS is a neuromuscular blocking agent. And, in more recent years, atypical antipsychotics have been implicated in cases of NMS, specifically olanzapine [53], quetiapine [54], clozapine [55], and risperidone [56].

The neurophysiologic causes of NMS have not been identified, and no way of preventing it has been found. Clinicians are thus forced to be vigilant for signs of early NMS, in order to immediately stop the antipsychotic medication or arrange for more supportive care, if necessary. NMS is clearly a condition where immediate recognition and aggressive response is necessary in order to prevent death. Unfortunately, in some cases, quick intervention is still too late.

Sexual Side Effects: Serotonin and Other Neurotransmitters

A number of neurochemicals affected by antipsychotics impact the sexual response cycle. Stage one of the cycle, *libido*, is enhanced by dopamine [4] and diminished by prolactin [4]. Antipsychotics therefore can potentially diminish libido by dopamine blockade and/or enhancing prolactin release.

Stage two, *arousal*, involves erection in men and lubrication in women. Arousal is enhanced by acetylcholine, and more indirectly by dopamine. Serotonin indirectly may reduce arousal, but this effect has been identified only in patients taking antidepressants [57]. Arousal, therefore, can be inhibited by both traditional and atypical antipsychotics through two mechanisms, anticholinergic- and dopamine-blocking activity.

Stage three, *orgasm*, is not affected by dopamine, acetylcholine, or other of the principle neurochemicals of antipsychotics. However, serotonin diminishes orgasm [4], which may explain orgasm difficulties found in those prescribed atypical antipsychotics.

Thus, most traditional and atypical antipsychotics invariably affect the gonadotropic hormonal system. Ultimate effects on relationships and marriages, as well as procreation, can be profound.

Priapism is a rare side effect in which blood is trapped in the erect penis because of circulatory changes [58]. This rare effect is associated with those antipsychotics, chlorpromazine and thioridazine in particular, with the greatest α-adrenergic blockade [58]. Fortunately, this reaction is very rare, enough that it should not be affecting prescribing decisions unless it has happened. An informed patient can recognize that priapism is medicine related, and can seek treatment in an emergency room without panic.

The management of sexual side effects is, well, a touchy subject. Many of those who take antipsychotics have very guarded boundaries and have difficulty broaching issues of sexuality. Impotence and sexual disinterest is embarrassing for them, and

often feeds into and off of a low self-esteem that becomes the major, chronic illness. This area is an example of the burden facing the psychiatrist to educate patients at the time of informed consent about sexual side effects, and to probe side effects beyond perfunctory general questions or questionnaires. However, questionnaires may satisfy standards of care, they do not represent quality care.

Seizures

Traditional antipsychotics lower the threshold at which someone with a history of seizures will experience a seizure [21]. In practice, this risk is primarily pertinent to those with already diagnosed seizure disorders. The atypical antipsychotic clozapine may directly cause seizures at higher dose, even in patients with no previous history [59]. If there are no treatment alternatives, that drawback does not outweigh the benefits of continuing to prescribe the medicine.

However, seizures from medications can be reduced in frequency with antiseizure medicines added to the regimen. Other interactions must then be addressed, specifically those resulting from the tendency of many antiseizure medicines to lower blood concentrations of antipsychotics.

Poor physician management of antipsychotic drug treatment is often the reason for intolerable side effects. If patients discontinue treatment because of unacceptable experiences with antipsychotics when medicines might have been helpful had they been competently managed, injury relating to unmanaged illness may establish a viable malpractice claim.

Interactions and Drug Metabolism

Ingested and injected antipsychotics are eventually broken down in the liver, through the enzyme system known as cytochrome P450 (CYP). From there, a transformed product, as well as unchanged drug, enters the bloodstream to exert their effects [4].

This CYP system involves many subsystems, or isoenzymes [45]. Research in recent years has increasingly delineated which of the isoenzyme systems is responsible for metabolizing which drugs, what drugs inhibit that metabolism, and what drugs stimulate that metabolism. Well over 30 isoenzymes in the CYP system have been identified to date (Table 7.2).

Table 7.2 The known isoenzymes associated with antipsychotic metabolism

CYP 1A2	Clozapine, chlorpromazine, thioridazine, olanzapine, trifluoperazine, thiothixene
CYP 2D6	Clozapine, olanzapine, thioridazine, risperidone, perphenazine, molindone, fluphenazine, chlorpromazine, thiothixene
CYP 3A4	Pimozide, quetiapine, ziprasidone, clozapine, chlorpromazine, haloperidol

Generally, antipsychotics are metabolized by multiple means; this may explain why the blood levels of antipsychotics, based on available research, tend to be less affected by medicines that activate or inhibit at the level of the CYP system [60]. Most combinations of medicines with antipsychotics have not yet been studied to the endpoint of clear impact of medicines on the metabolism of that specific drug, with a few exceptions.

Medicines that slow the metabolism of traditional antipsychotics do so by inhibiting those enzymes in the liver that would otherwise break down the antipsychotics. This causes the antipsychotics to accumulate, and side effects, including cognitive effects, to be more pronounced [1] (Table 7.3).

Table 7.3 Medicines that inhibit the breakdown of antipsychotics via enzymatic mechanisms

CYP system	Antipsychotic whose metabolism inhibited	Inhibiting medicine – type or use of medicine	Degree of inhibition, if known
1A2	Clozapine, chlorpromazine, thioridazine, olanzapine, trifluoperazine, thiothixene	Fluvoxamine – antidepressant	High
		Cimetidine – gastric distress	
		Ciprofloxacin – antibiotic	High
		Norfloxacin – antibiotic	
		Paroxetine – antidepressant	Moderate
		Moclobemide – antidepressant	
		Tertiary tricyclic antidepressants	Moderate
2D6	Clozapine, olanzapine, thioridazine, risperidone, perphenazine, fluphenazine, chlorpromazine	Ritonavir – anti-AIDS	Moderate
		Indinavir – anti-AIDS	Low
		Fluoxetine – antidepressant	High
		Paroxetine – antidepressant	High
		Sertraline – antidepressant	Moderate
		Fluvoxamine – antidepressant	Low
		Citalopram – antidepressant	Low
		Venlafaxine – antidepressant	Low
		Bupropion – antidepressant	Low
			Moderate
		Secondary tricyclic antidepressants	Low
		Moclobemide – antidepressant	Low
		Perphenazine – antipsychotic	Low
		Fluphenazine – antipsychotic	Low
		Mesoridazine – antipsychotic	Low
		Haloperidol – antipsychotic	Low
		Chlorpromazine – antipsychotic	
		Thioridazine – antipsychotic	
		Cimetidine – gastric distress	
		Cocaine	
		Methadone	
		Quinidine – antiarrhythmic	
		Amiodarone – antiarrhythmic	

(continued)

Table 7.3 (continued)

CYP system	Antipsychotic whose metabolism inhibited	Inhibiting medicine – type or use of medicine	Degree of inhibition, if known
3A	Pimozide, quetiapine, ziprasidone, clozapine, chlorpromazine, haloperidol	Ritonavir – anti-AIDS	High
		Indinavir – anti-AIDS	High
		Amprenavir – anti-AIDS	
		Nelfinavir – anti-AIDS	Moderate
		Saquinavir – anti-AIDS	High
		Fluvoxamine – antidepressant	High
		Fluoxetine – antidepressant	High
		Sertraline – antidepressant	Moderate
		Paroxetine – antidepressant	Moderate
		Nefazadone – antidepressant	High
		Tricyclic antidepressants	Moderate
		Thioridazine – antipsychotic	
		Haloperidol – antipsychotic	Low
		Erythromycin – antibiotic	High
		Clarithromycin – antibiotic	High
		Azithromycin – antibiotic	High
		Troleandomycin – antibiotic	
		Diltiazem – antihypertensive	High
		Verapamil – antihypertensive	
		Ketoconazole – antifungal	
		Fluconazole – antifungal	
		Omeprazole – antiulcer	
		Itraconazole – antifungal	
		Dexamethasone – steroid	Low
		Cimetidine – anti-gastric upset	High
		Amiodarone – antiarrhythmic	
		Mibefradil – antihypertensive	

Still other medicines add their own anticholinergic properties, and can heighten the cognitive impairing effects of traditional antipsychotics [1]. The antidepressants with the highest anticholinergic qualities are amitryptyline and imipramine.

While these medicines are far less commonly prescribed for depression and anxiety compared to previous years, tricyclic antidepressants often are prescribed to help treat pain. Therefore, particularly when patients are seeing more than one specialist, communication between all clinicians is vital to minimize risks associated with prescribing a patient an overly anticholinergic regimen.

Those medicines that stimulate CYP enzymes in the liver to break down antipsychotics faster gain forensic significance when a subsequent drop in medication levels leads to a relapse of symptoms, and behaviors or consequences of the relapsed condition (Table 7.4).

Table 7.4 Medicines that lower the blood levels of circulating antipsychotics

CYP system	Antipsychotic whose metabolism activated	Activating medicine – type or use of medicine	Degree of activation, if known
1A2	Clozapine, chlorpromazine, thioridazine, olanzapine, trifluoperazine, thiothixene	Ritonavir – anti-AIDS Phenytoin – antiseizure Carbamazepine – antiseizure/ mood stabilizer Barbiturates – antiseizure/sedative Marijuana Cigarettes Omeprazole – antiulcer	
2D6	Clozapine, olanzapine, thioridazine, risperidone, perphenazine, fluphenazine, chlorpromazine		
3A4	Pimozide, quetiapine, ziprasidone, clozapine, chlorpromazine, haloperidol	Ritonavir – anti-AIDS Rifampin – anti-TB Efavirenz – anti-AIDS Nevirapine – anti-AIDS Rifabutin – antibiotic St. John's wort – antidepressant Felbamate – antiseizure Topiramate – antiseizure Oxcarbazepine – antiseizure/ mood stabilizer Carbamazepine – antiseizure/ mood stabilizer Phenytoin – antiseizure Barbiturates – antiseizure/ sedative dexamethasone – steroids Troglitazone – antidiabetic	

Other Agents Affecting Antipsychotic Blood Levels

The antidepressant nefazadone has been shown to decrease the clearance of haloperidol from the body by about 33%. Given haloperidol's association with parkinsonism, and that effect's increase in risk associated with falls, coadministration of these drugs should be performed with attentive care. On the other hand, another antidepressant, venlafaxine, has been shown to increase the clearance of a single dose of haloperidol [61].

Tricyclic antidepressants increase the blood levels of one or both drugs when administered together with antipsychotics [61].

For some with psychotic illnesses, combination drug therapy with multiple antipsychotics is employed. This practice has been described as causing untoward and

unusual side effects, from increasing the likelihood of parkinsonism to neuroleptic malignant syndrome [31].

The antipsychotic thioridazine and the antiseizure medicine phenytoin have been shown to decrease circulating levels of quetiapine, however [62]. And, administration of the antipsychotic risperidone, or clozapine, with the antimanic valproate results in an inconsistent concentration of both drugs [62]. These interactions are clinically significant because of the life morbidity associated with relapsing bipolar disorder and unstable schizophrenia spectrum disorders, and the need to treat those conditions with strict compliance.

Clozapine, when administered together with a benzodiazepine, may result in confusion, excess sedation, or even rare respiratory collapse [43]. Caffeine increases blood levels of clozapine [62]; clinicians are wise to anticipate the scenario of a patient self-medicating for fatigue, with coffee, who initiates a cycle of more sedation and consequent self-medication with coffee. The SSRIs fluoxetine and paroxetine can increase clozapine blood levels by blocking CYP450 2D6. Because the SSRI fluvoxamine blocks all three major metabolic pathways of clozapine (CYP450 2D6, CYP450 3A4, and CYP450 1A2), its use with clozapine is strongly discouraged.

Risperidone increases blood levels of clozapine [45]. A clinician who adds risperidone to clozapine, expecting synergistic antipsychotic effects, may get more synergy than he bargained for.

Clozapine continues to represent a fascinating quandary for clinicians. For those with difficult-to-treat psychotic disorders, many experience that drug as the most likely antipsychotic to offer meaningful benefit. The drug has its loyalists who contend that it is the best antipsychotic psychiatry has to offer. However, clozapine's increased likelihood of problematic sedation, orthostatic hypotension, cardiomyopathy, myocarditis, weight gain, seizures, and effects on bone marrow poses civil medicolegal risks as well.

One study found that clozapine-treated patients were 3.6 times more likely to suffer sudden death compared to patients treated with other psychiatric agents. The same study, however, showed that those clozapine-treated patients were five times less likely to die of a condition related to their psychiatric disease [63].

Ultimately, the more potentially toxic the antipsychotic, the more significant a clinician should appraise a potential interaction, since even a small effect on the metabolism of that antipsychotic may elicit side effects that are intolerable even in minor or less frequent form. Alternatively, the seemingly minor effect of a small lowering of the blood level of a medicine may result in a relapse of terribly psychotic symptoms such as hallucinations or delusions.

The effect of medicines on each others' metabolism must be remembered when discontinuing a treatment. Medications that inhibited antipsychotic metabolism, such as paroxetine or fluoxetine, when discontinued, may have unexpected effects. Levels of the antipsychotic, no longer inhibited in its metabolism, may drop – resulting in far worse control over psychotic symptoms. In this manner, a person may be totally compliant yet demonstrate a "surprise" clinical change with forensic ramifications.

Theoretically – and this point must be emphasized – the same point can be made about smoking. Cigarette smoking activates the metabolism of CYP 1A2. Therefore,

a person who stops smoking may have a corresponding increase in blood levels of an antipsychotic metabolized through this pathway – along with serious side effects associated with that change, especially if dramatic.

Interactions of Antipsychotics with Other Agents

Antipsychotics are less appreciated for the significance of their influence on the metabolism of other medicines through the CYP system, although perphenazine and other antipsychotics' effects as a 2D6 inhibitor are particularly chronicled. This 2D6 inhibitor may become pertinent in reconstructive investigations involving drugs who are metabolized through that CYP isoenzyme – such as desipramine, nortryptyline, codeine, antiarrhythmics, and some β-blockers. All of these 2D6 medicines can accumulate to a lethal degree in the bloodstream; any drug that inhibits their metabolism, therefore, is of forensic interest.

Many psychotropics have sedating qualities. Not surprisingly, the sedating qualities of antipsychotics are additive to the effects of other medicines [1]. This may have forensic significance, particularly if such oversedation results in an accident.

However, additive effects of antipsychotics cannot be presumed. Thioridazine, as noted above, actually decreases circulating blood levels of quetiapine [64].

Individuality and Metabolism

Forensic examination that focuses on drug interactions must consider that 5–10% of the Caucasian population, genetically, has a poor capacity to metabolize drugs through the CYP isoenzyme 2D6 [65]. This point is especially important with antipsychotics, which are principally metabolized via this particular isoenzyme. If need be, a person's capacity to metabolize may be tested to resolve forensic questions.

Medicine appreciates the principle that metabolic potential worsens as a person advances into old age. Therefore, the elderly may be vulnerable to untoward effects of medicines dosed at prescriptions that may even be modest [66].

Differences in metabolism are increasingly identified that link to gender and race. Poor 2D6 metabolizers, for example, have been found to be less frequent among Asians and African-Americans, compared to Caucasian populations [67]. While isoenzyme activity of CYP 3A4 has been demonstrated to be 40% greater in younger women [68], however, the distinctions relating to other isoenzymes are less pronounced. Furthermore, the distinctions noted in 3A4, and in 2D6 (lower activity during the luteal phase of the menstrual cycle) [69], have not been linked by any research to findings that specifically relate to antipsychotic drug metabolism.

Still, this stage of understanding directs the forensic examiner to monitor the research in this rapidly evolving area, for research findings will increase the relevance of identifying ages and stages of culture and gender-distinct metabolism.

Implications for Criminal Law

Drug interactions in criminal law are far less pertinent to cases than the conditions antipsychotics are prescribed for. For example, most defendants who are unable to render a knowing or intelligent confession have moderate-to-severe mental retardation or significant brain damage that exists independent of the medicine they are taking. With respect to the voluntariness of their confession, antipsychotics again have little bearing; even in higher or toxic doses, involuntary actions are not attributable to the medicines themselves.

Forensic scrutiny of competency to stand trial, or to represent one's self, should incorporate a consideration of the medication regimen. Subtle issues noted below are clearly related to drug interactions. As in other criminal matters, however, symptoms that compromise competency are more likely to result from the condition itself than the treatments for it.

Criminal responsibility may be alleged to relate to involuntary intoxication with medicines, or an untoward reaction from a combination of psychotropics. However, antipsychotics do not cause violence or criminality. In the particular case of clozapine, the medicines may be responsible for preventing violence [70]. Mitigated criminal responsibility – as a by-product of antipsychotic use – would be theoretically more related to crimes clearly committed during a period of frank confusion, in the absence of sustained purposefulness. While obscure, such a plausible scenario will be depicted below.

Far more likely an issue, for an individual prescribed antipsychotics, is the influence of the condition itself – or an untreated co-occurring condition – on criminal responsibility.

Questioning Considerations

How do drug interactions involving antipsychotics impact a knowing and intelligent confession? Let us consider the following example:

> Jimmy Martin, a 25 year-old with a history of schizophrenia, has been admitted to the emergency room under arrest. He allegedly attacked his neighbor with a stick, after which the neighbor called the police, and Jimmy is psychotic.
>
> Seen by the ER attending, Jimmy declares that he is "allergic to Haldol." He is given chlorpromazine 25 mg, along with the benzodiazepine lorazepam. Thirty minutes later, he is seen with a stiff neck, and is diagnosed with dystonia. Given benztropine, Jimmy's dystonia lifts.
>
> Once he is calmer, police interview Jimmy, a man of average intelligence. He tells police he attacked his neighbor.
>
> Was his confession intelligent, and knowing? The forensic examiner needs to review the results of the examinations closest in time to the administration of his benztropine and chlorpromazine to appraise whether there were any signs of confusion or memory disturbance originating from anticholinergic effects.
>
> Reviewing the confession statement, should it be taped or transcribed, enables the examiner to match details of the confession with the alleged crime. Inconsistent details, a changing

story, and/or a confused pattern of relating may herald cognitive impairment originating from a drug interaction involving an anticholinergic antipsychotic.

Of course, should Jimmy be noted as difficult to rouse, due to the cumulative sedation of the lorazepam and chlorpromazine, the ER chart would indicate such a condition.

Adequate medical chart documentation of the mental status exam of prisoners helps resolve questions of knowing and intelligent communications. Never should side effects be presumed. On the contrary; traditional charting practices note changes in the mental status; no news in an ER, is more often no news (or not examined). A lack of documentation bespeaks an unmonitored patient, or a patient that did not call attention to himself through a deteriorating or obviously changed condition.

Irrespective of legal burdens, the medical chart defines events or nonevents. The burden is on a disagreeing party to prove documentation wrong. Later examiners should later raise suspicion of the role of drug interactions only when:

1. A change in cognitive ability is documented.
2. That change coincides with the administration schedule of the medicine, as well as the expected times of their expression of effects and side effects.

Criminal Competencies

When one considers the abilities being assessed, there is truly no basis to contest competency to stand trial on the basis of theoretical drug interactions alone. Given that the trial is extended, any communication between the attorney, or the court, and a defendant should elicit evidence that a person has memory, concentration, or attention problems attributable to the medication regimen. Because these effects are easily reversible, typically within hours to days, a simple telephone call to a caregiving physician can remedy a problem rather than derailing the administration of justice by months simply to lower the dose of a drug.

Mac Brown, a fifty-year old bank employee charged with robbery, has asked the court if he can represent himself. Currently prescribed mesoridazine and trihexyphenidyl, he seemed a bit confused in court, though he is relatively intelligent and educated.

An examination of Mr. Brown reveals him to have a mild delirium. Alteration of his medicines results in a full resolution of the confusion within 18 hours.

Of course, in such cases, modifying the medication may only provide temporary improvement. For lowering the medicines may prompt a relapse of dramatic symptoms of the underlying illness which may affect competency far more vividly than mere drug interactions.

For this reason, delaying the proceedings an additional several days to monitor for mental deterioration of other origin makes good clinical and judicial sense. In the end, drug interactions leading to compromised competency to stand trial need not result in the kinds of delays associated with allowing the effects of acute illness to simmer down.

Competency to be executed is, of course, a standard that is so easy to achieve that a person who is quite mentally impaired may still satisfy criteria. Advanced illness is invariably the causal factor behind such pronounced incapacitation. However, the desperate culture – among both doctors opposed to capital punishment and patients determined to evade the death penalty – makes for interesting possibilities.

> Barry Peterson, convicted of the sex murder of a child, is sentenced to death. Over the course of his stay on death row, and while receiving counseling, he is prescribed sedating antipsychotics to sleep. As his execution date approaches, he becomes progressively more confused. His attorney contests his competency to be executed.

The death row setting and the stress of impending execution are extreme enough to precipitate psychosis. But opposing counsel should still order a comprehensive drug screen, with quantification if necessary. Given the pills and drugs that circulate among prisoners and prison employees, the ease with which a prisoner can hoard and employ mind-altering medicines must be accounted for in any such forensic examination.

So, too, must the prescription decisions of physicians. A doctor may choose, for unconscious or conscious reasons, a prescription whose drug interactions render a death row patient exceptionally disoriented. Without careful accountability, this can be explained away in a medical chart as arising from illness.

Physicians are to be assumed to mean well. However, we must also remember that to many doctors, meaning well involves saving the life of a condemned person at all costs. Careful oversight into the prescribing history of the death row psychiatrist is therefore sensible diligence for the attorney presented with an inmate who has become less competent, perhaps incompetent, to be executed.

Medication Defenses

Antipsychotics do not directly disinhibit, and do not cause acute psychiatric illnesses. In unusual circumstances, interactions can result in crimes that reflect the product of untoward medication effects.

> Sharon Perez was prescribed thiothixene and benztropine. Her psychiatrist felt she looked a bit stiff in her previous appointment, and increased the benztropine. Ms. Perez became increasingly confused, and later exited her apartment at approximately 10:00P after hanging up with her mother. Her mother was worried enough after the conversation to drive over to Sharon's house.
>
> Too late. Sharon had already gone for a drive. She had driven aimlessly for about two miles, before pulling into a convenience store. In so doing, she ran over a customer walking to her car. Police personnel who arrived at the scene found Sharon, perplexed, surrounded by store customers. Asked to read her rights, Ms. Perez complained of blurry vision, though her answers were often irrational.

Notwithstanding the above bizarre example, a prescribed antipsychotic far more likely reflects diminished capacity through the suggestion that whatever the defendant was taking at the time of the crime, it may not have been enough.

Therefore, medicines that accelerate the metabolism of the antipsychotic may be pertinent to a criminal defense, especially if behavioral changes coincided with the time course of the regimen. If the patient followed a doctor's instructions, then the unexpected ineffectiveness of the medicine may be even further supportive to the defense [71].

> Jerry Kasner has been prescribed clozapine for a number of years. He is compliant with his appointments, sees his doctors every two weeks, and had blood levels taken of the drug that show him to be in the therapeutic range.
>
> Recently, he takes up smoking. At some point, between appointments, his friends notice he becomes increasingly withdrawn, taking poor care of his hygiene. On one occasion, ambling out in a mall, he attacks a young lady, whose screams alert passersby to intervene.
>
> Jerry is noted to be peculiar in his manner on arrest, but says very little. Follow-up blood testing reflects that clozapine is still in his system, but in a substantially lower blood concentration.

Typically, patients who consume intoxicants are judged as having become voluntarily intoxicated [72]. Laws may be more accommodating to the benefit of the defense if a defendant drank alcohol or took an illicit drug with the expectation of relief, especially if he were suffering from psychotic mental illness, and the existing antipsychotic regimen was ineffective [73].

Implications for Civil Cases

Antipsychotics have traditionally been the heaviest artillery in the psychiatric drug armamentarium. Also known as "major tranquilizers," the traditional antipsychotics assumed forensic significance because of the significant side effects that could appear fairly dramatically with relatively small fluctuations in dose of the medicine.

With the revolution of psychopharmacology, and the release and widespread use of atypical antipsychotics, forensic civil implications have changed for these medicines. Because there are medicines now available that are not as associated with significant side effects, future civil forensics will relate more directly to the decision to choose traditional vs. atypical antipsychotics.

American Disability Act (ADA)

Adaptation to the workplace when taking traditional antipsychotics was for long a major obstacle. As significant as the impairments from schizophrenia, schizoaffective disorder, bipolar disorder, and psychotic depression are, the impact of those illnesses on employability was worsened by the often-unavoidable side effects of traditional antipsychotics.

The effects of akathisia, driving a person to perpetual motion, would interfere with the essential functions of most work. The cognitive effects of other traditional

antipsychotics also limit even compliant patients with major psychiatric disorders from fulfilling the core demands of intellectual dexterity of many positions.

Parkinsonism also impacts on one's ability to perform essential functions. The condition, which limits the ability to move quickly and spontaneously, may substantially curtail the efficiency with which one can do any task that requires movement. Furthermore, the mask-like face of parkinsonism [74] calls attention to an employee as "medicated," and can further isolate someone who especially needs the support.

New Frontiers of Accommodation

With the release of clozapine, and later, olanzapine, and seroquel, treatments became available that do not affect movement, do not cause parkinsonism, and do not produce confusion. Employees can now engage in more intellectually competitive pursuits, even while taking atypical antipsychotics [75].

The obstacles of traditional antipsychotics have been removed by the next generation. Now, employers can more easily anticipate reversible side effects, and more easily accommodate side effects of interactions such as increased sedation (a side effect of all of the atypical antipsychotics), or dizziness upon rapidly standing (clozapine) [43].

Advances in antipsychotic technology are the most important development in the reintegration of employees under ADA. They render many questions of insurmountable side effects obsolete.

Poor compliance with treatment has also had a major impact on accommodating employees with psychotic mental illness. Atypical antipsychotics have been demonstrated to have superior compliance [76], which in turn promotes maintaining a symptom-free presentation and adherence to a plan worked out for an employee.

Tomorrow's Cases

Mark Frost, 28, has a history of bipolar disorder. He began psychiatric treatment for the first time last month. Six months removed from law school at the time of the onset of his illness, he had no health insurance. Upon admission to a city hospital, he was given fluphenazine and lithium. His symptoms resolved relatively quickly.

After his discharge, Mr. Frost began a new position. While he remained without manic symptoms, he noticed a subjective sense of great restlessness. Others at his firm noticed that he was pacing about the office. After gentle input, a senior partner demanded a drug test, suspecting Mark of being on cocaine or amphetamines.

No cocaine was found in Mark's blood; however, when he demonstrated traces of fluphenazine, and his firm confronted him, Mark disclosed his condition. The employer contacted Mark's psychiatrist to advise him of the firm's concerns; the psychiatrist changed Mark's antipsychotic to olanzapine. Soon afterward, Mark spent noticeably more time at his own desk, without pacing about, and others noted him to be more creative as well.

However, Mark would appear somewhat sluggish in the early morning. A follow-up call to the psychiatrist resulted in the firm's agreement to shift his starting time at work to 10:00 AM. Mark settled into the firm and remains a key part of the firm's future.

As we become more acquainted with the atypical drugs, previously unrecognized interactions will be discovered. Case reports describe panic attacks arising, for example, in those treated with two different antipsychotics [77]. Modifying the regimen and early intervention, in such cases, quickly reverses the side effects without necessarily having to accommodate the condition by changing occupational responsibilities.

Unfortunately for some, even those who derive benefit from the atypical antipsychotics, residual symptoms of the condition may linger. If these symptoms interfere with the performance of essential functions, then even the most tolerable medicines will not salvage the employee's job or warrant accommodation by the employer.

Whenever an employee on an antipsychotic raises an ADA issue, the workplace should immediately establish channels of communication with the treating psychiatrist. Should an employee demonstrate a sudden mental or physical deterioration, any necessary changes relating to contributing drug interactions can be recommended, with quick response. Such structure also reinforces the need for continued compliance with treatment. Adherence to boundaries of confidentiality can still be easily respected.

Malpractice and Other Tort Litigation

Malpractice litigation relating to interactions of antipsychotics is evolving. In the past, physicians confronted liability based on the consequences of traditional antipsychotic side effects, heightened by interactions. Tardive dyskinesia [78] and neuroleptics malignant syndrome [79] are well-established side effects of traditional antipsychotics implicated in later successful litigation following bad outcomes. In the future, malpractice suits may draw greater support based upon the physician's decision to prescribe a traditional antipsychotic that causes movement disorders instead of an atypical antipsychotic.

Informed consent requires disclosure of alternative forms of treatment. Atypical antipsychotics are drugs of choice; therefore, liability may be clear when a patient suffers from the side effects of a traditional antipsychotic when an atypical agent was available and this option was not presented to the patient or otherwise considered.

Yet the confidence in atypical antipsychotics was tempered by the medicines' association with metabolic side effects of its own, most notably glucose intolerance [80]. Personal injury law had traditionally ignored traditional antipsychotic prescription as a source to mine for litigants. However, controversies over Fen-Phen [81] and Vioxx [82] further established the pharmaceutical industry as an approachable, well-resourced target. A number of pharmaceutical-oriented attorneys began aggressively recruiting clients who have been prescribed atypical antipsychotics [83].

Yet an anticipated flurry of litigation has not replicated the Vioxx scenario. Courts continue to define the expectations of such litigation, most recently granting summary judgment against plaintiffs who charged that quetiapine caused his diabetes but

had preexisting history of obesity, hypertension, sedentary lifestyle, among other things[84]. Litigation involving the prescribing of atypical antipsychotics to agitated children, however, may prove to be the next litigation frontier.

Since psychiatric malpractice originates most commonly after unwanted death, particular attention needs to be directed to medication regimens in cases of sudden death. Postmortem toxicology studies may rule out overdose, but medications may still be responsible. Chlorpromazine and thioridazine are two antipsychotics which can cause substantial drops in blood pressure [28]. This effect can be more pronounced in patients given tricyclic antidepressants and monoamine oxidase inhibitors[28].

Significant hypotension has also been described with clozapine [28]. Since so many other medication options are available to treat acute agitation, and psychosis, clinical practice warrants accounting for why these medicines are prescribed instead of medicines that do not represent any risk to the circulatory system – particularly in the medically vulnerable or in those at risk for suicide by overdose.

Unwanted lethality may rarely arise from the very rare side effect of agranulocytosis, or loss of ability to make white blood cells, attributed to clozapine. Risk of this side effect may be heightened by a number of anti-AIDS [85] or anti-cancer agents [86], as well as with carbamazepine [87]. Again, accounting for this risk is sufficient, especially if clinical choices are more restricted.

Other interactions are not so easy to resolve in a cause–effect manner. Sometimes, polypharmacy can collectively worsen a condition. Sometimes the interactions of medicines prescribed for nonpsychiatric conditions can affect glucose metabolism, or worsen sexual function, or contribute to weight gain. These problems may lead to the development of diabetes, divorce, or cardiac problems, respectively. The prescribing physician has a duty to monitor for these difficulties, and to discuss and resolve the problems with his patient, regardless of the different possible causes.

Interactions with antipsychotics may impact tort liability if a patient's excessive sedation or confusion results in impaired operation of a motor vehicle or other lethal equipment. Interactions that increase blood levels of clozapine may be responsible for causing seizures[88], which can create a highway catastrophe. In this regard, standard psychiatric practice has reinforced the responsibility for psychiatrists to advise patients of risks associated with operating such items when prescribed antipsychotics.

Competency to Invest, Testamentary Capacity

Legal questions, often posthumous, arise over decisions to invest or to earmark assets. Since trusts and wills often concern individuals with health problems, such decisions may be affected by the interactions of prescribed drugs. Cases involving such competencies therefore warrant close scrutiny of medical, prescription, and pharmacy records. Comparison of decisions made, with corresponding dates, yields vital detail about the relevance of drug interactions.

As agitation in the medically ill, and in the elderly, is often treated with antipsychotics, confusion and sedation may be attributable to the medicine – if not the underlying condition. Careful consideration of the clinical course will enable the distinction of whether a drug interaction was responsible.

The elderly, and those incapacitated who are making financial decisions, are particularly vulnerable to undue influence. Loving relatives with self-serving motives can position themselves opportunistically. For this reason, sedation, heightened by drug interactions, should also be tracked. If undue influence is suspected, and the agent had continuous proximity to an ill but wealthy patient, the deceased's blood should be tested to ensure that no medicines were administered, in combination, that would have perpetuated mental incapacity or hastened death.

The study of drug interactions is ongoing. New discoveries from clinical use of combinations of an ever-growing pharmacopoeia add to our appreciation of interactions. These findings will one day provide answers to some of the peculiar forensic scenarios that we now suspect are influenced by drug interactions, but cannot yet explain.

References

1. Kaplan H, Sadock B (2007) Synopsis of psychiatry: behavioral sciences clinical psychology (10th ed.). Lippincott, Williams and Wilkins, Philadelphia
2. Stahl S (2001) "Hit-and-run" actions at dopamine receptors, part 1: Mechanism of action of atypical antipsychotics. J Clin Psychiat 62(9):670–671
3. Physicians' Desk Reference. 54th Ed. ©2000 Medical Economics Company, Inc. New Jersey
4. Stahl S (2008) Essential psychopharmacology. Cambridge University Press, United Kingdom
5. Lieberman J, Stroup T, Perkins, D (2006) Textbook of Schizophrenia American Psychiatric Publishing, Inc., Virginia
6. Seeman P (2002) Atypical antipsychotics: Mechanism of action. Can J Psychait 47(1):27–38
7. Wirshing W (2001) Movement disorders associated with neuroleptic treatment. J Clin Psych 62(21):15–18
8. Sethi K (2001) Movement disorders induced by dopamine blocking agents. Semin Neurol 21(1):59–68
9. Kaufman D (1990) Clinical neurology for psychiatrists (3 rd ed.). W.B. Saunders Company, Philadelphia
10. Wallis, L (1998) Textbook of women's health. Lippincott-Raven, Philadelphia
11. Mamo D, Sweet R, Mulsant B, et al (2002) Neuroleptic-induced parkinsonism in Alzheimer's Disease. Psychiat Ann 2(4):249–252
12. Stanilla J, Simpson G (2009) Drugs to treat extrapyramidal side effects. In: Schatzberg A, Nemeroff C. Textbook of Psychopharmacology (4th ed.). American Psychiatric Publishing, Virginia.
13. Hales R, Yudofsky S, Gaddard G (2008) Textbook of psychiatry (5th ed.). The American Psychiatric Publishing, Inc., Virginia:1088.
14. Haddad P, Dursun S (2008) Neurological complications of psychiatric drugs; clinical features and management. Hum Psychopharm Clin 23(1):15–26
15. Matsumoto R, Pouw B (2000) Correlation between neuroloeptic binding to Singam(1) and Sigma(2) receptors and acute dystonic reactions. Euro J Clin Pharmacol 401(2):155–160
16. Velickovic M, Benabou R, Brin M (2001) Cervical dystonia pathophysiology and treatment options drugs 6(13):1921–1943

17. Csernansky J, Schuchart E (2002) Relapse and rehospitalisation rates in patients with Schizophrenia: Effects of second generation antipsychotics. CNS Drugs 16(7):473–484
18. Gorman, Jack (1990) The essential guide to psychiatric drugs. St. Martins Press, New York
19. Holloman L, Marder S (1997) Management of acute extrapyramidal effects induced by antipsychotic drugs. Amer Jourl Health Syst Pharm 54(21):2461–2477
20. Lima A, Soares-Weiser K, Bacaltchuk J, et al (2002) Benzodiazepines for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev 1: CD001950
21. Bernstein J (1984) Clinical psychopharmacology (2nd ed.). John Wright, Massachussetts
22. Siris, S (2001). Suicide and Schizophrenia J Psychopharmacol 15(2): 127–135
23. Sachdev P (2000) The current status of Tardive Dyskinesia. Aust NZ J of Psychiat 34(3):355–369
24. Llorca P, Chereau I, Bayle F et al (2002) Tardive dyskinesias and antipsychotics: A Review. Eur J Psychiat 17(3):129–138
25. Ghadirian A, Annable L, Belanger M et al (1996) A cross-sectional study of Parkinsonism and Tardive Dyskinesia in lithium-treated affective disordered patients. J Clin Psychiat 57(1): 22–28
26. Ayd F (2000) Evaluation the interactions between herbal and psychoactive medications. Psychiatric Times 17(12): 45–47
27. Goldberg E (2001) The executive brain. Oxford University Press, New York 94.
28. Physicians Desk Reference 62nd Edition (2008). Thompson Healthcare Inc, Montvale: New Jersey
29. Asarnow R (1999) Neurocognitive impairments in Schizophrenia: A piece of the epigenetic puzzle. Eur Child Adoles Psy 8(1):15–18
30. American Psychiatric Association (2000) DSM-IV-TR. Washington, DC
31. Knegtering H, Eijck M, Hijsman A (1994) Effects of antidepressants on cognitive functioning of elderly patients. Drug Aging 5(3):192–199
32. Turrone P, Kapur S, Seeman M et al (2002) Elevation of prolactin levels by atypical antipsychotics. Am J of Psychiat 159(1):133–135
33. Haddad P, Sharma S (2007) Adverse effects of atypical antipsychotics: differential risk and clinical implications. CNS Drugs 21(11):911–936
34. Allison D, Mentore J, Heo M (1999) Antipsychotic-induced weight gain: a comprehensive research synthesis Am J Psychiat 156:1686–1696
35. McIntyre R (2002) Psychotropic drugs and adverse events in the treatment of Bipolar Disorders revisited. J Clin Psychiat 63(3):15–20
36. Haupt D, Newcomer J (2001) Hyperglycemia and antipsycotic medications. J Clin Psych 62(27):15–26
37. Jin H, Meyer J, Jeste D (2002) Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. Ann Clin Psychiatry 14(1):59–64
38. Nourian Z, Mow T, Muftic D, et al (2008) Orthostatic hypotensive effect of antipsychotic drugs in Wistar rats by in vivo and in vitro studies of a1-adrenoceptor function. Psychopharmacology 199:15–27
39. Jusic N, Lader M (1994) Post-mortem antipsychotic drug concentrations and unexplained deaths. Brit J Psychiat 165:787–791
40. Ray W, Meredith S, Thapa, P et al (2001) Antipsychotics and the risk of sudden cardiac death. Arch Gen Psych 58(11):1168–70
41. Markowitz J et al (1995) Interactions between antipsychotic and antihypertensive drugs. Ann Pharmacother 29:603–609
42. DeVane C, Markowitz J (2001) Avoiding psychotropic drug interactions in the cardiac patient. TEN 3(5):67–71
43. Grohman R, Ruther E, Sassim N et al (1989) Adverse effects of clozapine. Psychopharmacology 99:101–104
44. Killian J, Kerr K, Lawrence C et al (1999) Myocarditis and cardiomyopathy associated with clozapine. Lancet 354:1841–5

45. DeVane C, Nemeroff C (2000) Psychotropic drug interactions. Primary Psychiatry 7(10):66
46. Haddad P, Anderson I (2002) Antipsychotic-related QTc prolongation, Torsade de Pointes and sudden death. Drugs 62(11) 1649–71
47. Menkes D, Knight J (2002) Cardiotoxicity and prescription of thioridazine in New Zealand. Aust NZ J Psychiat 36(4):492–8
48. FDA Psychopharmacological Drugs Advisory Committee (2000, July 19). Briefing document for Ziprasidone Hydrochloride.
49. Glassman A, Bigger J (2001) Antipsychotic drugs: prolonged QTc interval, Torsades de Pointes and sudden death. Am J Psychiat, 158(11):1774–82
50. Young D (2002) Black-box warning for droperidol surprises pharmacists. Am J Health-Syst Ph 59(6):494, 497, 502–4
51. Smego R, Durack D (1982) The neuroleptic malignant syndrome. Arch Intern Med 142:1183–1185
52. Friedman J (1998) Recognition and treatment of the neuroleptic malignant syndrome. Curr Opin Neurol Neu 1(3): 310–311
53. Reeves R, Torres R, Liberto V et al (2002) Atypical Neuroleptic Malignant Syndrome associated with olanzapine. Pharmacotherapy 22(5):641–644
54. Sing K, Ramaekers G, Van Harten P (2002) Neuroleptic malignant syand quetiapine. Am J Psychiat 159(1):149–150
55. Blum M, Siegel A, Meier R et al (2001) Neuroleptic Malignant-Like Syndrome and Acute Hepatitis during tolcapone and clozapine medication. Eur J Neurol 46(3):158–160
56. Aboraya A, Schumacher J, Abdalla E, et al (2002) Neuroleptic Malignant Syndrome associated with risperidone and olanzapine in First-Episode Schizophrenia. W VA Med J 98(2):63–65
57. Clayton A (2001) Recognition and assessment of sexual dysfunction associated with Depression. J Clin Psychiat 62(3): 5–9
58. Compton M, Miller A (2001) Priapism associated with conventional and atypical antipsychotic medications: a review. J Clin Psychiat 62(5):362–6
59. Pacia S, Devinsky O (1994) Clozapine-related seizures: experience with 5,629 patients. Neurology 44(12):2247–2249
60. Jibson M, Tandon R (2001) An overview of antischizophrenic medications. CNS News Special Edition 2001:49–54
61. Weber S (2002) Drug interactions with antidepressants. CNS News February 2002:27–34
62. Mental Fitness Physician Resource Series (2000). Primary Psychiatry 36
63. Modai I, Hirschmann S, Rava A (2000) Sudden death in patients receiving clozapine treatment: a preliminary investigation. J Clin Psychopharm 20(3):525–327
64. DeVane C, Nemeroff C (2000) Quetiapine drug interactions. Primary Psychiatry 7(10)
65. Greenblatt D (2001) Symposium, American Association for Geriatric Psychiatry. Annual meeting, San Francisco
66. Pies R (1983) Geriatric psychopharmacology. Am Fam Physician 28(4):171–176
67. Pollock B (1994) Recent developments in drug metabolism of interest to psychiatrists. Harv Rev Psychiatry 2(4):204–213
68. Tsunoda S, Harris R, Mroczkowski P et al (1998) Preliminary evaluation of progestins as inducers of cytochrome activity in post-menopausal women. J Clin Pharmacol 38:1137–1143
69. Tamminga W, Werner J, Oostehuis B et al (1999) CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences. Euro J Clin Pharmacol 55(3):177–184
70. Volavka J (1999) The effects of clozapine on aggression and substance abuse in Schizophrenic patients. J ClinPsychol 60(12):43–46 1999
71. Perkins v. United States (1915). 228 F 408
72. Lexsee (2001). 73 ALR 3d 195; West Group
73. Teeters v. Commonwelath (1949). 310 Ky 546, 221 SW2d 85
74. Wyngaarden J, Smith L, Bennett J (1992) Cecil textbook of medicine (19th ed.). W.B. Saunders Company, Philadelphia

75. Meyer P, Bond G, Tunis S (2002) Comparison between the effects of atypical and traditional antipsychotics on work status for clients in a psychiatric rehabilitation program. J Clin Psychiat 63(2):108–116
76. Rosenheck R, Chang S, Choe Y et al (2000) Medication continuation and compliance: a comparison of patients treated with clozapine and haloperidol. J Clin Psych 61(5):382–386
77. Takahashi H, Sugita T, Yoshida K, et al (2004) Effect of queiapine in the treatment of panic attacks in patients with Schizophrenia: three case reports. J Nueropsych Clin N16(1):113–5
78. Accardo vs. Cenac (1998). 97 La. 2320; 722 So. 2d 302
79. Barcai vs. Betwee (2002). 98 Haw. 470; 50 P.3d 946
80. Henderson D, Cagliero E, Copeland P, et al (2005) Glucose metabolism in patients with Schizophrenia treated with atypical antipsychotic agents: a frequent sampled intravenous glucose tolerance test and minimal model analysis. Arch General Psychiat 62:19–28
81. Abelson R (2004, April 24) Texas jury rules against the maker of fen-phen, a diet drug. The New York Times
82. Berenson A (2005, August 20) Jury calls Merck liable in death of man on vioxx. The New York Times
83. Scheller P. (2009). The Largest Pharma Fraud Wistleblower Case in U.S. History. Press Release
84. Guinn vs. Astrazeneca (2009) 598 F. Supp. 2d 1239
85. Gillenwater D, McDaniel J (2001) Rational psychopharmacology for patients with HIV infection and AIDS. Psychiat Ann 31(1):28–32
86. Safdar A, Armstrong D (2001) Infectious morbidity in critically ill patients with Cancer. Crit Care Clin 17(3):531–570
87. Flanagan R, Dunk L (2008) Haemotological toxicity of drugs used in psychiatry. Hum Psychopharm Clin 23(1):27–41
88. Welch J, Manschreck T, Redmond D (1994) Clozapine-induced seizures and EEG changes. J Neuropsych Clin N 6(3):250–256
89. Knegtering H, Eijck M, Hijsman A (1994) Effects of antidepressants on cognitive functioning of elderly patients. Drug Aging 5(3):192–199

Chapter 8
Drugs of Abuse

Matthew P. Juhascik and Amanda J. Jenkins

Abstract The misuse/abuse of drugs is a serious problem in our community. In 2006, the Drug Abuse Warning Network (DAWN) estimated that 1,742,887 emergency room visits in the USA were drug related and that 958,164 were due to the use of an illicit drug [1]. Drugs are classified by the US Controlled Substance Act into categories based on abuse potential and acceptable medical use. Schedule I drugs have a high abuse potential with no currently approved medical uses. The remaining schedules are lesser variations with the abuse potential decreasing with acceptable medical uses. Drugs are abused based on their pharmacological properties which may include euphoria, increase in mood or energy. The use of some drugs causes an activation of the dopamine reward pathway which increases the likelihood of abuse.

There are several factors that affect studying interactions of over-the-counter and prescription drugs with drugs of abuse. First, clinical studies on humans using potentially dangerous drugs of abuse are difficult to get approved and when approved, for ethical reasons, have users of drugs of abuse as the test subjects. It can be difficult to correlate the data obtained from drug users to the general population as some consider that drug addicts are not healthy subjects and should be considered a subset of the general population. Second, any data obtained is based on carefully monitored doses of the pure drug which does not account for impurities/contaminants found in drugs of abuse obtained from street dealers.

In preparation of this chapter, a PubMed search was conducted for the most common drugs of abuse along with phrases such as "drug interaction," "drug–drug interaction," "pharmacokinetic interaction," and "pharmacodynamic interaction" (e.g., "cocaine drug drug interaction"). Articles after 1998 were included if applicable, with the

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exception of several papers considered to be relevant published before 1998. The choice of which drugs of abuse were considered in this chapter was made based on current trends in use and the published articles available. Thus, LSD was not included due to the lack of available data but ketamine was included due to its suggested current use in dance clubs and in drug-facilitated sexual assaults. Finally, several caveats are needed before interpreting the following data. In vitro or animal studies have been included when data from humans was not available. In vitro data may not account for the in vivo production of metabolites, and studies in animals may not translate to humans due to differences in the pharmacologic activity between species. In addition, interactions described below may not be observed in every individual due to differences in age, health status, and pharmacogenomics.

Keywords Cocaine • Amphetamine • Methamphetamine • MDMA • Cannabinoids • Ketamine • Flunitrazepam • GHB

Cocaine

Cocaine (benzoylmethylecgonine) is available clinically for use as a local anesthetic by topical application. This property is a result of increasing the threshold needed to generate an action potential by blocking sodium channel conductance. In addition, cocaine blocks the reuptake of dopamine, serotonin, and norepinephrine. The dopaminergic actions mediated by cocaine are responsible for the behavioral effects, including desirable effects such as euphoria. Cocaine is metabolized in humans by *N*-demethylation to the active metabolite, norcocaine, and by hydroxylation to benzoylecgonine and ecgonine methyl ester. The studies described below demonstrate effects on the pharmacokinetic and pharmacodynamic actions of this stimulant.

Nonhuman Data

Pharmacokinetic and pharmacodynamic interactions have been described for cocaine with other illicit drugs and therapeutic medications. In male Wistar rats, nifedipine and cocaine, administered 30 min after each other for 5 days, altered the quantity of CYP 450 in liver microsomes compared to when either was used alone [2]. Both drugs are substrates for CYP 450, and nifedipine induces cytochrome P450. Therefore, it was not surprising that nifedipine alone significantly increased CYP 450 compared with controls. Cocaine was found to decrease CYP 450 by 17% versus controls, and the drug combination increased CYP 450 by 11% compared with controls. The authors concluded the two compounds were substrate competitors for CYP 3A, and their combination could affect the pharmacokinetics of each drug. In contrast, brain levels of CYP 450 were not significantly altered. The level of CYP 450 in brain is significantly less compared with the liver, only 3% [3].

In another study with cocaine, Rofael and Abdel-Rahman administered cocaine (intravenous, cocaine hydrochloride, 5 mg/kg) and ketamine (gastric gavage, ketamine hydrochloride, 100 mg/kg), alone or in combination to male Sprague-Dawley rats. HPLC analysis of blood and tissue samples for cocaine, benzoylecgonine (BE), norcocaine, and ketamine revealed that coadministration resulted in decreased concentrations of cocaine and norcocaine at all time points measured (5, 15, 30 min). In contrast, BE levels were significantly higher in the combination drug group. The disposition of ketamine appeared not to be affected. The authors suggested competition for the CYP 450 3A isoform, ketamine inhibition of cholinesterases resulting in dominance of the methylesterase pathway for cocaine metabolism leading to BE formation, and ketamine-induced increase in renal and hepatosplanchnic blood flow in rats, as possible explanations [4]. Studies in rodents (rats) have demonstrated that phencyclidine (PCP) has been shown to increase cocaine hepatotoxicity through what the authors believed were changes in cellular sulfhydryl concentration [5]. Another investigation with adult male Sprague-Dawley rats reported that fluoxetine enhanced the stimulation of locomotion caused by cocaine through the suggested mechanism of inhibition of CYP3A by fluoxetine and norfluoxetine. Sertraline and citalopram, which do not affect CYP3A, did not enhance this effect of cocaine [6].

In a further study utilizing a rat model, Beyer et al. exposed male adult Wistar rats to repeated doses of toluene (daily 30 min, 8,000 ppm, for 10 days) or air. Approximately 24 h or 96 h after the last exposure, cocaine (15 mg/kg, intraperitoneal) or saline was administered. Cocaine administration increased locomotor activity and also the concentration of dopamine in the nucleus accumbens. The increases, however, were significantly greater in the animals preexposed to toluene. The authors attributed this to cross-sensitization between toluene and cocaine but did not proffer the mechanism (s) [7].

Diller et al. described the effects of MDMA and cocaine, administered alone and in combination to adult male Sprague-Dawley rats. Conditioned place preference [CPP] was utilized to measure drug effects. MDMA was administered subcutaneously (0, 5, 10 mg/kg) and cocaine, intraperitoneally (0, 2.5, 5 mg/kg). When cocaine was administered alone, preference for the drug increased with dose. For MDMA, preference increased at 5 mg/kg but was similar to control levels at the high dose. Antagonistic effects were observed when both drugs were present. For example, after 5 mg/kg MDMA, cocaine suppressed CPP in a dose-related manner. At the 10 mg/kg MDMA dose, the addition of cocaine resulted in reversal of the antagonism such that CPP was potentiated. The authors suggested the findings may be explained by changes in the pharmacodynamics of serotonin and/or dopamine [8]. It is suggested that depletion of serotonin increases the reinforcing efficacy of cocaine by raising dopamine levels.

Several studies utilizing the mouse as a model have been published. Pretreatment of male CF1-mice with cannabidiol (20 mg/kg, i.p.) increased levels of cocaine in the brain after administration of 40 mg/kg, i.p. Increases in cocaine brain concentrations were significant (2–4 fold) compared with vehicle-pretreated controls for a period up to 60 min. These increases also resulted in a corresponding increased pharmacological response, as assessed by changes in horizontal locomotor activity. Pretreatment with cannabidiol also resulted in increased levels of phencyclidine

following 40 mg/kg, i.p. PCP brain concentrations were increased 2–3 fold for 20–60 min following administration. Increased blood levels, no greater than a 50% increase, were also observed. Pharmacological response was assessed in this part of the study by observing drug-induced platform-fall activity. Three quarters of the mice pretreated with cannabidiol fell from the platform after PCP administration (5 mg/kg) compared to 1 of 12 pretreated with vehicle. The authors suggested drug metabolism, modulation of brain transporters, or alterations in plasma-binding proteins may be responsible. Specifically, the authors did not believe inactivation of CYP 450 was responsible for the findings, but suggested that increasing active transport of drugs into the brain or decreasing transport out of the brain may be responsible. The effects of cannabidiol on brain transporters are unknown, except for the P-glycoprotein Mdr-1 in mice, which it does not appear to modulate. The authors concluded that since cannabidiol increased brain concentrations of cocaine and PCP, cannabinoids may increase the abuse potential of other drugs [9].

The antipsychotic medication aripiprazole is an atypical drug for the treatment of schizophrenia since it is classified as a partial dopamine D_2 receptor agonist. This mechanism of action has generated interest in the drug for the treatment of psychostimulant addiction [10]. Leite et al. injected aripiprazole (0.1, 0.3, or 1 mg/kg) or vehicle to male Swiss mice. Fifteen minutes later amphetamine (3 mg/kg), or ketamine (60 mg/kg) or 30 min later cocaine (5 mg/kg) was administered. Drug effects were assessed by measuring motor hyperactivity. All doses of aripiprazole prevented the effects of amphetamine and cocaine. Only the 1 mg/kg dose of the antipsychotic prevented the stimulant activity of ketamine. The results suggested that aripiprazole exerts its action on dopaminergic and glutamatergic drugs through different mechanisms, possibly through partial D2 receptor agonism and activation of serotonin 1A receptors [11].

Human Data

The following represent case reports and limited studies that have been performed on humans. The coadministration of ethanol and cocaine produces cocaethylene (CE), which has a longer half-life than cocaine. A single oral dose of ethanol (1 g/kg) was administered to ten volunteers followed by deuterium-labeled cocaine (0, 0.3, 0.6, and 1.2 mg/kg, intravenous 15 min constant infusion). A mean (SD) of 17% ± 6% of the dose was converted into CE. In addition, urine BE concentrations were decreased by 48% with increased levels of urinary CE and metabolite, ecgonine ethyl ester [12].

In a review article by Winn et al., it was suggested that cocaine metabolism by CYP 3A4 to norcocaine may be inhibited by protease inhibitors such as ritonavir, indinavir, and efavirenz [13] and increased by antiretrovirals such as nevirapine [14, 15]. The authors recommended the monitoring of drugs that inhibit or induce CYP 3A4 in active cocaine users.

In a case report, Myrick et al. described a patient who presented to the ER following an overdose of trazodone. The patient had stable vital signs but noted priapism. A urine drug screen was positive for opioids and cocaine. Cocaine and psychotropic medications have been associated with cases of priapism in humans. The authors suggested that administration of two vasoactive drugs may pose a greater risk of priapism than a single compound [16]. A mechanism of action for cocaine in causing priapism was proposed by Fiorelli et al. [17]. Cocaine may cause long-lasting arteriosinusoidal dilatation which causes venous pooling of the blood in the corpora cavernosa of the penis.

Beta-adrenergic receptor antagonists are utilized in clinical medicine to treat patients with myocardial injuries unrelated to cocaine use. These drugs may be contraindicated in cocaine positive patients; however, there is limited data to support this position. Fareed et al. described the death of a patient treated with metoprolol after presenting with a cocaine-associated myocardial infarction [18]. The patient admitted snorting approximately 1 g of cocaine 3–4 h before hospital admission. Metoprolol was administered (2 h after admittance) in 2×2.5 mg intravenous doses 5 min apart. In discussion, the authors cited animal models which demonstrated the negative effects of beta-adrenergic receptor antagonists with concomitant use of cocaine [19, 20]. The proposed mechanism was unopposed alpha-adrenergic agonism leading to vasospasm, tissue ischemia, and infarction [18]. Myocardial ischemia was also the theory proposed in a study in humans with propranolol and cocaine with subsequent myocardial ischemia. The authors recommended not using beta-adrenergic antagonists if cocaine is suspected [21].

Atomoxetine, a drug prescribed for adult attention-deficit/hyperactivity disorder, has similar pharmacological effects of stimulants. It has received attention as a potential drug to treat cocaine dependence. Atomoxetine blocks reuptake of norepinephrine due to action at the transporter, and also increases extracellular dopamine concentrations in the prefrontal cortex [22]. Seven cocaine-dependent individuals were administered 4 oral doses of atomoxetine (0, 5, 10, 20 mg) four times per day for 3–5 days prior to administration of cocaine by the intranasal route. Multiple sessions were conducted at each maintenance atomoxetine dose with ascending cocaine doses (4, 20, 40 and 60 mg) self-administered 1.5 h apart. [23]. Atomoxetine decreased cocaine's effects on systolic and diastolic blood pressure and enhanced cocaine's effects on heart rate, without achieving clinical significance. The authors suggest that coadministration of cocaine with atomoxetine should be well tolerated.

Modafinil utilized in the treatment of narcolepsy is another drug being considered to treat cocaine dependence [24]. Its neurotransmitter actions are opposite to cocaine-induced neuroadaptations affecting dopamine and glutamate reward circuits and, therefore, may be useful in reversing the withdrawal symptoms of cocaine. To investigate the safety of this drug combination, seven subjects were administered placebo, low (200 mg/day) or high (400 mg/day) dose modafinil for 4 days prior to a single intravenous infusion of cocaine [24]. The authors reported that this regimen of drug coadministration did not pose medical risk with regard to blood pressure, pulse,

temperature, and electrocardiogram changes. Further, euphoria and cocaine-induced craving were not increased by the addition of modafinil.

Cocaine inhibits CYP 2D6. Therefore, pharmacokinetic drug interactions may be postulated with cocaine and drugs primarily metabolized by this isozyme. In recent years, piperazine-derived compounds have gained popularity as drugs of abuse. Examples include *N*-benzylpiperazine and (1-(3-chlorophenyl)piperazine (mCPP). The latter is metabolized exclusively by the 2D6 isozyme [25]. It is also a metabolite of the antidepressant trazodone. Staack et al. reported the case of a 29-year-old female in which blood and urine were tested for drugs and genotyping performed on blood. Ethanol, COC, CE, and mCPP were detected in addition to diltiazem and metabolites (CYP2D6 substrates). The individual showed the genotype CYP2D6*5/41 and was designated as an intermediate metabolizer. The authors suggested the mCPP and diltiazem in this case were present as adulterants of cocaine. The ratio of the mCPP metabolite to mCPP was abnormal, and the authors postulated that the metabolism of mCPP by CYP2D6 was altered due to cocaine (inhibition) and diltiazem (competition). Co-ingestion and genetic polymorphism with mCPP and cocaine may pose a greater risk for adverse effects, such as serotonin syndrome [26].

Drug interactions may also occur between cocaine and drugs used in therapy. Breccia et al. reported the effects of cocaine use on the treatment of two patients with imatinib. This drug was administered at a dose of 400 mg/day for Ph + chronic myeloid leukemia. Complete hematological remission (CHR) was achieved after 3 and 7 weeks of therapy. Thereafter, the patients lost CHR after 12 and 14 weeks concomitant with exhibiting severe side effects which included sweating, nervousness, muscle cramps, diarrhea, and headache. Imatinib is metabolized by CYP 3A4 and inhibits CYP 2D6 and CYP 4A isozymes. The authors suggested a drug interaction involving metabolism with cytochrome P450 may explain the decreased response to imatinib and increase in cocaine-related side effects [27].

The effects of cocaine on oral contraceptive administration in women have been studied. Seven women aged 21–25 years were taking a combination product of norgestimate and ethinyl estradiol. They were administered placebo or cocaine (intranasal, 0.9 mg/kg) four times during the menstrual cycle [28]. This oral contraceptive did not change the pharmacokinetic, cardiovascular, or subjective effects of cocaine. The authors suggested a possible explanation was that the dose was too low to alter cocaine affects or that the combination product negated any negative effects.

Winhusen et al. studied the effects of methylphenidate (MPH) on cocaine-dependent adults [29]. Since both drugs are stimulants with the potential for cardiovascular toxicity and increased central nervous system activity, coadministration may pose increased risk. The authors utilized a placebo-controlled crossover design with two factors: medication (placebo, 60 mg MPH, 90 mg MPH) and infusion (saline, 20 mg cocaine, 40 mg cocaine). Subjective measures (visual analog scales) and physiological measures (blood pressure, ECG, heart rate) were collected and pharmacokinetic parameters determined from measuring cocaine and MPH in plasma. No interaction was found for blood pressure and heart rate for the infusion part of their study. The medication part of the study had a significant interaction for MPH

which suggested MPH does increase heart rate but does not exacerbate the effects of cocaine on heart rate. There were no clinically significant effects on ECG with both drugs. MPH did not significantly change the pharmacokinetics (e.g., half-life, area under the curve, clearance) of cocaine. Therefore, the authors suggested that MPH use may be tolerated in individuals abusing cocaine.

Research and treatment therapies for cocaine dependence have tended to focus on the dopaminergic pathway. The hypothalamic-pituitary-adrenal axis (HPA) was investigated by Winhusen et al. [30] since cocaine activates this pathway by increasing ACTH and cortisol [31, 32]. Metyrapone suppresses cortisol synthesis and therefore may be beneficial to treat cocaine dependence. A double-blind placebo-controlled crossover design study was conducted with 12 participants. Metyrapone was administered orally in gelatin capsules (lactose, 750-mg metyrapone) and cocaine was administered intravenously as a saline solution (40 mg). Subjective, physiological, pharmacokinetic, and endocrine responses were measured. The authors concluded that metyrapone and cocaine administered at the doses in this study were not cause for safety concerns. Further, metyrapone did not increase the subjective effects of cocaine. The authors recommended that metyrapone should be considered as a potential agent to treat cocaine dependence.

Drug interacting with cocaine	Result of interaction
Nifedipine	Alters quantity of liver CYP450
Ketamine	Decreases [cocaine] and [norcocaine], increases [BE]
Phencyclidine	Increases cocaine hepatotoxicity
Fluoxetine	Increases cocaine-induced locomotion
Sertraline	No interaction
Citalopram	No interaction
Toluene	Increases cocaine-induced locomotion
Cannabidiol	Increases brain [cocaine]
Aripiprazole	Prevents hyperactivity from cocaine
Ethanol	Decreases urine [BE], increases urine [CE]
Ritonavir	Inhibits metabolism to norcocaine
Indinavir	Inhibits metabolism to norcocaine
Efavirenz	Inhibits metabolism to norcocaine
Nevirapine	Increases metabolism to norcocaine
Trazodone	Priapism
Metoprolol	Vasospasm, tissue ischemia, infarction
Atomoxetine	No clinically significant interaction
Modafinil	No negative interaction
mCPP	Change in mCPP metabolism
Imatinib	Decreases response of imatinib, increases cocaine's side effect
Norgestimate/ethinyl estradiol	No interaction
Methylphenidate	No interaction
Metyrapone	No negative interaction

Human data in bold print

Amphetamine/Methamphetamine

Amphetamine (α-Methylbenzeneethanamine) and methamphetamine (*N*, α-dimethylbenzeneethanamine) are sympathomimetic drugs used clinically in the treatment of obesity, attention-deficit disorder, and narcolepsy. Both stimulants have two isomers, d and l, with the d isomer exhibiting greater activity for both compounds. The mechanism of action in the CNS involves the release of neurotransmitters, most notably norepinephrine. They are abused for their stimulant properties and may activate the reward pathways through release of dopamine. Methamphetamine is metabolized by *N*-demethylation to amphetamine, and both drugs undergo aromatic hydroxylation in the liver. Amphetamine is oxidized to norephedrine and deaminated to phenylacetone. The following studies demonstrate drug interactions that may affect the pharmacodynamic activity of amphetamine and/or methamphetamine or change the pharmacokinetic profile of either drug.

Nonhuman Data

Studies in rodents (Wistar rats) demonstrated that sertraline (5 mg/kg, i.p.) and fluoxetine (5 mg/kg, i.p.) pretreatment increased the hyperactivity produced from amphetamine (0.5 mg/kg, i.p.) through a mechanism that did not include increased serotonergic function [33]. The authors suggested that the increase may be due to inhibition of CYP2D which is responsible for the metabolism of amphetamine. Also in Wistar rats, methamphetamine pretreatment (10 mg/kg, once a day for 6 days, i.p.) was found to increase the O-demethylation of dextromethorphan by CYP2D. The authors observed an increase in the metabolism of diclofenac and tolbutamide, with induction of CYP2C6 being the suggested mechanism [34].

Human Data

In a case report of an 18-year-old man, amphetamine reduced the ability of varenicline to aid smoking cessation. It was suggested that competitive or noncompetitive inhibition between the two drugs for the same nicotinic acetylcholine receptor or an increase in mesolimbic dopamine concentrations negated the decrease in withdrawal symptoms due to varenicline [35]. A case report of a 45-year-old man detailed the development of priapism (lasting >48 h and requiring surgery) after concurrent use of quetiapine and amphetamine. The authors did not have data to support any conclusion regarding the cause of the priapism, but suggested that before prescribing quetiapine, the patient should be educated of possible priapism following abuse of amphetamines [36]. In humans, a study on six healthy adults found that 0.5 mg of alprazolam decreased the ability to discriminate the stimulant effects of amphetamine (15 mg). The authors also

found a decrease in the stimulant effects of amphetamine through an undescribed/unknown mechanism, although GABAergic modification or pharmacokinetic changes such as decreased bioavailability were suggested [37]. In a double-blind, psychopharmacologic trial with 41 healthy adults, a high dose of amphetamine (0.25 mg/kg) with a sub-anesthetic dose of ketamine (0.23 mg/kg bolus, followed by a 1-h infusion of 0.5 mg/kg) produced less severe positive symptoms than when either was administered alone. The combination also produced more euphoria and thought disorder when given together, than when given alone. Amphetamine lessened the changes in working memory produced by ketamine. The authors believed that differences in the activation of glutamate and dopamine were responsible [38].

In humans at steady state, conditions for morning dosing of modafinil were not affected by afternoon doses of 20 mg of dextroamphetamine. Modafinil did not apparently affect the pharmacokinetics of steady-state dextroamphetamine [39].

Hydrocortisone (50 mg), which raises levels of cortisol, increased the unpleasant effects of methamphetamine (0.5 mg/kg) and decreased methamphetamine-craving. The decrease in craving may have been due to the increase in unpleasant effects. Coadministration of 750 mg of metyrapone (a cortisol synthesis inhibitor) and methamphetamine may increase the risk of cardiovascular problems through an increase of cardiac automaticity by deoxycortisol, which accumulates due to metyrapone blocking its metabolism to cortisol [40]. A study in humans with pretreatment using either lithium (900 mg/day) or sodium valproate (500 mg/day/3 days, followed by 1,000 mg/day) found that with either drug, changes in brain activity by dextroamphetamine (25 mg) were decreased. The authors suggested that rather than lithium and valoproate directly interacting with the release of dopamine, the mechanism may involve the phosphoinositol cycle, which exhibits increased activity following dextroamphetamine-induced release of dopamine and norepinephrine [41]. Due to a suspected drug–drug interaction following in vitro studies, the use of desipramine with dextroamphetamine was studied in children and adolescents. However, the authors failed to find any significant interaction when desipramine is combined with dextroamphetamine or methylphenidate [42].

Serotonin syndrome is a potentially fatal condition that occurs when excessive serotonin is active in the CNS. Two case reports indicated the development of serotonin syndrome following concurrent use of venlafaxine and dextroamphetamine and dextroamphetamine with citalopram. The authors believed that the SSRIs were blocking reuptake of serotonin and dextroamphetamine was increasing presynaptic release of serotonin and/or inhibiting MAOI's which resulted in toxicity [43].

Lastly, a study in humans to evaluate the coadministration of methamphetamine (0, 15, and 30 mg) and bupropion (150 mg) found that when administered simultaneously, the two drugs were generally well tolerated. Bupropion decreased methamphetamine's cardiovascular effects and reduced its metabolism, thus reducing the concentration of amphetamine. Methamphetamine did not affect the metabolism of bupropion. The pharmacokinetic changes induced by bupropion are thought to be due to the inhibition of CYP2D6 which metabolizes methamphetamine to amphetamine. The pharmacodynamic change may be due to bupropion inhibiting the inward transport of methamphetamine to the presynaptic terminal which would prevent the release of neurotransmitters [44].

Drug interacting with amphetamines	Result of interaction
Sertraline	Increase in hyperactivity
Fluoxetine	Increase in hyperactivity
Dextromethorphan	Increase in metabolism of dextromethorphan
Diclofenac	Increase in metabolism of diclofenac
Tolbutamide	Increase in metabolism of tolbutamide
Varenicline	Decrease in varenicline activity
Quetiapine	Priapism
Alprazolam	Decrease in amphetamine's effects
Ketamine	Variable increase and decrease in effects
Modafinil	No effect
Hydrocortisone	Increase in side effects, decrease in craving
Metyrapone	Increase in cardiovascular problems
Lithium	Decrease in brain activity
Sodium Valproate	Decrease in brain activity
Desipramine	No interaction
Venlafaxine	Serotonin syndrome
Citalopram	Serotonin syndrome
Bupropion	No significant interactions

Human data in bold print

Ecstasy (MDMA)

3,4-Methylenedioxymethamphetamine (*N*, α-Dimethyl-1,3, benzodioxole-5-ethanamine, MDMA) is a compound similar to methamphetamine that is currently not used clinically. Pharmacologically, it has both stimulant and psychedelic effects and is commonly abused at dance clubs or "raves." The main mechanism of action is on the release and reuptake inhibition of serotonin in the brain. However, MDMA may also affect dopamine in a similar manner. It is abused for its euphoric affects and an increased sense of well-being. MDMA is metabolized via breakage of the methylene bridge to a methoxy, hydroxy, and a dihydroxy metabolite by CYP2D6. An active metabolite, MDA (methylenedioxyamphetamine), is formed by *N*-demethylation and accounts for approximately 3–5% of the dose of MDMA. All metabolites may eventually be conjugated to enhance excretion.

In Vitro Data

An in vitro study found that MDMA inhibited the *N*-demethylation of methadone by inhibiting CYP2D6. The authors suggested that this interaction may reduce the clearance of methadone in the presence of MDMA [45].

Nonhuman Data

In Sprague-Dawley rats, a large dose of fluoxetine (10 mg/kg, i.p.) significantly altered the metabolism of MDMA (5 mg/kg, p.o.) and MDA through a suspected inhibition of CYP2D6. The half-lives for both compounds increased and the clearance decreased. The authors discouraged the use of fluoxetine as a neuroprotective agent for MDMA due to a possible increase in the toxic side effects of MDMA and MDA [46]. In Long-Evans rats, ethanol (1.5 g/kg, i.p.) was given with MDMA (6.6 mg/kg, i.p.) intermittently (to reflect casual use in humans) and tolerance was not seen in the synergism of ethanol on MDMA-induced hyperactivity or on the ability of ethanol to reduce MDMA-induced hyperthermia [47]. In Dark Agouti rats given large doses of ethanol (to reflect binge drinking in humans), MDMA-induced neuronal damage was increased. The damage was thought to be caused by an increase in free radicals and was dependent on the concentration of acetaldehyde. Acetaldehyde is metabolized by aldehyde dehydrogenase and the authors suggested that humans deficient in aldehyde dehydrogenase may demonstrate increased neuronal damage [48]. A study in Sprague-Dawley rats found that MDMA (10 mg/kg, i.p.) significantly increased serotonin concentrations when moclobemide (20 mg/kg, i.p.) was administered. The authors suggested this increase was due to inhibition of monoamine oxidase-A by moclobemide, which is responsible for serotonin metabolism [49]. In Fawn-Hooded rats, the combination of LSD (0.04 mg/kg) with a low dose of MDMA (0.15 mg/kg), produced a response similar to a normal dose of MDMA (1.5 mg/kg). The authors speculated that LSD was acting on serotonin receptors mimicking the actions of MDMA and leading to a synergistic effect [50]. In Sprague-Dawley rats, the combination of caffeine (10 mg/kg, s.c.) and MDMA (10 mg/kg, s.c.) resulted in a large increase in heart rate. Normally, MDMA causes a decrease in heart rate due to a suspected baroreceptor reflex; the authors hypothesized that caffeine may inhibit this reflex and that the drug combination in humans could result in a life-threatening cardiac episode [51]. Caffeine (5–20 mg/kg, i.p.) was also found to increase the hyperthermia induced by MDMA (15 mg/kg, i.p.) and MDA (7.5 mg/kg, i.p.) and to increase the loss of serotonin in Sprague-Dawley rats [52].

Human Data

In humans, fluoxetine pretreatment (20 mg/day) decreased the subjective (drug liking, mood elevation) and physiologic effects (heart rate) of MDMA (1.5 mg/kg). The authors cited preclinical studies that demonstrated SSRI prevent the uptake of MDMA into serotonin neurons as an explanation for their observations [53]. In men, a pharmacokinetic and a pharmacodynamic interaction with MDMA (100 mg) were seen following pretreatment with paroxetine (20 mg/day/3 days). Paroxetine increased the concentration of MDMA through a suspected inhibition of CYP2D6, which is responsible for the break of the methylene ring. However, even though the concentration

of MDMA was higher, paroxetine decreased the effects of MDMA, in agreement with the fluoxetine study and theoretically through the same pharmacodynamic interaction [54]. Also in humans, 40-mg citalopram reduced the psychological effects of MDMA (1.5 mg/kg) through a suspected serotonin interaction [55]. In nine men, the combination of ethanol (0.8 g/kg) and MDMA (100 mg) caused a decrease in the sedation seen with only ethanol, and an increase in duration of euphoria observed with only MDMA. While MDMA reduced the sedation caused by ethanol, it did not reduce the subjective feeling of drunkenness. The authors were unable to explain their findings through a pharmacodynamic or pharmacokinetic interaction [56]. A similar study with ethanol and MDMA confirmed these findings [57]. In humans, pretreatment with haloperidol (1.4 mg, i.v.) increased the anxiety and dysphoria from MDMA (1.5 mg/kg p.o.) but had no effect on MDMA-induced physiologic changes (heart rate, temperature). The authors suggested that MDMA acts on D2 receptors to produce euphoria and that haloperidol, a D2 antagonist, blocked these effects, which led to dysphoria [58]. In contrast, the same authors discovered 40 mg of citalopram when administered i.v. was able to reduce the increases in heart rate and blood pressure (but not temperature) induced by MDMA (1.5 mg/kg p.o.) [59].

In a case report, an AIDS patient taking the antiretroviral drugs, ritonavir (400 mg/twice a day) and saquinavir (400 mg/twice a day), experienced a much longer effect with MDMA than on previous occasions using MDMA alone. The authors suggested that ritonavir is an inhibitor of CYP2D6 which is partially responsible for the metabolism of MDMA, and that this inhibition might have increased the half-life of the drug [60]. A separate case report detailed a fatality with ritonavir (600 mg/twice a day) and MDMA suspected to have occurred due to CYP2D6 inhibition [61]. Finally, a case study of four deaths found the combination of MDMA with moclobemide could result in serotonin syndrome (as described above in rats) [62]. Fatal serotonin syndrome from moclobemide and MDMA was also suggested in a postmortem study from Australia [63].

Drug interacting with MDMA	Result of interaction
Methadone	Inhibition of methadone *N*-demethylation
Fluoxetine, rats	Altered MDMA metabolism, decreased MDMA/MDA clearance
Ethanol, casual use	No tolerance to synergistic effects
Ethanol, binge	Increase in MDMA neuronal damage
Moclobemide, rats	Increase in serotonin
LSD	Increase in MDMA-like activity
Caffeine	Increase in heart rate, hyperthermia, and loss of serotonin
Fluoxetine	Decrease in subjective and physiologic effects
Paroxetine	Increase in [MDMA], decrease in MDMA effect
Citalopram	Decrease in MDMA psychological effects
Ethanol	Decrease in ethanol-induced sedation, increase in duration of MDMA euphoria
Haloperidol	Increase in anxiety, dysphoria from MDMA
Citalopram, IV	Decrease in MDMA-induced heart rate and blood pressure increases
Ritonavir	Increase in duration of MDMA effect, possible death
Moclobemide	Serotonin syndrome

Human data in bold print

Cannabinoids

Δ^9-Tetrahydrocannabinol (THC) is one of the active ingredients found in marijuana. It is available as dronabinol for the treatment of nausea in cancer patients receiving chemotherapy and to help with weight gain in dangerously thin patients. It is abused for its euphoric and relaxant properties. Recently, specific THC receptors have been discovered in the brain that activate inhibitory mechanisms, the most studied being the CB1 receptor. THC is metabolized by oxidation to hydroxy compounds and further oxidized to a carboxylic acid (THC-COOH).

In Vitro Data

An in vitro study demonstrated that THC and its metabolites increased the metabolism of phenytoin through the activation of P450 enzyme CYP2C9 [64].

Nonhuman Data

In Glaxo-Wistar rats, fluoxetine pretreatment (10 mg/kg, i.p.) reduced hypothermia caused by THC (2 and 5 mg/kg, i.p.); however, fluoxetine administered after THC enhanced the hypothermia caused by THC. The authors suggested that THC causes hypothermia through the release of serotonin and that with pretreatment of fluoxetine, the serotonin neurons were not as active and thus a reduction in the hypothermia was seen. In the second scenario, the authors suggested that the increased serotonin from THC continues to act due to the reuptake inhibition caused by fluoxetine [65]. In CD1 mice, a low dose of THC (0.3 mg/kg, i.p.) was able to increase the behavioral effects of a low dose of MDMA (3 mg/kg, i.p.) through what the authors speculated was a change in dopamine levels in the nucleus accumbens [66].

In Sprague-Dawley rats, haloperidol (0.01–1 mg/kg, s.c.) and THC (0.5 mg/kg, i.p.) showed increased catalepsy through a possible interaction between CB1 and D2 receptor signal transduction; however, the combination of clozapine (0.5–20 mg/kg, s.c.) and THC (0.5 mg/kg, i.p.) did not show any catalepsy. The authors recommended that for known schizophrenic THC users, clozapine should be prescribed rather than haloperidol to potentially decrease side effects [67].

Human Data

In humans, a nicotine patch (21 mg, transdermal) increased several effects of THC. Men had an increased and longer effect from THC (1.99 or 3.51% THC, inhalation) both physiologically (e.g., heart rate) and subjectively (e.g., self-reported feelings), compared with women [68]. A study in HIV-infected humans found that smoked THC

decreased the concentration of indinavir (800 mg/8 h) and nelfinavir (750 mg/3/day) through either an induction of their metabolism or decreased absorption in the GI. However, the authors suggested that the change in concentration would not impact the efficacy of these drugs [69]. In humans, naltrexone (50 mg, oral) increased the effects of oral THC (30 mg) in chronic THC users, possibly through an interaction intracellularly with G-protein receptors for both drugs [70]. In human subjects, the combination of MDMA and THC caused a decreased ability to determine the direction of travel than in subjects using only THC or in drug-free subjects. The authors suggested that this may be due to serotonin and/or acetylcholine receptors and that the combination of MDMA and THC would impair the ability of the user to safely operate a motor vehicle [71].

A case report detailing four male teenagers (ages 15–18) taking tricyclic antidepressants found the development of delirium after the use of THC. The authors speculate that an increase in THC might have occurred due to inhibition of metabolism by the tricyclic antidepressants (nortriptyline or desipramine) [72]. Another case report in a 17-year-old male who was taking amitriptyline (25 mg) found the development of supraventricular tachycardia following the use of THC. The author did not suggest an explanation, but noted the possibility of a pharmacokinetic interaction [73].

Drug interacting with THC	Result of interaction
Phenytoin	Increase in phenytoin metabolism
Fluoxetine pretreatment	Decrease in THC-induced hypothermia,
Fluoxetine after THC	Increase in THC-induced hypothermia
MDMA, mice	Increase in MDMA behavioral effects
Haloperidol	Increase in catalepsy
Clozapine	No catalepsy
Nicotine patch, males	Increase in duration and effect of THC
Indinavir	Decrease in [indinavir]
Nelfinavir	Decrease in [nelfinavir]
Naltrexone	Increase in effects of oral THC
MDMA	Decrease in ability to determine direction of travel
Tricyclic antidepressants	Delirium

Human data in bold print

Ketamine

Ketamine (2-(2-chlorophenyl)-2-(methyl-amino)cyclohexanone) is a dissociative anesthetic similar to phencyclidine (PCP). It had previously been used in humans as an anesthetic, but is now primarily used in veterinary medicine for the induction of anesthesia before surgery. The main mechanism of action is blockade of glutamate at NMDA receptors; it also has effects on opioid receptors, serotonin receptors, muscarinic receptors, and can inhibit reuptake of neurotransmitters such as norepinephrine. Ketamine acts in the higher centers of the brain which prevent the perception of stimuli, such as pain. The combined effect is analgesia without loss of consciousness and a feeling that the body has separated from the mind. Ketamine is

abused for its stimulant and psychedelic properties, and sufficient doses may induce a phenomenon known as a "K hole" which produces an out-of-body experience. Ketamine is metabolized primarily by *N*-demethylation by CYP2B6 to norketamine which is further dehydrogenated to dehydronorketamine. All three compounds are hydroxylated and conjugated to increase elimination.

In Vitro Data

A study in human kidney cells found that ketamine inhibited transporter proteins for serotonin and norepinephrine. Pretreatment with desipramine and fluoxetine, serotonin and norepinephrine transport protein inhibitors, eliminated ketamine's inhibition [74].

Nonhuman Data

A study in Sprague-Dawley rats found that clozapine (5 mg/kg, i.p.) and olanzapine (5 or 10 mg/kg, i.p.) blocked ketamine's (25 mg/kg, i.p.) increase of 2-deoxyglucose uptake in the brain while risperidone (0.3 mg/kg, i.p.) had no effect [75]. Also in Sprague-Dawley rats, pretreatment with ketamine (10 mg/kg, i.v.) reduced the acute tolerance and rebound hyperalgesia of alfentanil. The authors suggested that the pharmacodynamic modulation is due to ketamine's blockade of NMDA receptors [76]. In male Wistar rats, ketamine pretreatment (80 mg/kg, i.p.) increased the metabolism of propofol (80 mg/kg, i.p.) with a subsequent decrease in propofol-induced sleep. The authors proposed induction of CYP2B by ketamine and suggested a possible interaction in humans when the drugs are coadministered [77].

Human Data

A study in humans was conducted to determine if ketamine's ability to decrease rebound hyperalgesia was due to opioid receptor activation. The authors tested this with the addition of naloxone, an opioid receptor blocker, and found no change in the decreased hyperalgesia. They also found that sedation from ketamine was not prevented by naloxone [78]. In healthy humans, pretreatment with 300-mg lamotrigine, a drug that decreases the release of glutamate, decreased ketamine-induced schizophrenic-like symptoms and disturbances in perception, learning, and memory. Lamotrigine increased the mood-elevating characteristics of ketamine. The authors suggested that when ketamine blocks NMDA receptors, the excess glutamate activates non-NMDA receptors resulting in schizophrenic-like behavior. Lamotrigine is able to attenuate this by decreasing the initial release of glutamate [79]. Another study found that pretreatment with 5 mg of haloperidol reduced ketamine-induced

impairment in executive cognitive function and the anxiogenic effects of ketamine. Ketamine-induced production of schizophrenic-like positive and negative symptoms, perceptual changes, amnesia, euphoria, and attention were not reduced by haloperidol. Haloperidol increased sedation and prolactin responses induced by ketamine. The authors suggested that this could be caused by an interaction with networks in the frontal cortex or blockaded D2 receptor stimulation [80].

In schizophrenic patients, ketamine (0.1–0.5 mg/kg) resulted in an increase in psychotic symptoms which haloperidol (0.3 mg/kg/day), an antipsychotic, was unable to prevent [81]. Another study in schizophrenic patients found that clozapine, another antipsychotic, prevented ketamine-induced positive symptoms (e.g., thought disturbances such as hallucinations or delusions) and conceptual disorganization, but did not prevent ketamine-induced negative symptoms. The authors believed this was due to the action of clozapine on NMDA receptors [82].

Drug Interacting with ketamine	Result of interaction
Clozapine	Decrease in ketamine-induced uptake of 2-deoxyglucose in the brain
Olanzapine	Decrease in ketamine-induced uptake of 2-deoxyglucose in the brain
Risperidone	No effect on ketamine-induced uptake of 2-deoxyglucose in the brain
Alfentanil	Decrease in alfentanil's acute tolerance and rebound hyperalgesia
Propofol	Increase in propofol metabolism, decrease in propofol effect
Naloxone	No effect
Lamotrigine	Decrease in ketamine-induced schizophrenia-like symptoms, increase in ketamine-induced mood elevation
Haloperidol	Decrease in ketamine-induced impairment, increase in ketamine-induced sedation and prolactin responses, no changes to schizophrenic-like symptoms
Haloperidol, schizophrenic patients	Increase in ketamine-induced positive and negative symptoms
Clozapine, schizophrenic patients	Decrease in ketamine-induced positive symptoms, no change on negative symptoms

Human data in bold print

Flunitrazepam and γ-Hydroxybutyrate

Two drugs commonly referred to as "date-rape" drugs are gamma-hydroxybutyric acid (GHB) and flunitrazepam. GHB is an endogenous breakdown product of GABA and is not currently used clinically. The metabolism of GHB is not well known but is thought to involve alcohol dehydrogenase. GHB may be used to facilitate sexual assault due to its sedative and possible amnestic properties. It is used by

body builders for a purported increase in muscle mass and as a drug of abuse for intoxicating properties similar to ethanol. Flunitrazepam (5-(2-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2*H*-1,4-benzodiazepin-2-one), a member of the benzodiazepines (7-nitro subclass), has also been implicated in drug-facilitated sexual assault. Flunitrazepam increases binding at omega-2 GABA receptors which causes amnesia. Small doses of flunitrazepam work very quickly to produce anterograde amnesia, which prevents the formation of new memories. It is metabolized by nitro reduction to 7-aminoflunitrazepam, and is also hydroxylated and *N*-demethylated. Drug–drug interaction studies are not as prevalent for these drugs as others; thus, in vitro and modeling studies are included below.

In Vitro Data

An in vitro study of buprenorphine and flunitrazepam found that neither drug inhibited the other drug's metabolism. They concluded that reported fatalities following coadministration of the two drugs were not due to a pharmacokinetic interaction but a pharmacodynamic interaction [83].

Nonhuman Data

In Sprague-Dawley rats pretreated with a relatively large dose of flunitrazepam (40 mg/kg, i.p.), the median lethal dose for methadone decreased two-fold, for buprenorphine it decreased six-fold, and it remained unchanged for morphine. The authors believed that a pharmacodynamic interaction was involved, but were unable to prove this hypothesis [84].

In Sprague-Dawley rats dosed with salicylic acid (175 mg/kg, i.v.) and GHB (165 mg/kg, i.v.), the sedation and hypnosis caused by GHB was eliminated. Through pharmacokinetic modeling, the authors suggested an interaction with transport mechanisms in the blood-brain barrier [85]. In Sprague-Dawley rats, catalepsy induced by GHB was not synergistically increased by haloperidol. The authors demonstrated that by using dizocilpine, an NMDA receptor antagonist, catalepsy was increased with GHB and decreased with haloperidol, suggesting different pharmacodynamic mechanisms for the induction of catalepsy [86]. Using Wistar rats, the enhancement of GHB's hypnotic effect by ethanol was studied to determine if a pharmacokinetic or pharmacodynamic interaction was responsible. The authors concluded that a pharmacodynamic interaction was responsible due to the lack of change in the concentration vs. time profile for GHB coadministered with ethanol [87]. These results were also mirrored in a study with humans, where an increase in adverse effects following ethanol and GHB use was observed, but no pharmacokinetic interaction demonstrated [88].

Human Data

A case report detailed a patient with AIDS who nearly died following a combination of GHB with antiretroviral medications. The patient had used MDMA (discussed in the MDMA section) and took GHB to counteract the anxiety from the MDMA but became unconscious after taking two doses. The authors suggested that the protease inhibitors, ritonavir and saquinavir, reduced the first-pass effect normally observed with GHB. This resulted in a larger bioavailable dose with subsequent toxic sequelae [60].

Drug Interacting with flunitrazepam	Result of interaction
Buprenorphine	No effect on metabolism, decrease in buprenorphine median lethal dose
Methadone	Decrease in methadone median lethal dose
Morphine	No change in median lethal dose
Drug Interacting with GHB	**Result of Interaction**
Salicylic acid	Elimination of GHB-induced sedation and hypnosis
Haloperidol	No increase in catalepsy
Dizocilpine	Increase in catalepsy
Ethanol	Increase in GHB-induced hypnosis and adverse effects
Ritonavir and saquinavir	Possible reduction in first-pass effect for GHB

Human data in bold print

References

1. Drug abuse warning network, 2006: National estimates of drug-related emergency department visits. Rockville, MD: 2008. Report No.: DAWN Series D-30, DHHS Publication No. (SMA) 08–4339.
2. Vitcheva V and Mitcheva M. Changes in liver and brain cytochrome p450 after multiple cocaine administration, alone and in combination with nifedipine. Arh Hig Rada Toksikol 58:287–291 (2007).
3. Bhagwat SV, Boyd MR, Ravindranath V. Rat brain cytochrome P450. reassessment of monooxygenase activities and cytochrome P450 levels. Drug Metab Dispos 23:651–654 (1995).
4. Rofael HZ and Abdel-Rahman MS. Reduction of tissue concentration of cocaine in rat by ketamine. J Toxicol Environ Health A 66:241–251 (2003).
5. Reid MJ and Bornheim LM. The effects of phencyclidine pretreatment on cocaine-mediated hepatotoxicity in mice. Toxicol Appl Pharmacol 172:194–202 (2001).
6. Fletcher PJ, Sinyard J, Salsali M, Baker GB. Fluoxetine, but not sertraline or citalopram, potentiates the locomotor stimulant effect of cocaine: Possible pharmacokinetic effects. Psychopharmacology (Berl) 174:406–413 (2004).
7. Beyer CE, Stafford D, LeSage MG, Glowa JR, Steketee JD. Repeated exposure to inhaled toluene induces behavioral and neurochemical cross-sensitization to cocaine in rats. Psychopharmacology (Berl) 154:198–204 (2001).
8. Diller AJ, Rocha A, Cardon AL, Valles R, Wellman PJ, Nation JR. The effects of concurrent administration of +/−3,4-methylenedioxymethamphetamine and cocaine on conditioned place preference in the adult male rat. Pharmacol Biochem Behav 88:165–170 (2007).
9. Reid MJ and Bornheim LM. Cannabinoid-induced alterations in brain disposition of drugs of abuse. Biochem Pharmacol 61:1357–1367 (2001).

10. Ohlsen RI and Pilowsky LS. The place of partial agonism in psychiatry: Recent developments. J Psychopharmacol 19:408–413 (2005).
11. Leite JV, Guimaraes FS, Moreira FA. Aripiprazole, an atypical antipsychotic, prevents the motor hyperactivity induced by psychotomimetics and psychostimulants in mice. Eur J Pharmacol 578:222–227 (2008).
12. Harris DS, Everhart ET, Mendelson J, Jones RT. The pharmacology of cocaethylene in humans following cocaine and ethanol administration. Drug Alcohol Depend 72:169–182 (2003).
13. Wynn GH, Cozza KL, Zapor MJ, Wortmann GW, Armstrong SC. Med-psych drug-drug interactions update. antiretrovirals, part III: Antiretrovirals and drugs of abuse. Psychosomatics 46:79–87 (2005).
14. Bornheim LM. Effect of cytochrome P450 inducers on cocaine-mediated hepatotoxicity. Toxicol Appl Pharmacol 150:158–165 (1998).
15. Pellinen P, Honkakoski P, Stenback F, Niemitz M, Alhava E, Pelkonen O, Lang MA, Pasanen M. Cocaine N-demethylation and the metabolism-related hepatotoxicity can be prevented by cytochrome P450 3A inhibitors. Eur J Pharmacol 270:35–43 (1994).
16. Myrick H, Markowitz JS, Henderson S. Priapism following trazodone overdose with cocaine use. Ann Clin Psychiatry 10:81–83 (1998).
17. Fiorelli RL, Manfrey SJ, Belkoff LH, Finkelstein LH. Priapism associated with intranasal cocaine abuse. J Urol 143:584–585 (1990).
18. Fareed FN, Chan G, Hoffman RS. Death temporally related to the use of a beta adrenergic receptor antagonist in cocaine associated myocardial infarction. J Med Toxicol 3:169–172 (2007).
19. Catravas JD and Waters IW. Acute cocaine intoxication in the conscious dog: Studies on the mechanism of lethality. J Pharmacol Exp Ther 217:350–356 (1981).
20. Guinn MM, Bedford JA, Wilson MC. Antagonism of intravenous cocaine lethality in nonhuman primates. Clin Toxicol 16:499–508 (1980).
21. Lange RA, Cigarroa RG, Flores ED, McBride W, Kim AS, Wells PJ, Bedotto JB, Danziger RS, Hillis LD. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. Ann Intern Med 112:897–903 (1990).
22. Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR, Perry KW. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: A potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 27:699–711 (2002).
23. Stoops WW, Blackburn JW, Hudson DA, Hays LR, Rush CR. Safety, tolerability and subject-rated effects of acute intranasal cocaine administration during atomoxetine maintenance. Drug Alcohol Depend 92:282–285 (2008).
24. Dackis CA, Lynch KG, Yu E, Samaha FF, Kampman KM, Cornish JW, Rowan A, Poole S, White L, O'Brien CP. Modafinil and cocaine: A double-blind, placebo-controlled drug interaction study. Drug Alcohol Depend 70:29–37 (2003).
25. Staack RF and Maurer HH. Metabolism of designer drugs of abuse. Curr Drug Metab 6:259–274 (2005).
26. Staack RF, Paul LD, Schmid D, Roider G, Rolf B. Proof of a 1-(3-chlorophenyl)piperazine (mCPP) intake: Use as adulterant of cocaine resulting in drug-drug interactions? J Chromatogr B Analyt Technol Biomed Life Sci 855:127–133 (2007).
27. Breccia M, Gentilini F, Alimena G. Cocaine abuse may influence the response to imatinib in CML patients. Haematologica 92:e41-2 (2007).
28. Kouri EM, Lundahl LH, Borden KN, McNeil JF, Lukas SE. Effects of oral contraceptives on acute cocaine response in female volunteers. Pharmacol Biochem Behav 74:173–180 (2002).
29. Winhusen T, Somoza E, Singal BM, Harrer J, Apparaju S, Mezinskis J, Desai P, Elkashef A, Chiang CN, Horn P. Methylphenidate and cocaine: A placebo-controlled drug interaction study. Pharmacol Biochem Behav 85:29–38 (2006).
30. Winhusen T, Somoza E, Harrer JM, Moore E, Ussery T, Kropp F, Singal B, Elkashef A, Mojsiak J. Metyrapone and cocaine: A double-blind, placebo-controlled drug interaction study. Pharmacol Biochem Behav 80:631–638 (2005).

31. Mendelson JH, Teoh SK, Mello NK, Ellingboe J, Rhoades E. Acute effects of cocaine on plasma adrenocorticotropic hormone, luteinizing hormone and prolactin levels in cocaine-dependent men. J Pharmacol Exp Ther 263:505–509 (1992).
32. Baumann MH, Gendron TM, Becketts KM, Henningfield JE, Gorelick DA, Rothman RB. Effects of intravenous cocaine on plasma cortisol and prolactin in human cocaine abusers. Biol Psychiatry 38:751–755 (1995).
33. Sills TL, Greenshaw AJ, Baker GB, Fletcher PJ. The potentiating effect of sertraline and fluoxetine on amphetamine-induced locomotor activity is not mediated by serotonin. Psychopharmacology (Berl) 143:426–432 (1999).
34. Dostalek M, Jurica J, Pistovcakova J, Hanesova M, Tomandl J, Linhart I, Sulcova A. Effect of methamphetamine on cytochrome P450 activity. Xenobiotica 37:1355–1366 (2007).
35. Whitley HP and Moorman KL. Interference with smoking-cessation effects of varenicline after administration of immediate-release amphetamine-dextroamphetamine. Pharmacotherapy 27:1440–1445 (2007).
36. Harrison G, Dilley JW, Loeb L, Nelson K. Priapism and quetiapine in an HIV-positive male. J Clin Psychopharmacol 26:100–101 (2006).
37. Rush CR, Stoops WW, Wagner FP, Hays LR, Glaser PE. Alprazolam attenuates the behavioral effects of d-amphetamine in humans. J Clin Psychopharmacol 24:410–420 (2004).
38. Krystal JH, Perry EB,Jr, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, Macdougall L, Abi-Saab W, D'Souza DC. Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: Implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch Gen Psychiatry 62:985–994 (2005).
39. Hellriegel ET, Arora S, Nelson M, Robertson P, Jr. Steady-state pharmacokinetics and tolerability of modafinil administered alone or in combination with dextroamphetamine in healthy volunteers. J Clin Pharmacol 42:450–460 (2002).
40. Harris DS, Reus VI, Wolkowitz OM, Mendelson JE, Jones RT. Altering cortisol level does not change the pleasurable effects of methamphetamine in humans. Neuropsychopharmacology 28:1677–1684 (2003).
41. Bell EC, Willson MC, Wilman AH, Dave S, Asghar SJ, Silverstone PH. Lithium and valproate attenuate dextroamphetamine-induced changes in brain activation. Hum Psychopharmacol 20:87–96 (2005).
42. Cohen LG, Prince J, Biederman J, Wilens T, Faraone SV, Whitt S, Mick E, Spencer T, Meyer MC, Polisner D, Flood JG. Absence of effect of stimulants on the phamacokinetics of desipramine in children. Pharmacotherapy 19:746–752 (1999).
43. Prior FH, Isbister GK, Dawson AH, Whyte IM. Serotonin toxicity with therapeutic doses of dexamphetamine and venlafaxine. Med J Aust 176:240–241 (2002).
44. Newton TF, Roache JD, De La Garza R,2nd, Fong T, Wallace CL, Li SH, Elkashef A, Chiang N, Kahn R. Safety of intravenous methamphetamine administration during treatment with bupropion. Psychopharmacology (Berl) 182:426–435 (2005).
45. Bomsien S and Skopp G. An in vitro approach to potential methadone metabolic-inhibition interactions. Eur J Clin Pharmacol 63:821–827 (2007).
46. Upreti VV and Eddington ND. Fluoxetine pretreatment effects pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA, ECSTASY) in rat. J Pharm Sci 97:1593–1605 (2008).
47. Ben Hamida S, Plute E, Bach S, Lazarus C, Tracqui A, Kelche C, de Vasconcelos AP, Jones BC, Cassel JC. Ethanol-MDMA interactions in rats: The importance of interval between repeated treatments in biobehavioral tolerance and sensitization to the combination. Psychopharmacology (Berl) 192:555–569 (2007).
48. Izco M, Orio L, O'Shea E, Colado MI. Binge ethanol administration enhances the MDMA-induced long-term 5-HT neurotoxicity in rat brain. Psychopharmacology (Berl) 189:459–470 (2007).
49. Freezer A, Salem A, Irvine RJ. Effects of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') and para-methoxyamphetamine on striatal 5-HT when co-administered with moclobemide. Brain Res 1041:48–55 (2005).

50. Schechter MD. 'Candyflipping': Synergistic discriminative effect of LSD and MDMA. Eur J Pharmacol 341:131–134 (1998).
51. McNamara R, Maginn M, Harkin A. Caffeine induces a profound and persistent tachycardia in response to MDMA ("ecstasy") administration. Eur J Pharmacol 555:194–198 (2007).
52. McNamara R, Kerans A, O'Neill B, Harkin A. Caffeine promotes hyperthermia and serotonergic loss following co-administration of the substituted amphetamines, MDMA ("ecstasy") and MDA ("love"). Neuropharmacology 50:69–80 (2006).
53. Tancer M and Johanson CE. The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl) 189:565–573 (2007).
54. Farre M, Abanades S, Roset PN, Peiro AM, Torrens M, O'Mathuna B, Segura M, de la Torre R. Pharmacological interaction between 3,4-methylenedioxymethamphetamine (ecstasy) and paroxetine: Pharmacological effects and pharmacokinetics. J Pharmacol Exp Ther 323:954–962 (2007).
55. Liechti ME, Baumann C, Gamma A, Vollenweider FX. Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. Neuropsychopharmacology 22:513–521 (2000).
56. Hernandez-Lopez C, Farre M, Roset PN, Menoyo E, Pizarro N, Ortuno J, Torrens M, Cami J, de La Torre R. 3,4-methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: Psychomotor performance, subjective effects, and pharmacokinetics. J Pharmacol Exp Ther 300:236–244 (2002).
57. Dumont GJ, Wezenberg E, Valkenberg MM, de Jong CA, Buitelaar JK, van Gerven JM, Verkes RJ. Acute neuropsychological effects of MDMA and ethanol (co-)administration in healthy volunteers. Psychopharmacology (Berl) 197:465–474 (2008).
58. Liechti ME and Vollenweider FX. Acute psychological and physiological effects of MDMA ("ecstasy") after haloperidol pretreatment in healthy humans. Eur Neuropsychopharmacol 10:289–295 (2000).
59. Liechti ME and Vollenweider FX. The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('ecstasy') in healthy volunteers. J Psychopharmacol 14:269–274 (2000).
60. Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Arch Intern Med 159:2221–2224 (1999).
61. Henry JA and Hill IR. Fatal interaction between ritonavir and MDMA. Lancet 352:1751–1752 (1998).
62. Vuori E, Henry JA, Ojanpera I, Nieminen R, Savolainen T, Wahlsten P, Jantti M. Death following ingestion of MDMA (ecstasy) and moclobemide. Addiction 98:365–368 (2003).
63. Pilgrim JL, Gerostamoulos D, Drummer OH, Bollmann M. Involvement of amphetamines in sudden and unexpected death. J Forensic Sci 54:478–485 (2009).
64. Bland TM, Haining RL, Tracy TS, Callery PS. CYP2C-catalyzed delta9-tetrahydrocannabinol metabolism: Kinetics, pharmacogenetics and interaction with phenytoin. Biochem Pharmacol 70:1096–1103 (2005).
65. Malone DT and Taylor DA. Modulation of delta9-tetrahydrocannabinol-induced hypothermia by fluoxetine in the rat. Br J Pharmacol 124:1419–1424 (1998).
66. Robledo P, Trigo JM, Panayi F, de la Torre R, Maldonado R. Behavioural and neurochemical effects of combined MDMA and THC administration in mice. Psychopharmacology (Berl) 195:255–264 (2007).
67. Marchese G, Casti P, Ruiu S, Saba P, Sanna A, Casu G, Pani L. Haloperidol, but not clozapine, produces dramatic catalepsy in delta9-THC-treated rats: Possible clinical implications. Br J Pharmacol 140:520–526 (2003).
68. Penetar DM, Kouri EM, Gross MM, McCarthy EM, Rhee CK, Peters EN, Lukas SE. Transdermal nicotine alters some of marihuana's effects in male and female volunteers. Drug Alcohol Depend 79:211–223 (2005).

69. Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, Abrams DI. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. AIDS 16:543–550 (2002).
70. Haney M, Bisaga A, Foltin RW. Interaction between naltrexone and oral THC in heavy marijuana smokers. Psychopharmacology (Berl) 166:77–85 (2003).
71. Rizzo M, Lamers CT, Sauer CG, Ramaekers JG, Bechara A, Andersen GJ. Impaired perception of self-motion (heading) in abstinent ecstasy and marijuana users. Psychopharmacology (Berl) 179:559–566 (2005).
72. Wilens TE, Biederman J, Spencer TJ. Case study: Adverse effects of smoking marijuana while receiving tricyclic antidepressants. J Am Acad Child Adolesc Psychiatry 36:45–48 (1997).
73. Mannion V. Case report: Adverse effects of taking tricyclic antidepressants and smoking marijuana. Can Fam Physician 45:2683–2684 (1999).
74. Zhao Y and Sun L. Antidepressants modulate the in vitro inhibitory effects of propofol and ketamine on norepinephrine and serotonin transporter function. J Clin Neurosci 15:1264–1269 (2008).
75. Duncan GE, Miyamoto S, Leipzig JN, Lieberman JA. Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. J Pharmacol Exp Ther 293:8–14 (2000).
76. Kissin I, Bright CA, Bradley EL,Jr. The effect of ketamine on opioid-induced acute tolerance: Can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? Anesth Analg 91:1483–1488 (2000).
77. Chan WH, Chen TL, Chen RM, Sun WZ, Ueng TH. Propofol metabolism is enhanced after repetitive ketamine administration in rats: The role of cytochrome P-450 2B induction. Br J Anaesth 97:351–358 (2006).
78. Mikkelsen S, Ilkjaer S, Brennum J, Borgbjerg FM, Dahl JB. The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. Anesthesiology 90:1539–1545 (1999).
79. Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: Support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry 57:270–276 (2000).
80. Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, Cassello K, Bowers MB,Jr, Vegso S, Heninger GR, Charney DS. Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl) 145:193–204 (1999).
81. Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19 (1995).
82. Malhotra AK, Adler CM, Kennison SD, Elman I, Pickar D, Breier A. Clozapine blunts N-methyl-D-aspartate antagonist-induced psychosis: A study with ketamine. Biol Psychiatry 42:664–668 (1997).
83. Kilicarslan T and Sellers EM. Lack of interaction of buprenorphine with flunitrazepam metabolism. Am J Psychiatry 157:1164–1166 (2000).
84. Borron SW, Monier C, Risede P, Baud FJ. Flunitrazepam variably alters morphine, buprenorphine, and methadone lethality in the rat. Hum Exp Toxicol 21:599–605 (2002).
85. Bhattacharya I and Boje KM. Potential gamma-hydroxybutyric acid (GHB) drug interactions through blood-brain barrier transport inhibition: A pharmacokinetic simulation-based evaluation. J Pharmacokinet Pharmacodyn 33:657–681 (2006).
86. Sevak RJ, France CP, Koek W. Neuroleptic-like effects of gamma-hydroxybutyrate: Interactions with haloperidol and dizocilpine. Eur J Pharmacol 483:289–293 (2004).
87. Van Sassenbroeck DK, De Paepe P, Belpaire FM, Buylaert WA. Characterization of the pharmacokinetic and pharmacodynamic interaction between gamma-hydroxybutyrate and ethanol in the rat. Toxicol Sci 73:270–278 (2003).
88. Thai D, Dyer JE, Benowitz NL, Haller CA. Gamma-hydroxybutyrate and ethanol effects and interactions in humans. J Clin Psychopharmacol 26:524–529 (2006).

Part III
Cardiovascular Drugs

Chapter 9
Cardiovascular Drugs

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Abstract This chapter examines various adverse drug reactions related to cardiovascular drugs by summarizing the mechanism of action of the drugs in each drug class and discussing the adverse drug reactions. Cardiovascular drugs addressed include antiarrhythmics, antihypertensives, intropic agents, nitrates, diuretics, anti-hemostatic, and lipid-lowering drugs. Adverse drug reactions and drug interactions are explained and detailed.

Keywords Cardiovascular • Antiarrhythmics • Antihypertensives • Intropic agents • Nitrates • Diuretics • Anti-hemostatic • Lipid lowering

Antiarrhythmics

Drug Classifications

According to the Vaughan Williams classification (Fig. 9.1):

Class I drugs block the fast sodium channel. They, in turn, may be divided into three subgroups:

> *Class IA*. Drugs that reduce V_{max} and prolong action potential duration: quinidine, procainamide, disopyramide; kinetics of onset and offset in blocking the Na^+ channel are of intermediate rapidity (<5 s).

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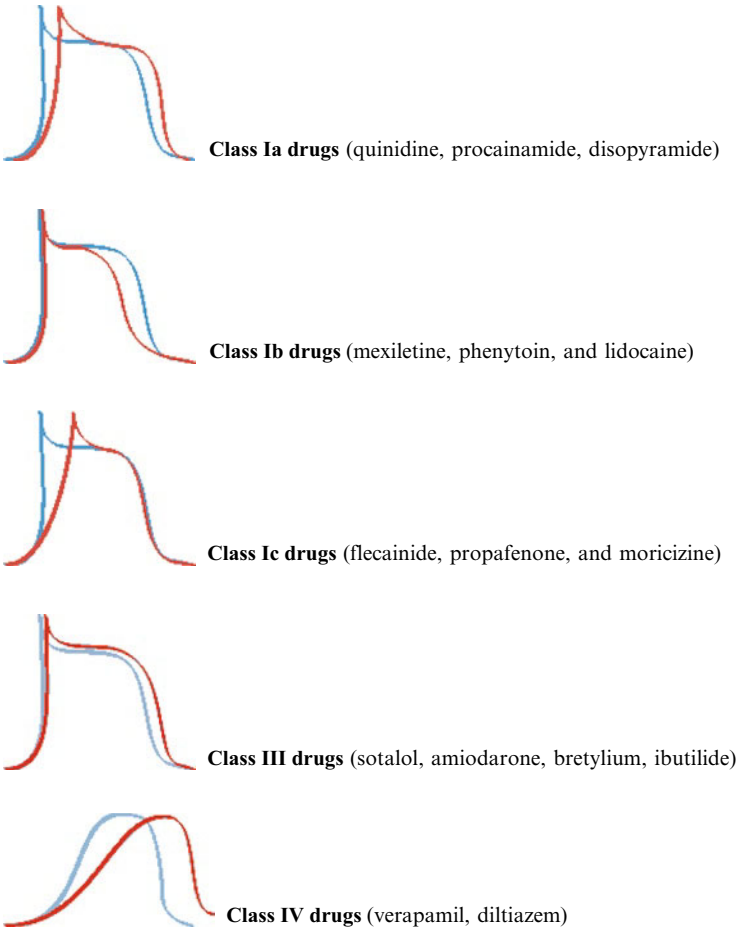


Fig. 9.1 Action potential and antiarrhythmic drug class (*red*=drug effect on action potential). *Class Ia drugs* (quinidine, procainamide, disopyramide). *Class Ib drugs* (mexiletine, phenytoin, and lidocaine). *Class Ic drugs* (flecainide, propafenone, and moricizine). *Class III drugs* (sotalol, amiodarone, bretylium, ibutilide). *Class IV drugs* (verapamil, diltiazem)

Class IB. Drugs that do not reduce V_{max} and that shorten action potential duration: mexiletine, phenytoin, and lidocaine; fast onset and offset kinetics (<500 ms).
Class IC. Drugs that reduce V_{max}, primarily slow conduction, and can prolong refractoriness minimally: flecainide, propafenone, and probably moricizine; slow onset and offset kinetics (10–20 s).

Class II drugs block beta-adrenergic receptors and include propranolol, timolol, metoprolol, esmololand, and acebutolol.
Class III drugs block potassium channels and prolong repolarization. They include sotalol, amiodarone, bretylium, ibutilide, dofetilide, and dronedarone.
Class IV drugs block the slow calcium channel and include verapamil, diltiazem.

Use of antiarrhythmic agents requires particular care because of the narrow therapeutic index of these drugs. Fortunately, we have reliable clinical end points for assessing efficacy and toxicity with a number of these agents. However, toxicities can manifest as the very same arrhythmias for which these drugs are instituted. As a consequence, the clinician can make the potentially fatal error of misdiagnosing toxicity as a lack of efficacy and responding in a manner antithetical to that required.

Class I agents are usually used to treat ventricular tachyarrhythmias, but their own inherent cardiotoxicity may be the same arrhythmia. It is important to emphasize that the pharmacologic effects of these drugs can often be quantified by measuring the Q-T interval, corrected for heart rate, and the duration of the QRS complex. If a patient manifests ventricular tachyarrhythmias with prolongation of the Q-T interval or widening of the QRS complex, one should suspect a toxic etiology for these arrhythmias rather than lack of efficacy of the drugs. If such toxicity is misdiagnosed and treatment is continued or higher doses are instituted, the consequences could be disastrous.

Side Effects

Antiarrhythmic drugs produce side effects that relate to excessive dosage and plasma concentrations, resulting in both noncardiac (e.g., neurological defects) and cardiac (e.g., heart failure, some arrhythmias) toxicities. Other idiopathic side effects include: procainamide-induced lupus syndrome, amiodarone-induced pulmonary toxicity, and some arrhythmias such as quinidine-induced torsades de pointes.

Drug-induced or drug-aggravated cardiac arrhythmias (*proarrhythmia*) are a major clinical problem. Electrophysiological mechanisms probably relate to prolongation of repolarization, the development of early afterdepolarizations to cause torsades de pointes, and alterations in reentry pathways to initiate or sustain ventricular tachyarrhythmias. Proarrhythmic events can occur in as many as 5–10% of patients. Heart failure increases proarrhythmic risk. Patients with atrial fibrillation treated with antiarrhythmic agents had a 4.7 relative risk of cardiac death if they had a history of heart failure compared with patients not so treated who had a 3.7 relative risk of arrhythmic death. Patients without a history of congestive heart failure had no increased risk of cardiac mortality during antiarrhythmic drug treatment. Reduced left ventricular function, treatment with digitalis and diuretics, and longer pretreatment Q-T interval characterize patients who develop drug-induced ventricular fibrillation. The more commonly known proarrhythmic events occur within several days of beginning drug therapy or changing dosage and are represented by such developments as incessant ventricular tachycardia, long Q-T syndrome, and torsades de pointes. However, in the Cardiac Arrhythmia Suppression Trial (CAST), encainide and flecainide reduced spontaneous ventricular arrhythmias but were associated with a total mortality of 7.7% versus 3.0% in the group receiving placebo. Deaths were equally distributed throughout the treatment period, raising the important consideration that another kind of proarrhythmic response can occur sometime after the

beginning of drug therapy. Such late proarrhythmic effects may relate to drug-induced exacerbation of regional myocardial conduction delay due to ischemia and heterogeneous drug concentrations that may promote reentry. Moricizine also increased mortality, leading to termination of CAST II. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management Trial (AFFIRM) evaluated rate control medications versus rhythm control medications in 4,060 patients with atrial fibrillation. In this randomized, multicentered trial, patients were evaluated for rhythm control drugs including amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide, and combinations of these antiarrhythmic agents. There were 310 deaths that occurred in the rhythm control group, and mortality at 5 years was 21.3%. More patients were hospitalized and more adverse drug effects were seen in the rhythm groups as well. Torsades de pointes and bradycardia also occurred more frequently in the rhythm control group.

Quinidine (Class IA)

The most common adverse effects of chronic oral quinidine therapy are gastrointestinal, including nausea, vomiting, diarrhea, abdominal pain, and anorexia. Gastrointestinal side effects may be milder with the gluconate form. Central nervous system toxicity includes tinnitus, hearing loss, visual disturbances, confusion, delirium, and psychosis. Cinchonism is the term usually applied to these side effects. Allergic reactions may be manifested as rash, fever, immune-mediated thrombocytopenia, hemolytic anemia, and rarely, anaphylaxis. Thrombocytopenia is due to the presence of antibodies to quinidine–platelet complexes, causing platelets to agglutinate and lyse. In patients receiving oral anticoagulants, quinidine may cause bleeding. Side effects may preclude long-term administration of quinidine in 30–40% of patients. Slow cardiac conduction, sometimes to the point of block, manifested as prolongation of the QRS duration or sinoatrial (SA) or AV nodal conduction disturbances can be seen. Quinidine-induced cardiac toxicity can be treated with molar sodium lactate. Prolongation of the Q-T interval can cause torsades de pointes in 1–3% of patients. Syncope may be present in 0.5–2.0% of patients, as a result of a self-terminating episode of torsades de pointes. Torsades de pointes may be due to the development of early afterdepolarizations, as noted. Magnesium given intravenously (2 g over 1–2 min, followed by an infusion of 3–20 mg/min) is the initial drug treatment of choice. Quinidine prolongs the Q-T interval in most patients, whether or not ventricular arrhythmias occur, but significant Q-T prolongation (Q-T interval of 500–600 ms) is often a characteristic of quinidine-induced syncope. Syncope is unrelated to plasma concentrations of quinidine or duration of therapy. Therapy for quinidine syncope requires immediate discontinuation of the drug and avoidance of other drugs that have similar pharmacological effects, such as disopyramide, since cross-sensitivity exists in some patients. Atrial or ventricular pacing can be used to suppress the ventricular tachyarrhythmia and may act by suppressing afterdepolarizations. For some patients, drugs that do not prolong the Q-T interval, such as lidocaine or phenytoin, can be tried. When pacing is not available, isoproterenol can be given with caution.

Drugs that induce hepatic enzyme production, such as phenobarbital and phenytoin, can shorten the duration of quinidine's action by increasing its rate of elimination. Quinidine may elevate serum digoxin and digitoxin concentrations by decreasing total body clearance of digitoxin, the volume of distribution, and the affinity of tissue receptors for digoxin.

Procainamide (Class IA)

Multiple adverse noncardiac effects have been reported with procainamide administration and include skin rashes, myalgias, digital vasculitis, and Raynaud's phenomenon. Fever and agranulocytosis may be due to hypersensitivity reactions. White blood cell and differential blood counts should be performed at regular intervals. Gastrointestinal side effects are less frequent than with quinidine, and adverse central nervous system side effects are less frequent than with lidocaine. Procainamide can also cause overexcitement, psychosis, hallucinations, and depression. Toxic concentrations of procainamide can diminish myocardial performance and promote hypotension. A variety of conduction disturbances or ventricular tachyarrhythmias can occur similar to those produced by quinidine, including prolonged Q-T syndrome and polymorphous ventricular tachycardia. The active metabolite, nacetylprocainamide (NAPA), can induce Q-T prolongation and torsades de pointes. In the absence of sinus node disease, procainamide does not adversely affect sinus node function. In patients with sinus dysfunction, procainamide tends to prolong corrected sinus node recovery time and can worsen symptoms in some patients who have the bradycardia-tachycardia syndrome. Procainamide does not increase the serum digoxin concentration. Arthralgia, fever, pleuropericarditis, hepatomegaly, and hemorrhagic pericardial effusion with tamponade have been described in a systemic lupus erythematosus (SLE)–like syndrome. The syndrome can occur more frequently and earlier in patients who are "slow acetylators" of procainamide. The aromatic amino group on procainamide appears important for induction of SLE syndrome, since acetylating this amino group to form NAPA appears to block the SLE-inducing effect. Sixty to seventy percent of patients who receive procainamide on a chronic basis develop antinuclear antibodies, with clinical symptoms in 20–30%, but this is reversible when procainamide is discontinued. When symptoms occur, SLE cell preparations are often positive. Positive serological tests are not necessarily a reason to discontinue drug therapy; however, the development of symptoms or a positive anti-DNA antibody is a reason to discontinue drug therapy, except for patients whose life-threatening arrhythmia is controlled only by procainamide. Steroid administration in these patients may eliminate the symptoms. In contrast to naturally occurring SLE, the brain and kidney are spared, and there is no predilection for females.

Disopyramide (Class IA)

Three categories of adverse effects follow disopyramide administration. The most common relates to the drug's potent parasympatholytic properties and includes

urinary hesitancy or retention, constipation, blurred vision, closed-angle glaucoma, and dry mouth. Symptoms may be minimized by concomitant administration of pyridostigmine. Second, disopyramide can produce ventricular tachyarrhythmias that are commonly associated with Q-T prolongation and torsades de pointes. Some patients can have "cross-sensitivity" to both quinidine and disopyramide and develop torsades de pointes while receiving either drug. When drug-induced torsades de pointes occur, agents that prolong the Q-T interval should be used very cautiously or not at all. Finally, disopyramide can reduce contractility of the normal ventricle, but the depression of ventricular function is much more pronounced in patients with preexisting ventricular failure. Occasionally, cardiovascular collapse can result.

Lidocaine (Class IB)

The most commonly reported adverse effects of lidocaine are dose-related manifestations of central nervous system toxicity: dizziness, paresthesias, confusion, delirium, slurred speech, hallucinations, coma, tremor, and seizures. Occasional sinus node depression and His-Purkinje block have been reported. Respiratory depression has also been reported with lidocaine use. In patients with atrial tachyarrhythmias, ventricular rate acceleration has been noted. Both lidocaine and procainamide can elevate defibrillation thresholds. Toxicities can be reduced by reducing the dose or rate of infusion.

Mexiletine and Tocainide (Class IB)

Drugs with a lidocaine-like spectrum of activity but active after oral administration, are both weak bases that demonstrate increased excretion with acidification of the urine. This phenomenon is unlikely to be clinically important, for the urine pH is normally acidic, and the amount of drug excreted in the urine unchanged is less than 10% and 30–50%, respectively. However, there remains the potential for patients with disorders of urinary acidification to accumulate either of these drugs to toxic levels. It does not appear that decreased renal function per se importantly influences the kinetics of either of these agents. Reported adverse events include: disorientation, lightheadedness, parasthesia, ataxia, vomiting, tremor, nausea, seizures, dizziness, confusion, hypotension, chest pain, and ventricular arrhythmias.

Flecainide (Class IC)

Proarrhythmic effects are one of the most important adverse effects of flecainide. Its marked slowing of conduction precludes its use in patients with second-degree AV block without a pacemaker and warrants cautious administration in patients with intraventricular conduction disorders. Aggravation of existing ventricular arrhythmias or onset of new ventricular arrhythmias can occur in 5–30% of patients, the increased percentage in patients with preexisting sustained ventricular tachycardia, cardiac decompensation, and higher doses of the drug. Failure of the

flecainide-related arrhythmia to respond to therapy, including electrical cardioversiondefibrillation, may result in a mortality as high as 10% in patients who develop proarrhythmic events. Negative inotropic effects can cause or worsen heart failure. Patients with sinus node dysfunction may experience sinus arrest, and those with pacemakers may develop an increase in pacing threshold. In the Cardiac Arrhythmia Suppression Trial, patients treated with flecainide had 5.1% mortality or nonfatal cardiac arrest compared with 2.3% in the placebo group over 10 months. Mortality was highest in those with non-Q-wave infarction, frequent premature ventricular complexes, and faster heart rates, raising the possibility of drug interaction with ischemia and electrical instability. Exercise can amplify the conduction slowing in the ventricle produced by flecainide and in some cases can precipitate a proarrhythmic response. Therefore, exercise testing has been recommended to screen for proarrhythmia. Central nervous system complaints, including confusion and irritability, represent the most frequent noncardiac adverse effect.

Propafenone (Class IC)

Minor noncardiac effects occur in about 15% of patients, with dizziness, disturbances in taste, and blurred vision the most common and gastrointestinal side effects next. Exacerbation of bronchospastic lung disease can occur. Cardiovascular side effects occur in 10–15% of patients, including conduction abnormalities such as AV block, sinus node depression, and worsening of heart failure. Proarrhythmic responses, more often in patients with a history of sustained ventricular tachycardia and decreased ejection fractions, appear less commonly than with flecainide and may be in the range of 5%. The applicability of data from the Cardiac Arrhythmic Suppression Trial about flecainide to propafenone is not clear, but limiting propafenone's application in a manner similar to other IC drugs seems prudent at present until more information is available. Its beta-blocking actions may make it different, however.

Moricizine (Class IC)

Usually, this drug is well tolerated. Noncardiac adverse effects primarily involve the nervous system and include tremor, mood changes, headache, vertigo, nystagmus, and dizziness. Gastrointestinal side effects include nausea, vomiting, and diarrhea. Worsening of congestive heart failure is uncommon but can happen. Proarrhythmic effects have been reported in about 3–15% of patients and appear to be more common in patients with severe ventricular arrhythmias. Advancing age increases the susceptibility to adverse effects.

Beta-Blockers (Class II)

Adverse cardiovascular effects from propranolol include unacceptable hypotension, bradycardia, and congestive heart failure. The bradycardia may be due to sinus

bradycardia or AV block. Sudden withdrawal of propranolol in patients with angina pectoris can precipitate or worsen angina and cardiac arrhythmias and cause an acute myocardial infarction, possibly owing to heightened sensitivity to beta-agonists caused by previous beta-blockade (upregulation). Heightened sensitivity may begin several days after cessation of propranolol therapy and may last 5 or 6 days. Other adverse effects of propranolol include worsening of asthma or chronic obstructive pulmonary disease, intermittent claudication, Raynaud's phenomenon, mental depression, increased risk of hypoglycemia among insulin-dependent diabetic patients, easy fatigability, disturbingly vivid dreams or insomnia, and impaired sexual function.

Amidodarone (Class III)

Adverse effects are reported by about 75% of patients treated with amiodarone for 5 years but compel stopping the drug in 18–37%. The most frequent side effects requiring drug discontinuation involve pulmonary and gastrointestinal complaints. Most adverse effects are reversible with dose reduction or cessation of treatment. Adverse effects become more frequent when therapy is continued long term. Of the noncardiac adverse reactions, pulmonary toxicity is the most serious; in one study, it occurred between 6 days and 60 months of treatment in 33 of 573 patients, with three deaths. The mechanism is unclear but may relate to a hypersensitivity reaction and/or widespread phospholipidosis. Dyspnea, nonproductive cough, and fever are common symptoms, with rales, hypoxia, a positive gallium scan, reduced diffusion capacity, and radiographic evidence of pulmonary infiltrates noted. Amiodarone must be discontinued if such pulmonary inflammatory changes occur. Steroids can be tried, but no controlled studies have been done to support their use. A 10% mortality in patients with pulmonary inflammatory changes results, often in patients with unrecognized pulmonary involvement that is allowed to progress. Chest roentgenograms at 3-month intervals for the first year and then twice a year for several years have been recommended. At maintenance doses less than 300 mg daily, pulmonary toxicity is uncommon. Advanced age, high drug maintenance dose, and reduced predrug diffusion capacity (DLco) are risk factors for developing pulmonary toxicity. An unchanged DLco volume may be a negative predictor of pulmonary toxicity. Although asymptomatic elevations of liver enzymes are found in most patients, the drug is not stopped unless values exceed two or three times normal in a patient with initially abnormal values. Cirrhosis occurs uncommonly but may be fatal. Neurological dysfunction, photosensitivity (perhaps minimized by sunscreens), bluish skin discoloration, corneal microdeposits (in almost 100% of adults receiving the drug more than 6 months), gastroenterological disturbances, and hyperthyroidism (1–2%) or hypothyroidism (2–4%) can occur. Amiodarone appears to inhibit the peripheral conversion of T4 to T3 so that chemical changes result, characterized by a slight increase in T4, reverse T3, and thyroid-stimulating hormone (TSH), and a slight decrease in T3. Reverse T3 concentration has been used as an index of drug efficacy. During hypothyroidism, TSH increases greatly while T3 increases in hyperthyroidism. Cardiac side effects include symptomatic bradycardias in about 2%, aggravation of ventricular tachyarrhythmias

(with occasional development of torsades de pointes) in 1–2%, possibly higher in women, and worsening of congestive heart failure in 2%. Possibly due to interactions with anesthetics, complications after open-heart surgery have been noted by some, but not all, investigators, including pulmonary dysfunction, hypotension, hepatic dysfunction, and low cardiac output. Important interactions with other drugs occur, and when given concomitantly with amiodarone, the dose of warfarin, digoxin, and other antiarrhythmic drugs should be reduced by one-third to one-half and the patient watched closely. Drugs with synergistic actions, such as beta-blockers or calcium channel blockers, must be given cautiously.

Bretylium (Class III)

Bretylium (Class III), which is used for refractory ventricular tachyarrhythmias, may present particular problems in patients with renal dysfunction because its kinetics appear complex and have not been defined for this group of patients. Therapy with this drug in patients with renal disease should be extremely conservative.

Sotalol (Class III)

Proarrhythmia is the most serious adverse effect. Overall, new or worsened ventricular tachyarrhythmias occur in about 4%, and this response is due to torsades de pointes in about 2.5%. The incidence of torsades de pointes increases to 4% in patients with a history of sustained ventricular tachycardia and is dose related, reportedly only 1.6% at 320 mg/day but 4.4% at 480 mg/day. Other adverse effects commonly seen with other beta-blockers also apply to sotalol. Sotalol should be used with caution or not at all in combination with other drugs that prolong the Q-T interval. However, such combinations have been used successfully.

Ibutilide (Class III)

Some of the most common effects associated are bradyarrythmia, hypertension, hypotension, palpitations, prolonged QT interval, nausea, and headache. Serious side effects include cardiac dysrrythmia, torsades de pointes, ventricular arrythmias, heart block, and heart failure. In a clinical trial, 586 patients were treated with ibutilide against placebo and sotolol. The most common noncardiac side effects reported were nausea and headache. Torsades de pointes was seen in 4.3% of which 2.6% were unsustained ventricular tachycardias and 1.7% developed sustained ventricular tachycardia. Atrial tachycardia was reported in 2.7% of patients.

Dofetilide (Class III)

This is a methanesulfonilamide agent and is FDA approved for the treatment of atrial flutter and atrial fibrillation. Common side effects associated are headache,

Table 9.1 Drugs that may induce torsades de pointes

Antiarrhythmic drugs	
Class I	Quinidine, disopyramide, procainamide
Class III	Sotalol, amiodarone
Non-antiarrhythmic drugs	
Antibiotic	Erythromycin, bactrim
Antifungal	Ketoconazole, itraconazole
Antihistamine	Terfenadine, astemizole
Psychiatric drugs	Tricyclic antidepressants, phenothiazines, haloperidol
Cholinergic antagonists	Cisapride, organophophates
Other drugs	Cocaine, arsenic

dizziness, insomnia, ventricular tachycardia, chest pain, torsades de pointes, rash, diarrhea, abdominal pain, back pain, respiratory tract infection, dyspnea, and flu-like symptoms. The incidence of torsades de pointes reported by the manufacturer is <1% and occurs with an increase in dosage. A trial that used information from the DIAMOND-CHE trial states that the approximate percentage of torsades de pointes is close to 3%.

Dronedarone (Class III)

This is a new antiarrhythmic agent being developed for the treatment of atrial fibrillation. A clinical trial conducted involving 4,628 patients showed that the most common adverse effects reported were bradycardia, QT prolongation, nausea, diarrhea, rash, and increased serum creatinine levels. In a second clinical conducted involving 199 patients, drug-induced QT prolongation was seen at higher doses. In addition, 22.6% of patients discontinued treatment due to GI effects.

Adenosine

Transient side effects occur in almost 40% of patients with supraventricular tachycardia given adenosine and are most commonly flushing, dyspnea, and chest pressure. These symptoms are fleeting, generally less than 1 min, and are well tolerated. Premature ventricular complexes, transient sinus bradycardia, sinus arrest, and AV block are common when a supraventricular tachycardia abruptly terminates. Induction of atrial fibrillation can be problematic in patients with the Wolff–Parkinson–White syndrome or rapid AV conduction (Table 9.1).

Drug Interactions

Drug interactions with antiarrhythmic agents can be enormous because many of the drugs are dependent on oxidative metabolism by means of the cytochrome

P450 process. Most drugs are either inducers or inhibitors of this process which could result in possible drug interactions.

Drug interactions associated with amiodarone are pharmacodynamic and/or pharmacokinetic in nature. The pharmacodynamic interactions associated with amiodarone occur primarily with other antiarrhythmics and are a consequence of additive or synergistic electrophysiologic effects. As the pharmacologic effects of amiodarone are delayed by several days even with adequate loading doses, concomitant use of another antiarrhythmic is often necessary. Should this be the case, the dose of the secondary antiarrhythmic should, in general, be decreased by 30–50% after the first few days of initiating amiodarone therapy. Discontinuation of the second antiarrhythmic agent should be attempted as soon as the therapeutic effects of amiodarone are observed.

Conversely, in patients requiring combination therapy, the dose of the second antiarrhythmic should, in general, be decreased by 50% until amiodarone is eliminated from the body. Proarrhythmia, including torsade de pointes and monomorphic ventricular tachycardia, can and has occurred when amiodarone was administered in combination with any number of antiarrhythmic compounds including Class IA agents, mexilitine and propafenone. Caution should be exercised when amiodarone is administered with any drug with electrophysiologic effects.

Amiodarone inhibits the activity of two cytochrome P450 enzymes – CYP2D6 and CYP2C9. As a consequence, it has been reported to reduce the metabolism of certain drugs. Of these drugs, the most significant interactions are reported with anticoagulants, antiarrhythmics, phenytoin, and cyclosporin. The anticoagulant effects of warfarin and nicoumalone are significantly increased when amiodarone is added.

Concurrent use of amiodarone with cyclosporin need not be avoided but cyclosporin serum levels can be increased and must be monitored. Cyclosporin dosage reductions are usually required. Amiodarone also increases serum digoxin concentrations.

Flecainide concentrations increase by an average of 60% with concomitant amiodarone therapy. Although the exact mechanism of the interaction is unknown, it is postulated that the hepatic metabolism and/or renal clearance of flecainide may be decreased. Careful clinical observation of the patient as well as close monitoring of the ECG and plasma flecainde concentrations is essential with adjustment of the flecainide dosing regimen performed as necessary to avoid enhanced toxicity or pharmacodynamic effects. An empiric reduction of the flecainide dose by 50% is suggested 2–3 days following initiation of amiodarone therapy.

Quinidine is an inhibitor of CYP2D6 and CYP3A4 and could potentially interact with a vast number of cardiac and noncardiac drugs. Quinidine serum concentrations generally increase by about 33% in patients receiving concomitant amiodarone therapy. Although the mechanism is unclear, it appears that hepatic and/or renal clearance may be diminished and quinidine may also be displaced from tissue- and protein-binding sites. Prolongation of the QT interval is well documented with quinidine, and the addition of amiodarone may dramatically increase this effect, placing the patient at an increased risk for the development of torsade de pointes. Careful clinical observation of the patient as well as close monitoring of the ECG and serum

quinidine concentrations is essential with adjustment of the quinidine dosing regimen performed as necessary to avoid enhanced toxicity or pharmacodynamic effects. An empiric reduction of the quinidine dose by 50% is suggested within 2 days following initiation of amiodarone therapy with consideration given to immediately discontinuing quinidine once amiodarone therapy is begun. Combining quinidine with digoxin can result in increased digoxin levels. If it is necessary to combine these drugs, it is recommended to reduce the digoxin dose by half.

Procainamide is the only Class 1 drug that does not necessitate oxidation metabolism by CYP. Procainamide and N-acetylprocainamide or NAPA concentrations increase by approximately 55% and 33%, respectively, during the first 7 days of concomitant amiodarone therapy. The precise pharmacokinetic mechanism of this interaction has not been elucidated, although a reduction in the renal clearance of both parent and metabolite, as well as a reduction in hepatic metabolism, seems likely. Additive electrophysiologic activity occurs with combination therapy and prolonged QT and QRS intervals or acceleration of preexisting ventricular tachycardia may result. Careful clinical observation of the patient as well as close monitoring of the ECG and serum procainamide and NAPA concentrations is essential with adjustment of the procainamide dosing regimen performed as necessary to avoid enhanced toxicity or pharmacodynamic effects. In general, it is recommended to discontinue completely or reduce the procainamide daily dose by 25% during the first week of initiating amiodarone therapy.

Concomitant administration of beta-blockers, or calcium channel blockers with amiodarone may result in additive electrophysiologic effects including bradycardia, sinus arrest, and atrioventricular block. This is particularly likely in patients with preexisting sinus node dysfunction. In general, these drugs should only be continued in patients at risk of significant bradycardia if a permanent artificial pacemaker is in place. In addition, amiodarone can decrease the clearance of drugs eliminated by hepatic metabolism. Severe cardiovascular reactions were observed when amiodarone was coadministered with metoprolol and propranolol.

Amiodarone increases serum levels of digoxin when given concomitantly, and an empiric 50% dosage reduction is advised upon initiation of amiodarone therapy. The degree to which digoxin serum concentrations will increase is not predictable and reassessment of the need for both drugs is prudent. As always, careful clinical observation of the patient and close monitoring of the ECG and serum digoxin concentrations is essential to ensure efficacy and to avoid enhanced toxicity with adjustment of the digoxin dose performed as necessary. The mechanism of the increase in digoxin serum concentration is complex and not well understood, but is thought to result from an amiodarone-induced displacement of digoxin from tissue-binding sites, an increase in bioavailability, and/or a decrease in renal or nonrenal clearance. Furthermore, amiodarone may induce changes in thyroid function and alter sensitivity to cardiac glycosides, and thyroid function should be monitored closely in patients receiving both drugs simultaneously.

Concurrent administration of amiodarone with coumarin or indandione anticoagulants (warfarin) results in at least a doubling of prothrombin time, significantly increasing the INR in virtually all patients receiving this drug combination and can

cause serious or potentially fatal hemorrhagic complications. This effect can occur as early as 4–6 days following the initial administration of the drugs in combination but can be delayed for weeks in some cases. Given the extremely long half-life of amiodarone, the interaction may persist for weeks or even months after discontinuance of amiodarone. A 50% reduction in the dosage of warfarin is recommended if amiodarone therapy is initiated with intensive clinical observation and frequent determination of PT and INR values to evaluate the extent of the interaction and guide further adjustments in therapy.

Concomitant administration of amiodarone and phenytoin may result in phenytoin toxicity, secondary to a two- or three-fold increase in total, steady-state serum phenytoin concentrations likely due to a amiodarone-induced decrease in phenytoin metabolism. Close monitoring for symptoms of phenytoin toxicity, including nystagmus, lethargy, and ataxia, and evaluation of serum phenytoin concentrations with appropriate dosage reduction as necessary, is essential in patients receiving these medications.

Amiodarone may enhance cardiovascular adverse effects such as hypotension and atropine-resistant bradycardia in patients receiving inhalation anesthetics, possibly due to a drug interaction.

Concomitant use of amiodarone with tricyclic antidepressants, phenothiazines, or any drug with the potential to prolong the QT interval may cause additive prolongation of the QT interval, and, rarely, torsades de pointes.

Although limited data exists, anecdotal reports have demonstrated a cholestyramine-induced reduction in amiodarone elimination half-life and subsequently serum concentrations. This interaction may be of benefit in temporally reducing the serum amiodarone, and presumably DEA concentrations prior to surgery in an attempt to limit the cardiac depressant effects of the drug in the immediate postsurgical period.

Two protease inhibitors, ritonavir and nelfinavir, are potent P450 enzyme inhibitors.

Theoretically, they would both be expected to produce a large increase in amiodarone concentrations, due to the inhibition of its metabolism. However, there are no published reports of this interaction to date, but it is suggested that there may be an increased risk of ventricular arrhythmias, so concurrent use should still be avoided.

Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as amitriptyline, calcium channel blockers, Class I antiarrhythmics,

Class III antiarrhythmics, monoamine oxidase inhibitors, citalopram, fluoxetine, nortriptyline, sertraline, and terfenadine, among others that prolong the QT interval. Levomethadyl is contraindicated in patients being treated with any of these agents.

Paroxetine impairs metabolism of the CYP2D6 (cytochrome P-450 isoenzyme 2D6) pathway at therapeutic doses. Paroxetine should be used cautiously in patients receiving type 1C antiarrhythmics (such as propafenone, flecainide, or encainide) and quinidine. Competition for hepatic CYP2D6 (cytochrome P-450 isoenzyme 2D6) by paroxetine may potentiate the toxicity of these antiarrhythmics.

Drug interaction between antifungal drugs and macrolide antibiotics, e.g., ketoconazole and erythromycin, which are metabolized by the same cytochrome P450 3A4 hepatic isoenzyme, can cause LQT-syndrome and torsades de pointes.

Sympathomimetics

Alpha-2 Receptor Adrenergic Agonists (Alpha-2-Agonists) and Other Centrally Acting Drugs

Alpha-2 receptor adrenergic agonists (clonidine, methyldopa, guanabenz, guanfacine) are a class of effective antihypertensive agents that lowers blood pressure by stimulating the alpha-2a adrenergic receptors in the central nervous system, leading to a reduction in central sympathetic outflow. In comparison, the alpha-2b receptors are responsible for causing vasoconstriction in vascular smooth muscle.

Clonidine and other alpha-2-receptor agonists should be used with caution in asthmatics and do not have adverse effects on lipid and carbohydrate metabolism. Oral doses of these agents do not change baseline air flow in asthmatics, but they do increase bronchial reactivity to inhaled histamine. Clonidine is well absorbed after oral administration and oral bioavailability is ~95%. The transdermal patch is available that provides stable serum concentrations for 1 week as an alternative to oral administration and application is once per week Clonidine is excreted unchanged by about 40–70% and protein binding is 20–30%. This does not change in renal disease. Half-life of clonidine is 7–18 h, and in end-stage renal disease 30–40 h. Dose adjustment according to creatinine clearance is required: (a) >50 mL/min: normal dose, (b) 20–50 mL/min: 1/2 normal dose, (c) <20 mL/min: 1/3–1/2 normal dose, and (d) Hemodialysis: no additional dose adjustment necessary. Dosing with the conventional formulation is twice a day. A variety of drugs, including hydralazine and methyldopa, have been identified as being causes of lupus.

Several drugs are known dopamine receptor antagonists, and raise serum prolactin by that mechanism. These include neuroleptic drugs, but also such antihypertensive drugs as methyldopa and reserpine, neither of which is commonly used now. Methyldopa inhibits dopamine synthesis, while reserpine inhibits dopamine storage.

Current use of these drugs is relatively limited, particularly as first-line therapy, due to a relatively high incidence of side effects such as dry mouth, sedation, and/or sexual dysfunction. In addition, there is a risk of rebound hypertension following sudden discontinuation of therapy, particularly with the shorter-acting clonidine.

Alpha-Blockers

Vascular smooth muscle has two primary types of alpha-adrenoceptors: alpha$_1$ (α_1) and alpha$_2$ (α_2). The α_1-adrenoceptors are located on the vascular smooth muscle. In contrast, α_2-adrenoceptors are located on the sympathetic nerve terminals as well as on vascular smooth muscle. α_1-adrenoceptor antagonists cause vasodilation by blocking the binding of norepinephrine to the smooth muscle receptors. Nonselective α_1- and α_2-adrenoceptor antagonists block postjunctional α_1- and α_2-adrenoceptors, which causes vasodilation; however, the blocking of prejunctional α_2-adrenoceptors leads to

increased release of norepinephrine, which attenuates the effectiveness of the α_1- and α_2-postjunctional adrenoceptor blockade. Furthermore, blocking α_2-prejunctional adrenoceptors in the heart can lead to increases in heart rate and contractility due to the enhanced release of norepinephrine that binds to beta$_1$-adrenoceptors.

Alpha-blockers block the effect of sympathetic nerves on blood vessels by binding to alpha-adrenoceptors located on the vascular smooth muscle. Most of these drugs act as competitive antagonists to the binding of norepinephrine that is released by sympathetic nerves synapsing on smooth muscle. Alpha-blockers are effective in acutely lowering blood pressure by dilating both arteries and veins because both vessel types are innervated by sympathetic adrenergic nerves; however, the vasodilator effect is more pronounced in the arterial resistance vessels. Because most blood vessels have some degree of sympathetic tone under basal conditions, these drugs are effective dilators. Although these drugs are effective in acutely lowering blood pressure, their effects are offset by an accompanying increase in cardiac output, and side effects are frequent and bothersome.

The selective alpha-1-blockers, such as prazosin, terazosin, and doxazosin, are the only class of antihypertensive agents that may have the combined effect of lowering LDL cholesterol, raising HDL cholesterol levels, and improving insulin sensitivity. The alpha-blockers, however, are associated with relatively bothersome side effects, including dizziness (rarely inducing syncope), headache, and weakness. As an example, a prospective trial in which six different antihypertensive drugs were compared found the highest incidence of adverse drug effects with prazosin. These problems appear to be minimized with long-acting doxazosin, which was as effective and as well tolerated as other antihypertensive drugs in the Treatment of Mild Hypertension Study.

Dizziness is most prominent with the first dose or with an increase in dose, particularly in patients who are volumes depleted (usually due to diuretic therapy) or who are taking other antihypertensive drugs. The incidence can be diminished by beginning with a low-dose of a long-acting agent such as 1 mg of doxazosin.

An interim analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found that doxazosin increases the risk of congestive heart failure compared to that associated with the administration of a diuretic, chlorthalidone. ALLHAT is a randomized prospective study of nearly 25,000 patients with hypertension and one additional risk factor for coronary heart disease designed to evaluate whether the incidence of a primary (e.g., fatal coronary heart disease and nonfatal myocardial infarction) or secondary outcome (e.g., all-cause mortality, stroke, and combined cardiovascular disease events [including congestive heart failure]) differed among those randomized to chlorthalidone versus one of three other antihypertensive drugs: amlodipine, lisinopril, or doxazosin. The doxazosin arm was prematurely terminated because of the finding of a markedly increased risk of congestive heart failure (8.13% versus 4.45% for chlorthalidone at 4 years $p<0.001$). Both drugs had equivalent risks of death from coronary heart disease and nonfatal myocardial infarction.

Why doxazosin was associated with an increased incidence of congestive heart failure is unclear; however, it was not felt to be due to the 2–3 mmHg difference in mean systolic blood pressure observed between the two groups.

The net effect is that the alpha-1-blockers should not be used as first-line treatment of hypertension. One possible exception is older men who also have symptomatic benign prostatic hyperplasia in whom an alpha-1-blocker may lead to symptomatic improvement.

Indications and Usage

Benign Prostatic Hyperplasia (BPH)

Prazosin, a short-acting alpha-1-antagonist, is occasionally used for BPH, but other medications are preferred. Due to the unfavorable results of the ALLHAT trial with doxazosin compared to diuretic therapy, alpha-blockers are less frequently used to treat patients with hypertension alone. The Food and Drug Administration (FDA) has approved 5 alpha-1-antagonists, (terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin) for treatment of the symptoms of BPH. Because of their favorable effects in BPH, doxazosin, terazosin, or prazosin are useful for men with both hypertension and BPH. Alfuzosin and tamsulosin are used exclusively for the treatment of prostatic hypertrophy, since compared to other oral alpha-blockers, they have less antihypertensive effects and are relatively more selective as antagonists at the alpha-1a subtype, the primary subtype located in the prostate.

Hypertension

Doxazosin mesylate is also indicated for the treatment of hypertension. Doxazosin mesylate may be used alone or in combination with diuretics, beta-adrenergic-blocking agents, calcium channel blockers, or angiotensin-converting enzyme inhibitors.

Contraindications/Precautions

Doxazosin mesylate is contraindicated in patients with a known sensitivity to quinazolines (e.g., prazosin, terazosin).

Syncope and “First-Dose” Effect

Doxazosin, like other alpha-adrenergic-blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1-mg dose. The 2-, 4-, and 8-mg tablets are not for initial therapy.

Dosage should then be adjusted slowly with evaluations and increases in dose every 2 weeks to the recommended dose. Additional antihypertensive agents should be added with caution. Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur, during both the day and night.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 h after the first dose, necessitating termination of the study. In this study, two of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials in hypertension involving over 1,500 hypertensive patients with dose titration every 1–2 weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

In placebo-controlled, clinical trials in BPH, 3 out of 665 patients (0.5%) taking doxazosin reported syncope. Two of the patients were taking 1-mg doxazosin, while one patient was taking 2-mg doxazosin when syncope occurred. In the open-label, long-term extension follow-up of approximately 450 BPH patients, there were three reports of syncope (0.7%). One patient was taking 2 mg, one patient was taking 8 mg, and one patient was taking 12 mg when syncope occurred. In a clinical pharmacology study, one subject receiving 2 mg experienced syncope.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

Priapism

Alpha$_1$ antagonists such as doxazosin have been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition.

Drug Interactions

Most (98%) of plasma doxazosin is protein bound. In vitro data in human plasma indicate that doxazosin mesylate has no effect on protein binding of digoxin, warfarin, phenytoin, or indomethacin. There is no information on the effect of other highly plasma protein–bound drugs on doxazosin binding. Doxazosin mesylate has been administered without any evidence of an adverse drug interaction to patients receiving

thiazide diuretics, beta-blocking agents, and nonsteroidal anti-inflammatory drugs. In a placebo-controlled trial in normal volunteers, the administration of a single 1-mg dose of doxazosin on day 1 of a 4-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin ($p=0.006$), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

In clinical trials, doxazosin mesylate tablets have been administered to patients on a variety of concomitant medications, while no formal interaction studies have been conducted, no interactions were observed. Doxazosin mesylate tablets have been used with the following drugs or drug classes:

1. Analgesic/anti-inflammatory (e.g., acetaminophen, aspirin, codeine and codeine combinations, ibuprofen, indomethacin)
2. Antibiotics (e.g., erythromycin, trimethoprim and sulfamethoxazole, amoxicillin)
3. Antihistamines (e.g., chlorpheniramine)
4. Cardiovascular agents (e.g., atenolol, hydrochlorothiazide, propranolol)
5. Corticosteroids
6. Gastrointestinal agents (e.g., antacids)
7. Hypoglycemics and endocrine drugs
8. Sedatives and tranquilizers (e.g., diazepam)
9. Cold and flu remedies

In a study ($n=24$) where terazosin and verapamil were administered concomitantly, terazosin's mean AUC_{0-24} increased 11% after the first verapamil dose and after 3 weeks of verapamil treatment it increased by 24% with associated increases in C_{max} (25%) and C_{min} (32%) means. Terazosin mean T_{max} decreased from 1.3 to 0.8 h after 3 weeks of verapamil treatment.

Statistically significant differences were not found in the verapamil level with and without terazosin. In a study ($n=6$) where terazosin and captopril were administered concomitantly, plasma disposition of captopril was not influenced by concomitant administration of terazosin and terazosin maximum plasma concentrations increased linearly with dose at steady state after administration of terazosin plus captopril.

Combined use with other antihypertensive drugs (e.g., beta-blockers, Ca-channel-blockers, diuretics, ACE inhibitors, see that section) can cause additive blood pressure lowering effects with severe symptomatic hypotension.

Prazosin has enhanced hypotensive effects with alcohol and antipsychotic drugs.

Beta-Adrenergic Antagonists (Beta-Blocking Agents)

Beta-adrenergic antagonists are identified by their affinity for binding to beta-adrenergic receptors, which is sufficiently high to antagonize the binding of

endogenous agonists like norepinephrine and epinephrine at blood and tissue concentrations that do not cause other undesirable effects. Historically, these agents have been classified according to their:

- Relative *selectivity* for the beta1- or beta2-adrenergic receptors.
- Their ability to bind *other adrenergic receptors*, usually alpha receptors.
- And their *interactions with other molecular targets* at clinically relevant doses, for example the K+ channel antagonist activity of the [+]enantiomer of sotalol.
- Many beta-adrenergic antagonists are characterized by their ability not only to prevent the binding of endogenous catecholamines but also to act as *partial agonists* (so-called intrinsic sympathomimetic activity [ISA]).
- And also by *chemical characteristics* of the compound itself (for example lipophilicity) that determine the tissue distribution, oral bioavailability, and clearance mechanisms of each compound.

Beta-adrenergic antagonists are used for the treatment of a variety of cardiovascular diseases: These include stable and unstable angina pectoris, hypertension, acute myocardial infarction, congestive heart failure due to systolic or diastolic dysfunction, and the therapy and prevention of some arrhythmias. There are many available in the market, and although they all have the similar mechanism of action, i.e., blockade of the beta-adrenoreceptor, there are various characteristics that differ among these agents; these characteristics primarily impact upon drug metabolism and the side effect profile but not efficacy.

Beta-adrenergic antagonists are competitive inhibitors of catecholamines at beta-adrenoreceptor sites. They act to reduce the effect of the catecholamine agonist on sensitive tissues. Most beta-adrenergic antagonists exist as pairs of optical isomers and are marketed as racemic mixtures. Almost the entire beta-blocking activity is found in the negative levorotatory L-stereoisomer, which can be up to 100 times more active than the positive dextrorotatory D-isomer. The D-isomers of beta-blocking drugs have no apparent clinical value except for D-sotalol, which has type III antiarrhythmic properties, i.e., it blocks the potassium channel and prolongs membrane repolarization, thereby increasing the QT interval. D-propranolol has type I (quinidine-like) membrane-stabilizing activity that is manifested only when very high doses of racemic propranolol are administered (Table 9.2).

Although beta-blockers have similar pharmacotherapeutic effects, their pharmacokinetic properties differ significantly in ways that may influence their clinical usefulness and side effects. Among individual drugs, there are differences in completeness of gastrointestinal absorption, amount of first-pass hepatic metabolism, lipid solubility, protein binding, extent of distribution in the body, penetration into the brain, concentration in the heart, rate of hepatic biotransformation, pharmacologic activity of metabolites, and renal clearance of the drug and its metabolites.

On the basis of their pharmacokinetic properties, the beta-blockers can be classified into two broad categories: Those eliminated by hepatic metabolism, and those excreted unchanged renally. Drugs in the first group (such as propranolol and metoprolol) are lipid soluble, almost completely absorbed by the small intestine, and largely metabolized by the liver. They enter the central nervous system (CNS) in

Table 9.2 Beta-adrenergic blocking agents – summary of indications[a]

Indications					Metoprolol[b]				Propranolol[b]		
Hypertension	√	√	√	√	√	√	√	√	√		√
Angina pectoris		√			√	√			√		
Cardiac arrhythmias											
Supraventricular arrhythmias/tachycardias				√					√		
Sinus tachycardia				√							
Intraoperative and postoperative tachycardia and hypertension				√							
Ventricular arrhythmias/tachycardias									√	√[c]	
Premature ventricular contractions (PVCs)	√								√		
Digitalis-induced tachyarrhythmias									√		
Resistant tachyarrhythmias (during anesthesia)									√		
Atrial ectopy					x						
Maintenance of normal sinus rhythm										√	
MI		√			√				√		√
CHF (stable)[d]				x	√[e]						
Pheochromocytoma									√		
Migraine prophylaxis		x			x	x			√		√
Hypertrophic subaortic stenosis									√		
Parkinsonian tremors						x			x[f]		
Akathisia, antipsychotic-induced					x				x		
Variceal bleeding in portal hypertension		x			x	x			x		x
Atrial fibrillation											
Rapid heart rate control					x						
Maintenance heart rate control					x						
Generalized anxiety disorder									x		
Angina											
Stable	x			x							
Unstable		x			x						

√ = labeled, x = unlabeled

[a]For more detailed information, see preceding indications and individual monographs

[b]Includes long-acting formulation

[c]Not *Betapace AF*

[d]See precautions or warnings

[e]*Toprol-XL* 25 mg only

[f]Sustained-release only

high concentrations, possibly resulting in an increased incidence of CNS side effects. They tend to have highly variable bioavailability and relatively short plasma half-lives. In contrast, drugs in the second category (such as atenolol and sotalol) are more water soluble, incompletely absorbed through the gut, eliminated unchanged by the kidney, and do not as readily enter the central nervous system. They show less variance in bioavailability and have longer plasma half-lives. Ultra-short-acting beta-blockers (such as esmolol) with a half-life of no more than 10 min offer advantages in some patients. They can be given for the treatment of supraventricular arrhythmias and, as a test dose, to a patient who has a questionable history of congestive heart failure. The short half-life of esmolol is due to its rapid metabolism by blood tissue and hepatic esterases (Table 9.3).

Beta-blockers are generally well tolerated but have a well-recognized set of potential side effects that can limit their use. Summarized briefly, the following are the major concerns with beta-blocker therapy:

1. Decreases in heart rate, contractility, and AV node conduction can lead to severe sinus bradycardia, sinus arrest, heart failure, and AV block.
2. Bronchoconstriction, due to β2-receptor blockade, can be induced by nonselective agents and high doses of cardioselective agents. Nonselective agents are generally contraindicated in patients with asthma and most patients with chronic obstructive lung disease; cardioselective agents or those with ISA must be used very cautiously in these settings.
3. Nonselective beta-blockers can cause worsening of symptoms of severe peripheral vascular disease or Raynaud's phenomenon but usually not milder disease with mild-to-moderate intermittent claudication. Cardioselective beta-blockers are probably preferable in such patients.
4. Fatigue may be due to the reduction in cardiac output or to direct effects on the central nervous system. Other central side effects that can occur include depression, nightmares, insomnia, and hallucinations. Impotence can also be a problem.
5. Nonselective beta-blockers (including labetalol) can mask the early, sympathetically mediated symptoms of hypoglycemia in patients with insulin-dependent diabetes mellitus; they can also delay the rate of recovery of the blood glucose concentration.
6. Perturbations of lipoprotein metabolism accompany the use of beta-blockers. Nonselective agents cause greater rises in triglycerides and falls in cardioprotective high-density lipoprotein-cholesterol levels, whereas ISA agents cause less or no effect and some agents such as celiprolol may raise HDL cholesterol levels. Patients with renal failure may take beta-blockers without additional hazard, although modest falls in renal blood flow and glomerular filtration rate have been measured, presumably from renal vasoconstriction.

Caution is advised in the use of beta-blockers in patients suspected of harboring a pheochromocytoma, because unopposed alpha-adrenergic agonist action may precipitate a serious hypertensive crisis if this disease is present. Moreover, caution is advised in the use of beta-blockers in patients suspected of harboring Prinzmetal angina and Mb. Raynaud, because use of beta-adrenergic anatagonists in such patients may cause or enhance vasospasm.

Table 9.3 Pharmacologic/pharmacokinetic properties of beta-adrenergic blocking agents

Drug									Metabolism/excretion
Acebutolol	β_1[a]	+[b]	+	Low	90	20–60	3–4	26	Hepatic; renal excretion 30–40%; nonrenal excretion 50–60% (bile; intestinal wall)
Atenolol	β_1[a]	0	0	Low	50	50–60	6–7	6–16	≈50% excreted unchanged in feces
Betaxolol	β_1[a]	+	0	Low	≈100	89	14–22	≈50	Hepatic; >80% recovered in urine, 15% unchanged
Bisoprolol	β_1[a]	0	0	Low	≥90	80	9–12	≈30	≈50% excreted unchanged in urine, remainder as inactive metabolites; <2% excreted in feces
Esmolol	β_1[a]	0	0	Low	na[c]	na[c]	0.15	55	Rapid metabolism by esterases in cytosol of red blood cells
Metoprolol	β_1[a]	0[b]	0	Moderate	≈100	40–50	3–7	12	Hepatic; renal excretion, <5% unchanged
Metoprolol, long-acting						77[d]			
Nadolol	β_1 β_2	0	0	Low	30	30–50	20–24	30	Urine, unchanged
Penbutolol	β_1 β_2	0	+	High	≈100	≈100	≈5	80–98	Hepatic (conjugation, oxidation); renal excretion of metabolites (17% as conjugate)
Pindolol	β_1 β_2	0	+++	Low	>95	≈100	3–4[e]	40	Urinary excretion of metabolites (60–65%) and unchanged drug (35–40%)

Propranolol	β_1 β_2	++	0	High	<90	30	3–5	90	Hepatic; <1% excreted unchanged in urine
Propranolol, long-acting						9–18	8–11		
Sotalol	β_1 β_2	0	0	Low	nd[f]	90–100	12	0	Not metabolized; excreted unchanged in urine
Timolol	β_1 β_2	0	0	Low to moderate	90	75	4	<10	Hepatic; urinary excretion of metabolites and unchanged drug

0 = none, + = low, ++ = moderate, +++ = high

[a]Inhibits β_2 receptors (bronchial and vascular) at higher doses

[b]Detectable only at doses much greater than required for beta-blockade

[c]Not applicable (available IV only)

[d]Average bioavailability; not absolute

[e]In elderly hypertensive patients with normal renal function, $t_{/2}$[1] variable: 7–15 h

[f]No data

The use of beta-blockers during pregnancy has been clouded by scattered case reports of various fetal problems. Moreover, prospective studies have found that the use of beta-blockers during pregnancy may lead to fetal growth retardation.

When a beta-blocker is discontinued, angina pectoris and myocardial infarction may occur. Therefore, patients with ischemic heart disease must be warned not to rapidly discontinue treatment, since this can lead to a withdrawal syndrome characterized by accelerated angina, myocardial infarction, and even death. These findings, which can occur even in patients without previously known coronary disease, probably result from upregulation of the beta-receptors following chronic beta-blockade (Tables 9.4 and 9.5).

Table 9.4 Major drug interactions with beta-blockers

Drug	Possible effects	Precautions
Absorption		
Aluminum	Decreased beta-blocker adsorption and therapeutic effect	Avoid beta-blocker-aluminum hydroxide combination
Cholestyramine, colestipol	Decreased beta-blocker adsorption	Avoid beta-blocker-cholestyramine-combination
Metabolism		
Cimetidine	Prolongs half-life of propranolol	Combination should be used with caution
Aminophylline	Mutual inhibition	Observe patient's response
Lidocaine	Propranolol pretreatment increases	Combination should be used with caution; use lower doses of lidocaine
	Lidocaine levels with potential toxicity	
Rifampin	Increased metabolism of beta-blockers	Observe patient's response
Smoking	Increased metabolism of beta-blockers	Observe patient's response
Pharmacodynamic interactions		
AV-node		
Calcium channel inhibitors (verapamil, diltiazem)	Potentiation of bradycardia, myo-depression and hypotension	Avoid use, although few patients show ill effects
Amiodarone	May induce cardiac arrest	Combination should be used with caution
Digitalis glycosides	Potentiation of bradycardia	Observe patient's response; interactions may benefit angina patients with abnormal ventricular function
Conduction/ventricular function		
Phenytoin	Additive cardiac depressant effects	Administer IV phenytoin with great caution

(continued)

Table 9.4 (continued)

Drug	Possible effects	Precautions
Quinidine	Additive cardiac depressant effects	Observe patient's response; few patient show ill effects
Tricyclic antidepressants	Inhibits negative inotropic and chrono-tropic effects of beta-blockers	Observe patient's response
Hypertension/hypotension		
Clonidine	Hypertension during clonidine withdrawal	Monitor for hypertensive response; withdraw beta-blocker before withdrawing clonidine
Levodopa	Antagonism of levodopa's hypotensive and positive inotropic effects	Monitor for altered response; interaction may have favorable results
Methyldopa	Hypertension during stress	Monitor for hypertensive episodes
Epinephrine	Hypertension; bradycardia	Administer epinephrine cautiously; cardioselective
Phenylpropanolamine	Severe hypertensive reaction	Beta-blocker may be safer doses of phenothiazines
Indomethacin	Inhibition of antihypertensive response To beta-blockade	Observe patient's response
Reserpine	Excessive sympathetic blockade	Observe patient's response
Isoproterenol	Mutual inhibition	Avoid concurrent use or choose cardiac-selective beta-blocker
Phenothazines	Additive hypotensive effects	Monitor for altered response, especially with high doses
Halofenate	Reduced beta-blocking activity; induction of propranolol withdrawal rebound	Observe for impaired response to beta-blockade
Vasoconstriction		
Ergot alkaloids	Excessive vasoconstriction	Observe patient's response; Few patients show ill effects
Glucose metabolism		
Glucagon	Inhibition of hyperglycemic effect	Monitor for reduced response
Antidiabetic agents	Enhanced hypoglycemia; hypertension	Monitor for altered diabetic response
Others		
MAO inhibitors	Uncertain, theoretical	Manufacturer of propanolol considers concurrent use contraindicated
Tubocurarine	Enhanced neuromuscular blockade	Observe response in surgical patients, especially after high doses of propranolol

Table 9.5 Drug interactions

Beta-blocker drug interactions			
Precipitant drug	Object drug		Description
Aluminum salts, barbiturates, calcium salts, cholestyramine, colestipol, penicillins (ampicillin), rifampin	β-Blockers	↓	The bioavailability and plasma levels of certain β-blockers may be decreased by these agents, possibly resulting in a decreased pharmacologic effect
Calcium channel blockers	β-Blockers	↑	Pharmacologic effects of β-blockers as well as nifedipine and verapamil may be synergistic or additive. Diltiazem and nicardipine may decrease the metabolism of certain beta-blockers, thus increasing the pharmacologic effects
Cimetidine	β-Blockers Metoprolol Propranolol	↑	Pharmacokinetic parameters of β-blockers metabolized by cytochrome P450 may be altered by cimetidine; pharmacodynamic effects may be increased
Contraceptives, oral	β-Blockers	↑	Bioavailability and plasma levels of certain β-blockers may be increased
Diphenhydramine	β-Blockers	↑	Diphenhydramine may increase plasma concentrations and cardiovascular effects of certain β-blockers through inhibition of CYP2D6-mediated metabolism
Flecainide β-Blockers	β-Blockers Flecainide	↑	The bioavailability of either agent may be increased, possibly increasing the pharmacologic effects
Haloperidol β-Blockers Propranolol	β-Blockers Propranolol Haloperidol	↑	Pharmacologic effects (hypotensive episodes) of both drugs may be increased
Hydralazine β-Blockers Metoprolol Propranolol	β-Blockers Metoprolol Propranolol Hydralazine	↑	Serum levels and, hence, pharmacologic effects of β-blockers and hydralazine may be enhanced
Hydroxychloroquine	β-Blockers	↑	Plasma concentrations and cardiovascular effects of certain β-blockers may be increased because hydroxychloroquine inhibits the CYP2D6-mediated β-blocker metabolism
Loop diuretics	β-Blockers Propranolol	↑	Propranolol plasma levels and cardiovascular effects may be enhanced. Atenolol was not affected
MAO inhibitors	β-Blockers Metoprolol Nadolol	↑	Bradycardia may develop during concurrent use

(continued)

Table 9.5 (continued)

Beta-blocker drug interactions			
Precipitant drug	Object drug		Description
NSAIDs, salicylates, sulfinpyrazone	β-Blockers	↓	NSAIDs, salicylates, and sulfinpyrazone may inhibit the synthesis of prostaglandins involved in the antihypertensive activity of β-blockers
Phenothiazines	β-Blockers Propranolol	↑	Propranolol bioavailability and plasma levels and phenothiazine plasma levels may be increased, possibly resulting in increased effects
β-Blockers Propranolol	Phenothiazines		
Propafenone	β-Blockers Metoprolol Propranolol	↑	Plasma levels of β-blockers metabolized by the liver may be increased
Quinidine	β-Blockers	↑	Plasma β-blocker levels may be increased in "extensive metabolizers," possibly resulting in increased effects
Quinolones Ciprofloxacin	β-Blockers	↑	Bioavailability of β-blockers metabolized by cytochrome P450 may be increased
SSRIs	β-Blockers Metoprolol Propranolol	↑	Certain SSRIs may inhibit the metabolism (CYP2D6) of certain β-blockers, leading to excessive β-blockade
Thioamines	β-Blockers Metoprolol Propranolol	↑	The pharmacokinetics of the β-blockers may be altered, increasing the pharmacologic effects
Thyroid hormones	β-Blockers Metoprolol Propranolol	↓	The actions of certain β-blockers may be impaired when the hypothyroid patient is converted to the euthyroid state
β-Blockers Propranolol	Anticoagulants	↑	Propranolol may increase the anticoagulant effect of warfarin
β-Blockers Metoprolol Propranolol	Benzodiazepines	↑	Effects of certain benzodiazepines may be increased by lipophilic β-blockers. Atenolol does not interact
β-Blockers	Clonidine	↑	Life-threatening and fatal increases in blood pressure have occurred after discontinuation of clonidine in patients receiving a β-blocker or after simultaneous withdrawal
β-Blockers	Disopyramide	↔	Difficult to predict; disopyramide clearance may be decreased; adverse effects may occur (e.g., sinus bradycardia, hypotension) or there may be no occurrence of synergistic or additive negative inotropic effects
β-Blockers	Epinephrine	↑	Nonselective β-blockade allows alpha receptor effects of epinephrine to predominate. Increasing vascular resistance leads to initial hypertensive episode followed by bradycardia

(continued)

Table 9.5 (continued)

Beta-blocker drug interactions			
Precipitant drug	Object drug		Description
β-Blockers	Ergot alkaloids	↑	Peripheral ischemia manifested by cold extremities, possible peripheral gangrene may develop due to ergot alkaloid-mediated vasoconstriction and β-blocker-mediated blockade of peripheral β_2 receptors, allowing for unopposed ergot action
β-Blockers Propranolol	Gabapentin	↑	Gabapentin adverse reactions may be increased
β-Blockers	Lidocaine	↑	Increased lidocaine levels may occur, resulting in toxicity
β-Blockers	Nondepolarizing muscle relaxants	↔	β-blockers may potentiate, counteract, delay, or have no effect on the actions of the nondepolarizing muscle relaxants
β-Blockers	Prazosin	↑	Concurrent administration may increase the postural hypotension produced by prazosin
β-Blockers	Sulfonylureas	↓	Hypoglycemic effects of sulfonylureas may be attenuated
β-Blockers Nonselective	Theophylline	↔	Reduced elimination of theophylline may occur Pharmacologic antagonism can also be expected, thus reducing the effects of one or both agents. Cardioselective agents may be preferred

↑Object drug increased, ↓ = object drug decreased, ↔ = undetermined clinical effect

Direct Acting Vasodilators

Nitroprusside

Nitroprusside is a powerful vasodilator with potent afterload-reducing properties. It is the agent most frequently used early in the treatment of acute heart failure, particularly when a rapid and substantial reduction in systemic vascular resistance is necessary. Common clinical conditions would include complications of myocardial infarction such as acute mitral regurgitation secondary to papillary muscle dysfunction or rupture, ventricular septal defect, and acute aortic regurgitation. Nitroprusside relaxes arterial and venous smooth muscles via the production of nitric oxide and nitrosothiols leading to an increase in cyclic guanosine monophosphate and smooth muscle relaxation. Similar to nitroglycerin, nitroprusside causes preload reduction by diminishing heightened venous tone and increasing venous capacitance with a concomitant shift in central blood volume to the periphery. This causes a reduction in right ventricular pressure and volume. Unique to nitroprusside is its rapid and

powerful effect on afterload. This agent reduces the major components of aortic impedance (mean and hydraulic vascular load), resulting in an improved and often dramatic increase in forward stroke volume and cardiac output with reductions in left ventricular filling pressure, volume, and valvular regurgitation.

In most patients with heart failure, judicious titration of nitroprusside can result in a fall in aortic impedance, increased cardiac output, and reduced ventricular filling pressures without the undesirable effects of a decrease in systemic blood pressure or rise in heart rate. The combined balanced vasodilator effect of nitroprusside can therefore rapidly improve the hemodynamic abnormalities associated with acute heart failure when preload and afterload reduction is desired.

Generally, by improving ventricular wall stress and reducing myocardial oxygen consumption, nitroprusside will have a favorable effect on myocardial energetics. Nitroprusside may also improve coronary blood flow and myocardial perfusion by directly reducing coronary vascular resistance and by increasing coronary perfusion pressure. The latter will occur as long as there is a reduction in ventricular diastolic pressure that is greater than aortic coronary diastolic pressure. In patients with occlusive coronary artery disease, care must be taken to avoid excessive reductions in systemic pressure or elevations in heart rate that would reduce coronary perfusion and increase myocardial oxygen demand. Unlike nitroglycerin, nitroprusside may cause "coronary steal" whereby arteriolar dilatation in nonischemic zones diverts coronary flow away from areas of ischemia. The frequency with which this occurs in heart failure is not well documented.

Dosing

Nitroprusside is an arteriolar and venous dilator, given as an intravenous infusion. Initial dose: 0,25–0,5 μg/kg/min; maximum dose: 8–10 μg/kg/min. Nitroprusside acts within seconds and has a duration of action of only 2–5 min. Its effects are evident within 60–90 s after initiation of the infusion and should an adverse effect such as symptomatic hypotension occur, the vasodilating properties usually abate within 20–30 min after discontinuation.

Continuous monitoring of central hemodynamics with an indwelling flow-directed thermodilution pulmonary artery catheter is mandatory to safely and effectively target the optimal dose. In acute heart failure, an arterial catheter for continuous systemic blood pressure recording and monitoring and frequent blood gas determinations is also recommended. It should be recognized, however, that during nitroprusside infusion, the pressure measured in a peripheral artery (usually radial artery) may not reflect a reduction in central aortic pressure because of nitroprusside-induced changes in the amplitude and timing of reflected waves within the central aorta. One must remain cognizant of this when the clinical findings are consistent with systemic hypoperfusion despite a seemingly acceptable peripheral arterial pressure. Nitroprusside can be rapidly titrated to achieve the desired clinical and hemodynamic endpoints including a reduction in pulmonary capillary-wedge pressure to

18–20 mm Hg, a decrease in systemic vascular resistance to 1,000–1,200 dynes/s/cm^5; reduction in valvular regurgitation; and an improvement in stroke volume, cardiac output, and systemic perfusion while avoiding significant hypotension and tachycardia. Although the target blood pressure is variable depending on the individual patient, a systolic blood pressure of 80 mm Hg or greater is usually acceptable. A higher systolic blood pressure may be required in the elderly or in patients with a recent history of hypertension or cerebrovascular disease. The target pulmonary capillary-wedge pressure is usually higher in acute heart failure than in patients with decompensated chronic heart failure. In the latter condition, the stroke volume of the dilated ventricle is not preload-dependent, and therefore, relatively normal left ventricular filling pressures can be targeted. In acute heart failure, particularly when myocardial ischemia is present, attention to Starling mechanisms with respect to preload and augmentation of stroke volume remains important. While titrating nitroprusside to achieve hemodynamic goals, doses are rarely greater than 4 mcg/kg/min to maintain adequate vasodilation in the acute heart failure setting, and dosing this high should generally be avoided for prolonged periods (more than 72 h) due to the risk of thiocyanate and cyanide toxicity.

Adverse Drug Reactions

The most common serious adverse effect of nitroprusside administration in acute heart failure is systemic hypotension. One should be particularly cautious when initiating nitroprusside in a patient with ischemia or infarction and a systolic arterial pressure of less than 100 mm Hg. An increase in heart rate during the infusion is an ominous finding and usually precedes hypotension. This typically occurs when stroke volume has not increased appropriately, often because of ongoing or worsening ischemia, valvular regurgitation, and inadequate cardiac reserve. A reduction or cessation of the nitroprusside infusion is usually warranted.

Alternatively, the addition of a positive inotropic agent such as dobutamine is often advantageous and may allow for the continuation of nitroprusside. Such a combination is commonly used while stabilizing particularly severe, low-output heart failure until more definitive therapy can be instituted. When systemic hypotension and poor peripheral perfusion is present at the outset, nitroprusside should generally be avoided as initial treatment.

Thus, hypotension can be easily reversed by temporarily discontinuing the infusion. However, the potential for cyanide toxicity limits its prolonged use. Nitroprusside is metabolized to cyanide, which rarely causes toxicity because it is converted to thiocyanate by the enzyme rhodonase, which is a thiosulfate-cyanide transferase. The thiosulfate is substrate limiting. If it is depleted, cyanide accumulates sufficiently to cause toxicity. Conversely, such an event can be treated by administering thiosulfate. Once thiocyanate is formed, it is excreted by the kidney. If it accumulates, it causes adverse CNS effects. The half-life of thiocyanate is 2.7 days, and in end-stage renal disease 9 days. Thiocyanate can accumulate, and its levels should be monitored in patients with decreased renal function.

As noted above, thiocyanate toxicity is a potentially serious side effect of prolonged nitroprusside infusion and is manifest clinically by nausea, disorientation, psychosis, muscle spasm, and hyperreflexia when plasma thiocyanate concentrations exceed 6 mg%. This is uncommon in the management of acute heart failure where nitroprusside therapy is usually a temporary means of support while awaiting definitive therapy. Cyanide toxicity is extremely rare in heart failure management and only occurs during prolonged, high-dose infusions, usually in the setting of significant hepatic dysfunction. The concept of intravenous vasodilator therapy in acute heart failure is based on correction of hemodynamic derangement and stabilization of the patient while a therapeutic plan is devised. The necessity for prolonged treatment (>72 h) often portends a poor prognosis, particularly in the absence of a reversible underlying disorder.

Hydralazine

Hydralazine, like diazoxide, is a direct arteriolar vasodilator with little or no effect on the venous circulation. Thus, the same precautions apply in patients with underlying coronary disease or a dissecting aortic aneurysm, and a β-blocker should be given concurrently to minimize reflex sympathetic stimulation. The hypotensive response to hydralazine is less predictable than that seen with other parenteral agents, and its current use is primarily limited to pregnant women.

Hydralazine is given as an intravenous bolus. The initial dose is 5–10 mg, with the maximum dose being 20 mg. The fall in blood pressure begins within 10–30 min and lasts 2–4 h.

Potassium-Channel Openers

Minoxidil

In the case of refractory hypertension, powerful additional hypertension agents such as minoxidil may be necessary. Minoxidil represents a third-line antihypertensive drug and should not be used as a first- or second-line drug (due to adverse effects and reflex stimulation of norepinephrine and angiotensin II release). Diuretic therapy is usually needed with diazoxide or minoxidil therapy. Minoxidil may produce pericardial reactions by non-Lupus mechanisms.

Bioavailability is 95% and less than 5% from cutaneous application. About 12–20% of the drug is excreted unchanged. Minoxidil sulfate is the active moiety. The glucuronide metabolite appears to have some activity either alone or possibly as a reservoir for endogenous cleavage back to the parent compound. The drug has a half-life 3–4 h and in case of impaired renal function 9 h. Hemodialysis decreases serum concentration by 24–43%. Minoxidil is also removed by peritoneal dialysis. Accumulation of glucuronide and parent drug occurs, and pharmacologic effect

may be enhanced in patients with decreased renal function. Patients with end-stage renal disease should receive half of the normal doses. In patients being dialyzed, the dose should be administered after dialysis.

In general, lowering the blood pressure with antihypertensive agents, weight loss, or dietary sodium restriction decreases cardiac mass in patients with left ventricular hypertrophy.

Regression is largely absent with direct vasodilators (such as hydralazine or minoxidil) despite adequate blood pressure control. The ineffectiveness of direct vasodilators probably reflects the reflex stimulation of norepinephrine and angiotensin II release induced by these drugs, since these hormones may directly promote the development of left ventricular hypertrophy.

Diazoxide

Diazoxide, in comparison to nitroprusside and nitroglycerin, is an arteriolar vasodilator that has little effect on the venous circulation. Diazoxide is also longer acting and, in the currently recommended doses, requires less monitoring than nitroprusside, since the peak effect is seen within 15 min and lasts for 4–24 h. Diazoxide can be administered either as an intravenous bolus or infusion. A β-blocker such as propranolol or labetalol is usually given concurrently to block reflex activation of the sympathetic nervous system. This protection, however, is not complete, and it is recommended that diazoxide not be used in patients with angina pectoris, myocardial infarction, pulmonary edema, or a dissecting aortic aneurysm.

Diazoxide can also cause marked fluid retention and a diuretic may need to be added if edema or otherwise unexplained weight gain is noted. For these reasons, diazoxide is now rarely used.

Diazoxide has a bioavailability of 85–90% and is excreted unchanged by about 20%. More than 90% are protein bound, which decreases in uremia or hypoalbuminemia. Plasma half-life is 15–30 h and 20–53 h in end-stage renal disease. Decreased binding in uremia or the nephrotic syndrome results in increased free drug in the circulation and increased response. Dose adjustment according to creatinine clearance: (a) >50 mL/min: normal dose, (b) 20–50 mL/min: 2/3 of normal dose, and (c) <20 mL/min: 1/2–2/3 normal dose. Hemodialysis requires no additional dose adjustment.

Adverse effects include marked edema (which may require high doses of loop diuretics) and hirsutism.

Medical therapy for insulinoma should be considered in the patient whose insulinoma was missed during pancreatic exploration, who is not a candidate for or refuses surgery, or who has metastatic insulinoma. The therapeutic choices to prevent symptomatic hypoglycemia include diazoxide, verapamil, phenytoin, and the somatostatin analogue octreotide. Diazoxide (which must be given in divided doses of up to 1,200 mg/day) is the most effective drug for controlling hypoglycemia. However, its use is often limited by marked edema (which may require high doses of loop diuretics) and hirsutism.

Calcium Channel Blockers

Calcium channel blockers are widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, and other disorders, and the longer-acting preparations have been prescribed with increasing frequency since 1989.

Calcium channel blockers have become the most popular class of agents used in the treatment of hypertension.

Types of Calcium Channel Blockers

The calcium channel blockers currently available are divided into two major categories based upon their predominant physiologic effects: the dihydropyridines which preferentially block the L-type calcium channels, and verapamil and diltiazem. The L-type calcium channels are responsible for myocardial contractility and vascular smooth muscle contractility; they also affect conducting and pacemaker cells.

Dihydropyridines

The dihydropyridines are potent vasodilators that have little or no negative effect upon cardiac contractility or conduction. They can be further divided into three categories based upon half-life and effect on contractility:

1. Short-acting liquid nifedipine
2. Longer-acting formulations with little cardiac depressant activity – felodipine, isradipine, nicardipine, nifedipine GITS and CC, and nisoldipine
3. Long-acting agents with no cardiac depressant activity – amlodipine, lacidipine

Verapamil and Diltiazem

Verapamil and, to a lesser extent, diltiazem are less potent vasodilators but have negative effects upon cardiac conduction and contractility.

Side Effects

The side effects that may be seen with the calcium channel blockers vary with the agent that is used. The potent vasodilators can, in 10–20 % of patients, lead to one or more of the following: headache, dizziness or lightheadedness, flushing, and peripheral edema. The peripheral edema, which is infrequent with verapamil, is related to redistribution of fluid from the vascular space into the interstitium, possibly induced by vasodilation which allows more of the systemic pressure to be

transmitted to the capillary circulation. In one study of 12 healthy subjects, for example, a single dose of nifedipine increased the foot volume despite also increasing sodium excretion. Thus, treatment of this form of edema with a diuretic will not relieve the edema. On the other hand, edema is much less common when a dihydropyridine is given with an angiotensin-converting enzyme inhibitor. This effect is probably related to venodilation by the ACE inhibitor which helps remove the fluid sequestered in the capillary bed by the arteriolar dilation from the calcium channel blocker. This form of combination therapy is likely to become much more common since the Food and Drug Administration has approved fixed (low) dose combination preparations of these drugs. The major adverse effect with verapamil is constipation, which can occur in over 25% of patients.

Along with freedom from most of the side effects seen with other classes of antihypertensive agents, calcium antagonists may be unique in not having their antihypertensive efficacy blunted by nonsteroidal anti-inflammatory agents

Effects on Cardiac Function

Verapamil and, to a lesser degree, diltiazem can diminish cardiac contractility and slow cardiac conduction. As a result, these drugs are relatively contraindicated in patients who are taking beta-blockers or who have severe left ventricular systolic dysfunction, sick sinus syndrome, and second- or third-degree atrioventricular block.

The dihydropyridines have less cardiac depressant activity in vivo for two reasons: (1) The doses employed are limited by the peripheral vasodilation; as a result, plasma levels sufficient to impair contractility and atrioventricular conduction are not achieved and (2) Acute vasodilation leads to a reflex increase in sympathetic activity that can counteract the direct effect of calcium channel blockade.

Specific Drug Interactions

Israpidine

Drugs that affect cytochrome CYP (P450) 3A can alter the metabolism of isradipine. Anticonvulsants (such as phenytoin, phenobarbital, and carbamazepine) induce both the intestinal and hepatic forms of this isoenzyme. Induction increases the first-pass metabolism of isradipine and decreases its bioavailability. On the other hand, ketoconazole, erythromycin, clarithromycin, cimetidine, grapefruit juice, and other calcium channel blockers can inhibit cytochrome P450 3A. The calcium channel blocker effect is greatest with verapamil, which can slow metabolism of substrates for this isoenzyme by up to 50%. Diltiazem is less potent and other dihydropyridines (such as nicardipine and nisoldipine) appear to have negligible effects. Cytochrome inhibition diminishes first-pass metabolism and increases (as much as two-fold) the bioavailability of isradipine. Elimination of absorbed isradipine is also

reduced, and the combined effect causes dramatic increases in the plasma level and activity of this drug. Cautious dosing is required in this setting. In addition to being a substrate for CYP3A, isradipine is also capable of inhibiting this isoenzyme. As a result, its coadministration with other drugs that are metabolized by this isoenzyme (such as terfenadine and quinidine) can lead to a clinically important interaction and careful monitoring is important.

Felodipine

Anticonvulsants (phenytoin, phenobarbital, and carbamazepine) can induce intestinal and hepatic cytochrome CYP (P450) 3A. Induction of this enzyme increases the first-pass effect of felodipine and decreases its bioavailability. As a result, higher doses may be required. In comparison, inhibitors of this isoenzyme lead to an increase in plasma drug levels. The effect of grapefruit juice appears to be mediated by selective downregulation of CYP3A in the intestine. The clinical significance of the change in felodipine metabolism with more usual amounts of grapefruit juice ingestion is uncertain. Inhibition of cytochrome CYP3A diminishes the first-pass metabolism of felodipine and increases (as much as two-fold) its bioavailability. The elimination of absorbed felodipine is also diminished. The net effect may be a dramatic elevation in the plasma felodipine concentration and in drug activity. Cautious dosing is required in this setting.

Nicardipine, Nifedipine, Nimodipine

Drugs that affect cytochrome CYP (P450) 3A can alter the metabolism of nicardipine. Elimination of absorbed nicardipine is also reduced, and the combined effect causes dramatic increases in the plasma level and activity of this drug. Cautious dosing is required.

Nisoldipine

Drugs that affect cytochrome CYP (P450) 3A can alter the metabolism of nisoldipine. Propranolol also slows nisoldipine elimination. It is unlikely that this effect occurs by enzyme inhibition, since these two drugs are metabolized by different cytochrome P450 isoenzymes. Propranolol and presumably other β-blockers may act by decreasing hepatic blood flow.

Verapamil

Drugs that affect cytochrome CYP (P450) 3A can alter the metabolism of verapamil. It is of interest that verapamil itself has the greatest inhibitory effect of the calcium channel blockers, decreasing the metabolism for substrates of cytochrome

CYP3A by up to 50%. As a result, its coadministration with other drugs that are metabolized by this isoenzyme can lead to a clinically important interaction and careful monitoring is important. Examples of this interaction with verapamil include cyclosporine, digoxin, digitoxin, quinidine, terfenadine, and most of the dihydropyridines (such as felodipine, nifedipine, nicardipine, nisoldipine, and isradipine). Moreover, verapamil can displace digitalis from tissue-binding sites and may enhance free digitalis that could cause toxicity. *Pharmacodynamic interactions* of verapamil include exerting negative inotropic effects and slowing conduction through the atrioventricular node (negative dromotropic action). A number of other cardiovascular drugs may have pharmacodynamic interactions with verapamil. (*Beta-blockers* have negative inotropic and negative dromotropic effects that may be additive to those of verapamil. *Digoxin*, which slows AV nodal conduction via its vagotonic activity, can have an additive pharmacologic effect on AV nodal conduction with verapamil, independent of the metabolic interaction described above. *Adenosine* is a rapidly acting agent that slows conduction through the AV node. Thus, the dose of adenosine necessary to produce AV nodal blockade is lower for patients being treated with verapamil.)

ACE Inhibitors and AT-1 Antagonists

ACE Inhibitors

ACE inhibitors were synthesized as specific inhibitors of the converting enzyme that breaks the peptidyldipeptide bond in angiotensin I, preventing the enzyme from attaching to and splitting the angiotensin I structure. Because angiotensin II cannot be formed and angiotensin I is inactive, the ACE inhibitor paralyzes the renin-angiotensin system, thereby removing the effects of endogenous angiotensin II as both a vasoconstrictor and a stimulant to aldosterone synthesis.

Mechanism of Action

Interestingly, the plasma angiotensin II levels actually return to previous readings with chronic use of ACE inhibitors while the blood pressure remains lowered. This suggests that the antihypertensive effect may involve other mechanisms. Since the same enzyme that converts angiotensin I to angiotensin II is also responsible for

inactivation of the vasodepressor hormone bradykinin, by inhibiting the breakdown of bradykinin, ACE inhibitors increase the concentration of a vasodepressor hormone while they decrease the concentration of a vasoconstrictor hormone. The increased plasma kinin levels may contribute to the improvement in insulin sensitivity observed with ACE inhibitors, but they are also responsible for the most common and bothersome side effect of their use, a dry, hacking cough. ACE inhibitors may also vasodilate by increasing levels of vasodilatory prostaglandins and decreasing levels of vasoconstricting endothelins. Their effects may also involve inhibition of the renin-angiotensin system within the heart and other tissues.

Regardless of the manner in which they work, ACE inhibitors lower blood pressure mainly by reducing peripheral resistance with little, if any, effect on heart rate, cardiac output, or body fluid volumes. After a year of treatment with an ACE inhibitor, the structure and function of subcutaneous resistance vessels were improved whereas no changes were observed with a beta-blocker. The lack of a rise in heart rate despite a significant fall in blood pressure has been explained by a blunting of the adrenergic nervous system.

Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension and congestive heart failure. In addition to efficacy, these agents have the additional advantage of being particularly well tolerated, since they produce few idiosyncratic side effects and do not have the adverse effects on lipid and glucose metabolism seen with diuretics or β-blockers. Although captopril therapy was initially associated with a variety of presumed sulfhydryl group–related complications such as rash, neutropenia, taste abnormalities, and even the nephrotic syndrome, these problems have become uncommon since the maximum dose was reduced to 100–150 mg/day. It has also been proposed that ACE inhibitors are associated with an improved quality of life compared to some other antihypertensive drugs, such as propranolol and methyldopa. However, later studies have not confirmed a significant advantage of any antihypertensive drug in terms of quality of life.

In summary, these drugs are widely used for all degrees and forms of hypertension. Their use is likely to increase further because of their particular ability to decrease intrarenal hypertension, to unload the hemodynamic burden of congestive heart failure, and to protect against ventricular dysfunction after myocardial infarction.

Side Effects

Most patients who take an ACE inhibitor experience neither side effects nor the biochemical changes often seen with other drugs that may be of even more concern even though they are not so obvious; neither rises in lipids, glucose, or uric acid nor falls in potassium levels are seen, and insulin sensitivity may improve.

ACE inhibitors may cause both specific and nonspecific adverse effects. Among the specific ones are rash, loss of taste, glomerulopathy manifested by proteinuria, and leukopenia. In addition, these drugs may cause a hypersensitivity reaction with angioneurotic edema194 or a cough, although often persistent, is infrequently associated with pulmonary dysfunction.

The side effects that do occur are primarily related directly or indirectly to reduced angiotensin II formation. These include hypotension, acute renal failure, hyperkalemia, and problems during pregnancy. There are other complications – cough, angioneurotic edema, and anaphylactoid reactions – that are thought to be related to increased kinins since ACE is also a kininase. This is an important distinction clinically because the side effects related to reduced angiotensin II, but not those related to kinins, are also seen with the angiotensin II receptor antagonists.

Hypotension

Weakness, dizziness, or syncope may result from an excessive reduction in blood pressure. First dose hypotension, which can be marked in hypovolemic patients with high baseline renin levels, can be minimized by not beginning therapy if the patient is volume depleted and by discontinuing prior diuretic therapy for 3–5 days. Hypotension can also occur after the initiation of therapy in patients with congestive heart failure. The risk can be minimized by beginning with a very low dose, such as 2.5 mg BID of enalapril.

Acute Renal Failure

A decline in renal function, that is usually modest, may be observed in some patients with bilateral renal artery stenosis, hypertensive nephrosclerosis, congestive heart failure, polycystic kidney disease, or chronic renal failure. In each of these disorders, intrarenal perfusion pressure is reduced, a setting in which maintenance of glomerular filtration rate is maintained in part by an angiotensin II-induced increase in resistance at the efferent (postglomerular) arteriole. Blocking this response with an ACE inhibitor will sequentially relax the efferent arteriole, lower intraglomerular pressure, and reduce the glomerular filtration rate. The rise in the plasma creatinine concentration generally begins a few days after the institution of therapy, since angiotensin II levels are rapidly reduced. Thus, renal function should be checked at 3–5 days when an ACE inhibitor is begun in a patient who has renal artery stenosis or who is at high risk for this problem (as in an older patient with severe hypertension and atherosclerotic vascular disease). Another rare cause of acute renal failure that is of unproven relation to ACE inhibitors is the development of renal artery thrombosis. This complication appears to occur most often in patients with marked (≥95%) stenotic lesions who have an excessive reduction in blood pressure. It is therefore unclear if there is any specific predisposing effect of the ACE inhibitor.

Hyperkalemia

Angiotensin II and an elevation in the plasma potassium concentration are the major factors that increase the release of aldosterone, which is the major hormonal stimulus

to urinary potassium excretion. In addition to the direct effect of systemic angiotensin II, angiotensin II generated locally within the adrenal zona glomerulosa may mediate the potassium-induced stimulation of aldosterone. Blocking both of these actions with an ACE inhibitor will reduce aldosterone secretion, thereby impairing the efficiency of urinary potassium excretion. The overall incidence of hyperkalemia (defined as a plasma potassium concentration above 5.1 meq/L) is approximately 10%. However, there is a marked variability in risk. ACE inhibitors generally raise the plasma potassium concentration by less than 0.5 meq/L in patients with relatively normal renal function. In contrast, more prominent hyperkalemia may be seen in patients with renal insufficiency, concurrent use of a drug promoting potassium retention such as a potassium-sparing diuretic or a nonsteroidal anti-inflammatory drug, or among the elderly. Among those with renal dysfunction (GFR $\leq$ 60 mL/min), limited evidence suggests that increases in serum potassium may be less pronounced with an angiotensin receptor blocker than with an ACE inhibitor (0.12 versus 0.28 meq/L). The use of very low doses of ACE inhibitors may lessen the incidence of hyperkalemia, but still provide some benefit. One well-designed study of 13 patients with proteinuria and mild renal insufficiency evaluated the incidence of hyperkalemia and the antiproteinuric and antihypertensive effects with low (1.25 mg/day) and high-dose (10 mg/day) ramipril, and placebo. Equivalent antiproteinuric effects were observed with both doses of ramipril (4.4–3.7 g/day); by comparison, lose-dose ramipril did not alter the blood pressure or plasma potassium level, while the higher dose resulted in an increase in the plasma potassium (4.5–4.8 mEq/L, $p < 0.05$) and a decrease in blood pressure.

Cough

A dry, hacking cough may develop in 3–20% of patients treated with an ACE inhibitor. The cough has the following clinical features:

1. It usually begins within 1–2 weeks of instituting therapy, but can be delayed up to 6 months.
2. It generally recurs with rechallenge, either with the same or a different ACE inhibitor.
3. It does not occur more frequently in asthmatics than in nonasthmatics, but it may be accompanied by bronchospasm.
4. Women are affected more frequently than men.
5. It typically resolves within 1–4 days of discontinuing therapy, but can take up to 4 weeks.

The mechanism responsible for the ACE inhibitor–induced cough is not known, but increased local concentrations of kinins, substance P, prostaglandins, or thromboxane may be important.

Both kinins and substance P are metabolized by converting enzyme; thus, their levels are increased by converting enzyme inhibition. Kinins, for example, may induce bronchial irritation and cough via enhanced production of prostaglandins

which may then stimulate afferent C-fibers in the airway. Activation of the arachidonic acid pathway with ACE inhibition may also lead to elevated levels of thromboxane which can potentiate bronchoconstriction. The possible role of thromboxane in ACE inhibitor–induced cough was evaluated in a double-blind crossover study of nine patients who had developed cough while taking enalapril. The patients were treated with placebo or picotamide (600 mg BID), an agent which inhibits thromboxane synthetase and antagonizes the thromboxane receptor. Active therapy resulting in a significant reduction in thromboxane levels stopped the cough in eight of the nine patients within 72 h.

Inadequate absorption of picotamide occurred in the one nonresponder.

Cough is not a problem with angiotensin II receptor antagonists, such as losartan, which block only the effect of angiotensin II and have no effect on other hormonal mediators. It remains unclear why cough occurs in only some patients treated with ACE inhibitors. It has been suggested that genetic factors may be important. However, common genetic variants for angiotensin-converting enzyme, the B2-bradykinin receptor, or chymase (another enzyme that can convert angiotensin I to angiotensin II) do not explain the variation in susceptibility to cough. Treatment consists of lowering the dose or discontinuing the drug, which will lead to resolution of the cough. Improvement often begins within 4–7 days but may persist for 3–4 weeks or more in some patients. Patients who have had a good antihypertensive response to the ACE inhibitor can be switched to an angiotensin II receptor antagonist.

Angioneurotic Edema and Anaphylactoid Reactions

Angioneurotic edema is a rare (0.1–0.2%) but potentially fatal complication of ACE inhibitors. This problem usually appears within hours or at most 1 week, but can occur as late as 1 year or more after the onset of therapy. It is typically characterized by swelling of the mouth, tongue, pharynx, and eyelids, and occasionally laryngeal obstruction. Patients should be advised to discontinue the drug and call the physician if they develop facial edema or a sore throat independent of an upper respiratory infection. All ACE inhibitors can induce angioneurotic edema, although it is unclear if they do so with same frequency. The mechanism responsible for the angioneurotic edema is not well understood, but increased kinins may play a role. It is possible, for example, that genetic mild deficiencies in kinin degradation could predispose selected patients to the development of this complication when kinin levels are enhanced following administration of an ACE inhibitor. It is likely, however, that kinins do not provide the entire explanation since some cases of angioneurotic edema have been described with the angiotensin II receptor antagonists which do not raise kinin levels. Another hypothesis is that susceptible patients have a subclinical hereditary or acquired deficiency of complement 1-esterase inactivator, which is another cause of angioneurotic edema. The risk of recurrence of angioedema if ACE inhibitors are continued was addressed in a report of 82 patients who had a first episode of angioedema while on an ACE inhibitor. The overall rate of recurrence during an average follow-up of 2.3 years was 8.5 per 100 patient years;

however, the risk was much higher in those with continued exposure to ACE inhibitors (18.7 versus 1.8 per 100 patient years). Review of the medical records revealed that physicians often attributed the angioedema to other causes even after multiple recurrences. Similar factors may contribute to the high incidence of anaphylactoid reactions seen when ACE inhibitors are used in patients treated with high-flux hemodialysis using polyacrylonitrile (PAN) dialyzers

Contraindication in Pregnancy

ACE inhibitors are contraindicated in pregnancy, since they are associated with an increased incidence of fetal complications.

Poisoning

Symptoms of ACE inhibitor overdosing are usually mild. If, however, severe hypotension occurs, intravenous fluids and inotropic support may be required.

Drug Interactions

Antacids can decrease the GI absorption of captopril if administered simultaneously. Captopril, and possibly other ACE inhibitors, can enhance the activity of oral antidiabetic agents. Hypoglycemia has occurred when captopril was added to either glyburide or biguanide therapy. Caution should be observed when captopril is added to the regimen of patients receiving these drugs.

Captopril can enhance the effects of antihypertensive agents and diuretics on blood pressure if given concomitantly. This additive effect may be desirable, but dosages must be adjusted accordingly. Patients with hyponatremia or hypovolemia may become hypotensive and/or develop reversible renal insufficiency when given captopril and diuretics concomitantly.

Indomethacin has been shown to inhibit the antihypertensive response to captopril. Other nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and other salicylates may also exert a similar effect on captopril's action; however, other ACE inhibitors may not be affected to the same degree as captopril. It is thought that the antihypertensive action of captopril is highly dependent on its ability to stimulate the synthesis of vasodilatory prostaglandins. NSAIDs inhibit prostaglandin synthesis, thereby attenuating captopril's ability to lower blood pressure. Loss of antihypertensive effect should be considered if a NSAID is added to a regimen that includes captopril. In addition, patients on captopril should be cautioned about routine use of aspirin or over-the-counter NSAIDs.

Many of the ACE inhibitor trials were performed on a background of ASA, suggesting their effects may be additive, although some data also suggest there may be a negative interaction between the two drugs.

Inhibition of ACE results in decreased aldosterone production and potentially decreased potassium excretion, leading to small increases in serum potassium. Hyperkalemia can occur if captopril is given to patients receiving drugs that also increase serum potassium concentration, including potassium-sparing diuretics such as amiloride or spironolactone, potassium salts, or heparin.

Serum digoxin concentrations can rise by 15–30% in patients with congestive heart failure who are given digoxin and captopril concomitantly. However, captopril-induced hyperkalemia can offset the increased digoxin concentrations, and captopril and digoxin have been administered to patients with congestive heart failure with no apparent adverse effects. The clinical significance of this interaction is not clear.

Probenecid decreases the renal tubular secretion of captopril, resulting in higher captopril serum concentrations. If probenecid is given to a patient stabilized on captopril, hypotension may occur. This interaction would appear to be of lesser significance if captopril is added after probenecid therapy is in place.

Captopril can decrease the renal elimination of lithium, which can lead to lithium toxicity. Plasma lithium concentrations should be monitored carefully during concomitant captopril therapy. Clinicians should note that some other antihypertensive agents may also interact with lithium.

Possible Differences Between ACE Inhibitors

It has generally been assumed that the different ACE inhibitors are equally well tolerated. In one large study, for example, enalapril and captopril were equally effective, had the same incidence of usual side effects (such as cough), and had the same frequency of drug withdrawal. However, careful quality of life evaluations suggested that patients treated with captopril had a more favorable overall quality of life and an increase in general perceived health; these effects were most prominent in those patients who began with a higher quality of life. How this difference might occur is unclear, but differences in penetration into the central nervous system may be important. The clinical significance of this observation is at present uncertain. Other studies plus the experience of most practitioners do not support the observation that enalapril or other ACE inhibitors lead to an important reduction in the quality of life in many or most patients.

AT-1-Receptor Antagonists

There are a number of approved nonpeptide selective blockers of the binding of angiotensin II to type 1 (AT1) angiotensin receptors on the cell membrane, thereby inhibiting the action of angiotensin II. Thus, these drugs, angiotensin II receptor antagonists or blockers (ARBs), represent the third class that antagonizes the renin-angiotensin-aldosterone system: β-blockers reduce the release of renin by inhibiting β-1 receptor stimulation; and the angiotensin-converting enzyme (ACE) inhibitors

block the conversion of inactive angiotensin I to the active hormone angiotensin II. Blockade of the action of angiotensin II leads to elevations in plasma levels of renin, angiotensin I, and angiotensin II. However, this buildup of precursors does not overwhelm the receptor blockade, as evidenced by a persistent fall in both blood pressure and plasma aldosterone levels. Angiotensin II receptor blockers may offer all of the advantages of ACE inhibitors and fewer side effects.

Side Effects

The angiotensin II receptor antagonists are generally well tolerated. The side effect profile is similar to that with the ACE inhibitors (e.g., increased incidence of hyperkalemia and of acute renal failure in renovascular hypertension), except for those side effects that may be mediated by kinins, particularly cough which is the most common reason that patients discontinue use of an ACE inhibitor, and much less often angioedema. The incidence of cough with angiotensin II receptor antagonists is similar to that with placebo (3%) and well below that seen with ACE inhibitors (approximately 10%). One large study evaluated patients with a prior history of ACE inhibitor–induced cough; the incidence of recurrent cough was much higher with readministration of an ACE inhibitor (67%) than with either valsartan or hydrochlorothiazide (19%). However, this protection does not appear to be absolute. Thus far, at least 19 cases of angioedema have been described in patients taking losartan; this complication is typically characterized by swelling of the mouth, tongue, pharynx, and eyelids, and occasionally laryngeal obstruction. How this might occur is unclear but nonkinin factors are presumably involved. Another uncommon adverse effect of uncertain origin is dysgeusia.

Use in Pregnancy

As with ACE inhibitors, angiotensin II receptor antagonists are contraindicated in pregnancy. An additional concern is that AT1 receptor blockade results in the disinhibition of renin release by angiotensin II and increased formation of all angiotensin peptides. These peptides could activate the AT2 receptor, which is known to have high prevalence in the fetus. The availability of the first new class of antihypertensive agents in over 10 years has added a great deal of excitement to the treatment of hypertension. It is at present unclear if angiotensin II receptor antagonists will turn out to be a minor addition (an ACE inhibitor without cough, which would still be useful) or a major advance. They may provide a better way to overcome the adverse effects of the renin-angiotensin system. However, outcome data are needed before they are recommended instead of ACE inhibitors.

Drug Interactions

Some of the AT1 blockers are metabolized by the cytochrome P450 (CYP) enzyme system to a significant extent, and as a result, are subject to potential metabolism-related

drug interactions. Other drug interaction studies with common medications such as digoxin, warfarin, oral contraceptives, and nifedipine have not revealed any significant drug interactions.

Like nearly all other AT1 blockers, losartan has relatively poor bioavailability, but its absorption is not significantly affected by food. Following absorption, losartan is converted to an active metabolite, EXP3174, in the liver by the CYP2C9 and possibly CYP3A enzymes. This metabolite is responsible for the majority of the drug's effects. Medications which inhibit the drug-metabolizing enzymes CYP2C9 (Fluvastatin, Fluvoxamine, Fluoxetine, Metronidazole, Ritonavir) and possibly CYP3A may inhibit the conversion of losartan to its metabolite, possibly decreasing its effectiveness.

Unlike losartan, valsartan does not require enzymatic conversion to an active form, and valsartan is only minimally metabolized by the body, decreasing the risk of significant drug interactions.

Irbesartan is not a prodrug, but it is metabolized in the liver by the CYP2C9 enzyme. Therefore, drugs that affect this enzyme may interact with irbesartan. Specifically, inducers of CYP2C9 may increase the metabolism and decrease the effectiveness of irbesartan. CYP2C9 inhibitors would be expected to have the opposite effect.

Eprosartan also does not require activation in the body and is not metabolized significantly, lowering the risk of drug interactions.

The effects of candesartan cilexetil are maintained for more than 24 h due to slow dissociation of the drug from the AT1 receptor. Candesartan cilexetil is a prodrug that is converted into the active drug, candesartan, during absorption. Preliminary drug interaction studies have not revealed any significant interactions.

Excretion of lithium reduced (increased plasma-lithium concentration).

Digitalis

Cardiac glycosides can be used for patients with symptoms of systolic heart failure secondary to ischemic, valvular, hypertensive, or congenital heart disease, dilated cardiomyopathies, and cor pulmonale. Improvement of depressed myocardial contractility by glycosides increases cardiac output, promotes diuresis, and reduces the filling pressure of the failing ventricle, with the consequent reduction of pulmonary vascular congestion and central venous pressure. It is widely accepted that cardiac glycosides are of benefit in the treatment of patients with heart failure accompanied by atrial fibrillation or atrial flutter and a rapid ventricular response. The chemical structure of cardiac glycosides includes a steroid nucleus containing an unsaturated lactone at the C17 position and one or more glycosidic residues at C3. Digoxin is now the most commonly prescribed cardiac glycoside owing to its convenient pharmacokinetics, alternative routes of administration, and the widespread availability of serum drug level measurements.

Mechanism of Action

Congestive Heart Failure

For many years, cardiac glycosides have been known to increase the velocity and extent of shortening of cardiac muscle, resulting in a shift upward and to the left of the ventricular function (Frank Starling) curve relating stroke work to filling volume or pressure. This occurs in normal as well as failing myocardium and in atrial as well as ventricular muscle. The positive inotropic effect is due to an increase in the availability of cytosolic Ca^{++} during systole, thus increasing the velocity and extent of sarcomere shortening. This increase in intracellular Ca^{++} is a consequence of cardiac glycoside–induced inhibition of the sarcolemmal Na^{+}, K^{+} ATPase.

Supraventricular Arrhythmias

Cardiac glycosides works through direct suppression of the A-V node conduction to increase effective refractory period and decrease conduction velocity – positive inotropic effect, enhanced vagal tone, and decreased ventricular rate in patients with atrial arrhythmias.

Pharmacokinetics

The elimination half-life for digoxin ranges from 36 to 48 h in patients with normal renal function. This long half-life permits once-a-day dosing. In the absence of loading doses, steady-state blood levels can be achieved after four to five half-lives, which is approximately 1 week after initiation of daily chronic therapy in patients with normal renal function. Digoxin is largely excreted unchanged, with a clearance rate proportional to the GFR, resulting in the excretion of approximately one-third of body stores daily. In patients with heart failure and reduced cardiac reserve, increased cardiac output and renal blood flow in response to treatment with vasodilators or sympathomimetic agents may increase renal digoxin clearance, necessitating dosage adjustment. Digoxin is not removed effectively by peritoneal dialysis or hemodialysis because of its large (4–7 L/kg) volume of distribution. The principal body reservoir is skeletal muscle and not adipose tissue. Accordingly, dosing should be based on estimated lean body mass.

Neonates and infants tolerate and may require higher doses of digoxin for an equivalent therapeutic effect than older children or adults. Digoxin crosses the placenta, and drug levels in maternal and umbilical vein blood are similar.

Current tablet preparations of digoxin average 70–80% oral bioavailability. The elixir has a bioavailability of approximately 80% and encapsulated gel preparations approaching 90–100%. Parenteral digoxin is 100% bioavailable. Loading or

maintenance doses can be given by intravenous injection, which should be carried out over at least 15 min to avoid vasoconstrictor responses to more rapid injection. Intramuscular digoxin is absorbed unpredictably, causes local pain, and is not recommended.

Drug Interactions

Drugs may interact with digoxin through pharmacokinetic pathways (e.g., alter bioavailability and metabolism) and pharmacodynamic pathways (e.g., counteract inotropic effects). Several drugs interact with digoxin through both pathways. Table 9.6 is a summary of the interactions.

Digitalis Toxicity and Therapeutic Drug Monitoring

Overt digitalis toxicity tends to emerge at two- to three-fold higher serum concentrations than the target 1.8 nmol/L, but it must always be remembered that a substantial overlap of serum levels exists among patients exhibiting symptoms and signs of toxicity and those with no clinical evidence of intoxication. If ready access to serum digoxin assays is available, a reasonable approach to the initiation of therapy is to begin at 0.125–0.375 mg/day, depending on lean body mass and estimated creatinine clearance, and to measure a serum digoxin level 1 week later with careful monitoring of clinical status in the interim. Patients with impaired renal function would not yet have reached steady state and need to be monitored closely until four to five clearance half-lives have elapsed (as long as 3 weeks). Generally a plasma digoxin concentration of 1–2 μg/L is considered to be within therapeutic range. However, recent evidence has shown that in patients with CHF, a lower range of 0.5–1 μg/L is effective with lesser side effects. Oral or intravenous loading with digoxin, although generally safe, is rarely necessary as other safer and more effective drugs exist for short-term inotropic support or for initial treatment of supraventricular arrhythmias.

Blood samples for serum digoxin level measurement should be taken at least 6–8 h following the last digoxin dose. Serum level monitoring is justified in patients with substantially altered drug clearance rates or volumes of distribution (e.g., very old, debilitated, or very obese patients). Adequacy of digoxin dosing and risk of toxicity in a given patient should never be based on a single isolated serum digoxin concentration measurement.

Although the incidence and severity of digitalis intoxication are decreasing, vigilance for this important complication of therapy is essential. Disturbances of cardiac impulse formation, conduction, or both are the hallmarks of digitalis toxicity. Among the common electrocardiographic manifestations are ectopic beats of AV junctional or ventricular origin, first-degree atrioventricular block, an excessively

Table 9.6 Summary of drug interactions with digoxin

Interacting drug	Mechanism	Effects	Management
Cholestyramine, colestipol	Decrease bioavailability of digoxin by 30%	Suboptimal digoxin concentration	Separate administration by at least 2 h; monitor digoxin concentration
kaolin-pectin	Decrease bioavailability of digoxin by 60%	Suboptimal digoxin concentration	Separate administration by at least 2 h; monitor digoxin concentration
Antacids	Decrease bioavailability of digoxin by 25–35%	Suboptimal digoxin concentration	Separate administration by at least 2 h; monitor digoxin concentration
Acarbose	Decrease bioavailability of digoxin	Suboptimal digoxin concentration	Monitor digoxin concentration and clinical response
Amiodarone	Decrease renal and nonrenal clearance of digoxin; addition bradycardic effects	Increase risk for digoxin toxicity	Reduce digoxin dose by 30–50% with start of amiodarone; monitor for digoxin concentration and toxic effects of digoxin
Carvedilol, beta-blockers	Enhance bradycardic effects of digoxin	Increase risk for bradycardia	Monitor heart rate
Cyclosporine	Reduce digoxin elimination by 50%	Increase risk for digoxin toxicity	Monitor for digoxin level and toxicity
Erythromycin, clarithromycin, and tetracyclines	Suppress GI flora that metabolize digoxin	Increase serum digoxin concentration by two- to fourfold	Monitor for digoxin level and toxicity
Azole antifungals (except Miconazole)	Inhibit p-glycoprotein	Increase serum digoxin concentration by 100%	Monitor for digoxin level and toxicity
Protease inhibitors	Inhibit p-glycoprotein	Increase serum digoxin concentration	Monitor for digoxin level and toxicity
Quinine	Decrease digoxin clearance	Increase serum digoxin concentration	Monitor for digoxin level and toxicity
Oral neomycin	Decrease absorption of digoxin	Decrease serum digoxin concentration	Monitor therapeutic effects of digoxin
Propafenone	Inhibit p-glycoprotein	Increase digoxin blood levels up to 60%	Monitor for digoxin level and toxicity
Atorvastatin	Inhibit p-glycoprotein	Increase digoxin blood level	Monitor for digoxin level and toxicity
Propylthiouracil, methimazole	Reduce thyroid hormone	Increase digoxin blood level	Monitor for digoxin level and toxicity

(continued)

Table 9.6 (continued)

Interacting drug	Mechanism	Effects	Management
Dronedarone	Digoxin enhances AV blocking effects of dronedarone; dronedarone increases serum concentration of digoxin	Increase digoxin blood level	Avoid concurrent use if possible. If concurrent use, reduce digoxin dose by 50% and increase monitoring for both agents
Milnacipran	Unknown	Increase risk of postural hypotension and tachycardia	Avoid concurrent use of IV digoxin and milnacipran if possible
Quinidine	Displace digoxin from protein-binding sites, inhibits p-glycoprotein	Increase digoxin blood levels by 100%	Monitor digoxin blood levels/effect closely; reduce digoxin dose by 25–50% with start of quinidine
Rifampin, phenytoin, phenobarbital, and carbamazepine	Reduce clearance of digoxin by the induction of intestinal P-glycoprotein	Decrease therapeutic effects of digoxin	Monitor therapeutic effects and level
Spironolactone, Amiloride	Unknown	Reduce effects of digoxin	Monitor therapeutic effects
Sulfasalazine	Decrease absorption of digoxin	Reduce effects of digoxin	Monitor therapeutic effects
Penicillamine	Unknown	Reduce effects of digoxin	Monitor therapeutic effects
Calcium preparations (intravenous), calcitriol	Unknown	Increase arrhythmogenic effects of digoxin	Monitor for cardiac arrhythmias
Neuromuscular blocking agents (Succinylcholine)	Unknown	Increase arrhythmogenic effects of digoxin	Monitor for cardiac arrhythmias
Calcium channel blockers (non-dihydropyridine)	Enhance AV blocking effects; reduce digoxin metabolism	Increase therapeutic effects or toxic effects of digoxin	Monitor digoxin level and toxicity
Potassium-depleting diuretics (thiazide and loop diuretics)	Increase risk for hypokalemia	Enhance toxic effects of digoxin	Monitor signs of toxicity
Telmisartan	Unknown	Increase digoxin concentration	Monitor digoxin level and toxicity
Amphotericin B	Increase risk for hypokalemia	Enhance toxic effects of digoxin	Monitor signs of toxicity

slow ventricular rate response to atrial fibrillation, or an accelerated AV junctional pacemaker. These manifestations may require only a dosage adjustment and monitoring as clinically appropriate. Sinus bradycardia, sinoatrial arrest or exit block, and second- or third-degree atrioventricular conduction delay often respond to atropine, but temporary ventricular pacing is sometimes necessary and should be available. Potassium administration is often useful for atrial, AV junctional, or ventricular ectopic rhythms, even when the serum potassium is in the normal range, unless high-grade atrioventricular block is also present. Magnesium may be useful in patients with atrial fibrillation and an accessory pathway in whom digoxin administration has facilitated a rapid accessory pathway–mediated ventricular response. Lidocaine or phenytoin, which in conventional doses have minimal effects on atrioventricular conduction, are useful in the management of worsening ventricular arrhythmias that threaten hemodynamic compromise. Electrical cardioversion can precipitate severe rhythm disturbances in patients with overt digitalis toxicity, and should be used with particular caution.

Potentially life-threatening digoxin or digitoxin toxicity can be reversed by antidigoxin immunotherapy. Purified Fab fragments from digoxin-specific antisera are available at most poison control centers and larger hospitals in North American and Europe. Clinical experience in adults and children has established the effectiveness and safety of antidigoxin Fab in treating life-threatening digoxin toxicity, including cases of massive ingestion with suicidal intent. Doses of Fab are calculated on the basis of a simple formula based on either the estimated dose of drug ingested or the total body digoxin burden and are administered intravenously in saline over 30 min.

Nitrates

Angina pectoris is a symptom complex caused by transient myocardial ischemia. Metabolism in cardiac myocytes is aerobic; as a result, myocardial ischemia occurs when there is an imbalance between oxygen demand and oxygen supply. Myocardial oxygen demand varies with heart rate, contractility, and left ventricular wall stress, which is proportional to left ventricular systolic pressure and left ventricular size. Myocardial oxygen supply is dependent upon coronary blood flow which is limited in patients with critical coronary artery stenoses or prominent coronary vasoconstriction. In addition, the subendocardium receives most of its blood supply during diastole. Conditions which decrease the duration of diastole, such as tachycardia, make the subendocardium susceptible to ischemia. Thus, the treatment of angina is aimed at decreasing oxygen demand and/or increasing oxygen supply.

Nitrates (as well as beta-blocking agents and calcium channel blockers – that are reviewed in the antihypertensives section) are used for pharmacological treatment of angina.

Variant angina (also called Prinzmetal's angina) is a form of angina in which angina pectoris spontaneously occurs in association with ST segment elevation on

the EKG. Although it was thought to have been first described by Prinzmetal, this form of angina had actually been recognized in the 1930s by other investigators. Prinzmetal proposed that episodic "temporary increased tonus" in a high-grade obstruction of a major coronary artery was responsible for the syndrome of variant angina. It is now accepted that this hypothesis is correct. Coronary vasospasm is a transient, abrupt, marked reduction in the luminal diameter of an epicardial coronary artery that results in myocardial ischemia. This process can usually be reversed by nitroglycerin or a calcium channel blocker. Spasm occurs in the absence of any preceding increase in myocardial oxygen demand and in either normal or diseased vessels. The reduction in diameter is focal and usually at a single site, although spasm in more than one site and diffuse spasm have recently been reported. Spasm typically occurs near an atherosclerotic plaque in a diseased vessel.

The syndrome of unstable angina includes new-onset or crescendo effort angina, rest angina, early post-MI angina, variant angina, and angina occurring soon after percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG).

The primary pathophysiologic event in unstable angina is thought to be a reduction in coronary blood flow due to transient platelet aggregation, coronary thrombosis, or coronary artery spasm. However, small increases in myocardial oxygen demand can also induce this syndrome.

Electrocardiography during episodes of unstable angina frequently demonstrates ST segment depressions or T wave changes, although transient ST segment elevations (that express transmural ischemia) can also be observed. Thus, the underlying nature of unstable angina is similar to that of non-Q wave and transmural MI. The principle differences between these disorders are the duration and intermittency of coronary occlusion and the extent of collateral supply to the ischemic area of the myocardium. The major steps involved in the pathogenesis of unstable angina are thought to be plaque rupture followed by thrombus formation.

Alterations of the ST segment include elevation and depression. The most important cause of ST segment elevation is transmural injury. Outside this setting, ST elevation can be found in combination with other signs of "chronic" or recent infarction and is associated with ventricular asynergy (usually hypokinesia, but also dyskinesia or akinesia). Depression of the ST segment occurs during myocardial ischemia, directly from subendocardial injury or as a mirroring change of ST elevation.

A proximal left anterior descending MI carries a high mortality and is attributed to an occlusion of the left anterior descending before or at the first septal perforator. All of the precordial leads and I and avL show ST segment elevation. The proximal location of occlusion is associated with compromised perfusion to the His-Purkinje conduction tissue owing to loss of septal supply, and often accompanied by a new bundle branch block. Usually left anterior hemiblock or right bundle branch block is present, but bifasicular blocks, left bundle branch block, or Mobitz II atrioventricular block are all possible. Cardiogenic shock is not unexpected in this subgroup, unless there has been effective reperfusion established.

Nitroglycerin

Although the clinical effectiveness of amyl nitrite in angina pectoris was first described in 1867, organic nitrates are still the drugs most commonly used in the treatment of patients with this condition. By their ability to enhance coronary blood flow by coronary vasodilation and to decrease ventricular preload by increasing venous capacitance, sublingual nitrates are indicated for most patients with an acute coronary syndrome. It is now understood that actions by which nitrovasodilators lead to the relaxation of vascular smooth muscle are through mimicking the activity of nitric oxide and its congeners. Nitrogen oxides were originally identified as bioactive factors responsible for endothelium-dependent relaxation of blood vessels. Nitroglycerin is considered a cornerstone of antianginal therapy. The beneficial effect is thought to occur predominantly via reduction in myocardial oxygen demand secondary to venodilation-mediated decrease in preload. In addition, nitrates are clearly capable of arterial, in particular coronary vasodilation, reduction in afterload, improvement in the coronary collateral circulation, redistribution of transmural coronary blood flow from subepicardial to subendocardial regions, relief of coronary spasm, and some antiplatelet activity. Despite extensive clinical use, there is remarkably little objective information documenting the effectiveness of nitroglycerin in unstable angina. Several small trials have evaluated the ability of an open-label infusion of nitroglycerin to reduce the frequency of ischemic chest pain; symptomatic relief was noted in each of the reports. One randomized trial found that, compared to placebo, intravenous nitroglycerin reduced the frequency and duration of ischemic episodes. In addition, a single randomized trial compared the intravenous, oral, and transdermal nitroglycerin preparations.

There was no difference in response among the preparations with regard to symptomatic improvement. However, the small size of this study (40 patients) makes it difficult to draw definitive conclusions.

Nitroglycerin administered sublingually remains the drug of choice for the treatment of acute angina episodes and for the prevention of angina. Because sublingual administration avoids first-pass hepatic metabolism, a transient but effective concentration of the drug rapidly appears in the circulation. The half-life of nitroglycerin itself is brief (1–4 min), and it is rapidly converted to two inactive metabolites,1,3-glyceryl dinitrate, 1,2-glyceryl dinitrate, both of which are found in the urine after nitroglycerin administration. The liver possesses large amounts of hepatic glutathione organic nitrate reductase, the enzyme that breaks down nitroglycerin, but there is also evidence that blood vessels (veins and arteries) may metabolize nitrates directly. Within 30–60 min, hepatic breakdown has abolished the hemodynamic and clinical effects.

The usual sublingual dose is 0.3–0.6 mg, and most patients respond within 5–10 min to one or two 0.3-mg tablets. If symptoms are not relieved by a single dose, additional doses of 0.3 mg may be taken at 5-min intervals, but no more than 1.5 mg should be used within a 15-min period. The development of tolerance (see below) is rarely a problem with intermittent usage. Sublingual nitroglycerin is

especially useful when it is taken prophylactically shortly before physical activities that are likely to cause angina are undertaken. Used for this purpose, it may prevent angina for up to 40 min.

In patients with acute myocardial infarction, it seems reasonable to conclude that nitroglycerin should usually be given as an intravenous infusion because of the ease of titration, rapidity of action, and uncertainties about dose delivery with the topical or oral preparations. Intravenous nitroglycerin is usually started at a dose of 5 μg/min and is then increased by 5 μg/min every 3–5 min up to 20 μg/min. If no response is observed at 20 μg/min, the dose should be increased by 10 μg/min every 3–5 min up to a dose of 200 μg/min.

Nitrate Tolerance

The rapid development of tolerance to the venous and arteriolar vasodilating effects of the nitrovasodilators has been known for over a century. Patients taking nitrates will usually see some form of tolerance within days of beginning chronic nitrate therapy. Although nitrate tolerance is well documented, the mechanisms responsible are not clearly understood. There are many proposed mechanisms by which nitrate tolerance develops. One is through the production of free radicals. Nitrate therapy has been found to increase the production of superoxide anion which could potentially be reversed by antioxidants. The use of antioxidants was examined in a randomized, double-blinded study of 24 healthy volunteers and 24 volunteers with ischemic heart disease (IHD). Participants were given 0.3-mg sublingual nitroglycerin combined either with vitamin E 200 mg ($n=12$) three times a day or placebo ($n=12$) and forearm blood flow was measured on the first day, after 3 days and then after 6 days. Participants were then given continuous transdermal nitroglycerin for another 3 days combined with either vitamin E of placebo. On day 6, percent changes in forearm blood flow in the placebo group (normal volunteers,17±9%; IHD patients, 17±8%) showed significant reduction compared with that on days 0 and 3 ($p < .01$). Conversely, in the vitamin E group, percent increases of forearm blood flow after sublingual nitroglycerin (normal volunteers, 30±12%; IHD patients, 28±14%) did not show decreases in blood flow on day 6 and were significantly greater than the participants taking placebo ($p < .01$).

Side Effects and Contraindications

The primary adverse effects induced by nitrate therapy include hypotension (especially in patients with ventricular ischemia or hypovolemia), headache, flushing, and tachycardia. Hypovolemia or nitrate-induced hypotension respond promptly to volume replacement. Despite presumed correction of preload by the infusion of saline, the antiischemic effect of nitroglycerin persists.

Prolonged infusion of high-dose nitroglycerin may lead to the development both of methemoglobinemia (which can be treated with intravenous methylene blue) and of heparin resistance. In addition, commercial preparations of intravenous

nitroglycerin contain alcohol (0.01–0.14 mL/mg of nitroglycerin). Thus, a substantial alcohol load may be delivered to the patient.

Nitrates are contraindicated in patients with hypertrophic cardiomyopathy with outflow tract obstruction. Nitrates can induce or increase outflow tract obstruction in this setting and should be used with caution, even in patients not known to have a resting gradient. Nitrates should also be avoided in patients with suspected right ventricular infarction because of the increased risk of inducing hypotension. Further contraindications comprise pericarditis constrictiva, and pericardial effusion with compression of the right ventricle.

Drug interactions have been reported with phosphodiesterase 5 inhibitors such as sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®). Combining these two drug classes increases cGMP levels causing severe vasodilation and hypotension.

Action of Nitrates and Other Vasodilatators (Nitroprusside)

Similar to nitroglycerin, nitroprusside causes preload reduction by diminishing heightened venous tone and increasing venous capacitance with a concomitant shift in central blood volume to the periphery. Unique to nitroprusside is its rapid and powerful effect on afterload. In chronic heart failure, both medications (intravenous nitroglycerin and nitroprusside) produce desirable effects on cardiac filling pressures and cardiac output, but the magnitude of the response to nitroprusside appears to be significantly greater, particularly with respect to afterload reduction.

Severe drug-induced hypotension in patients with coronary artery disease may result in reflex tachycardia (e.g., with short-acting drugs like nifedipine), increased cardiac output, and untoward precipitation of angina, and ischemic events (including tachyarrhythmias).

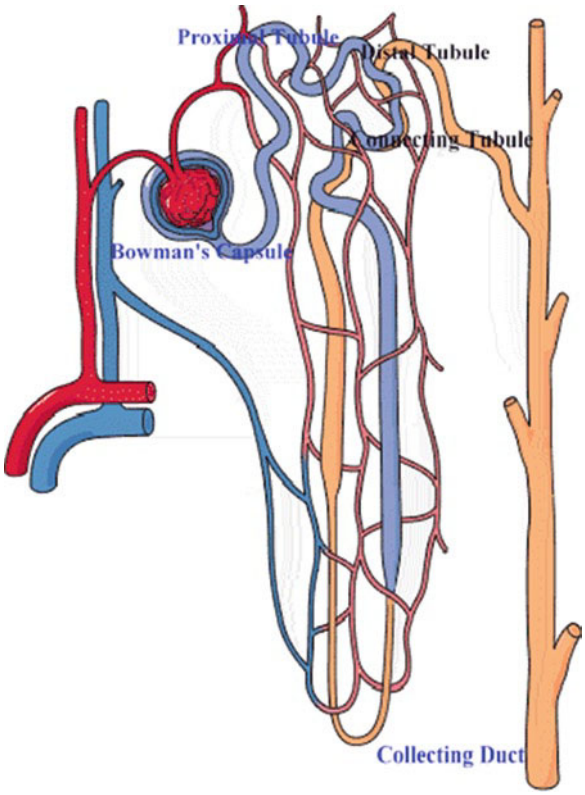
In patients with occlusive coronary artery disease, care must be taken to avoid excessive reductions in systemic pressure or elevations in heart rate that would reduce coronary perfusion and increase myocardial oxygen demand. Unlike nitroglycerin, nitroprusside may cause “coronary steal” whereby arteriolar dilatation in nonischemic zones diverts coronary flow away from areas of ischemia.

Diuretics

Diuretics act by diminishing sodium chloride reabsorption at different sites in the nephron, thereby increasing urinary sodium chloride and water losses. The ability to induce negative fluid balance has made diuretics useful in the treatment of a variety of conditions, particularly edematous states and hypertension.

The importance of diuretics in the treatment of the syndrome of congestive heart failure relates to the central role of the kidney as the target organ of many of the neurohumoral and hemodynamic changes that occur in response to a failing myocardium. Diuretics do not influence the natural history of the underlying heart

disease responsible for the decline in cardiac output. However, they can improve symptoms of heart failure by acting directly on solute and water reabsorption by the kidney and therefore may slow the progression of cardiac chamber dilation by reducing ventricular filling pressures.



Mechanisms of Action

The diuretics are generally divided into three major classes, which are distinguished by the site at which they impair sodium reabsorption:

1. Loop diuretics act in the thick ascending limb of the loop of Henle
2. Thiazide-type diuretics act in the distal tubule and connecting segment (and perhaps the early cortical collecting tubule)
3. Potassium-sparing diuretics act in the aldosterone-sensitive principal cells in the cortical collecting tubule.
4. Others: *Acetazolamide* inhibits the activity of carbonic anhydrase, which plays an important role in proximal bicarbonate, sodium, and chloride reabsorption. As a result, this agent produces both NaCl and NaHCO3 loss. The net diuresis, however, is relatively modest.

Mannitol is a nonreabsorbable polysaccharide that acts as an osmotic diuretic, inhibiting sodium and water reabsorption in the proximal tubule and more importantly the loop of Henle. In contrast to other diuretics, mannitol produces a relative water diuresis in which water is lost in excess of sodium and potassium. The major clinical use of mannitol as a diuretic is in the early stages of oliguric, postischemic acute renal failure in an attempt to prevent progression to acute tubular necrosis. It is not generally used in edematous states, since initial retention of the hypertonic mannitol can induce further volume expansion which, in heart failure, can precipitate pulmonary edema.

Sites of Diuretic Action

(a) *Proximal tubule* high metabolic activity (secretion/resorption)
Recovery of:

- Sixty to eighty percent of sodium and water (Na/Cl co-transport, water follows)
- Ninety-nine percent of glucose, protein, amino acids recovered

(b) Descending limb – *Loop* of Henle

- Passive diffusion of urea, H_2O, Na (thin wall)
- Source of countercurrent multiplier

(c) *Ascending limb – Loop* of Henle

- Strong active transport – Na
- Not permeable to H_2O, urea

(d) *Distal tubule* – diluting segment

- As for ascending limb – *loop*

(e) *Distal tubule/Collecting tubule*

- Not permeable to urea
- Active sodium resorption
- Sodium//potassium exchange

Thiazide Diuretics

Hydrochlorothiazide (HCTZ) is a thiazide diuretic used in the management of edema and hypertension. In hypertension, thiazide diuretics are often used as initial therapy, either alone or in combination with other agents. Unlike the loop diuretics, their efficacy is diminished in patients with renal insufficiency. Hydrochlorothiazide also has been used to treat diabetes insipidus and hypercalciuria, although these are

not FDA-approved indications. Hydrochlorothiazide was approved by the FDA in 1959. Other thiazide diuretics include chlorothiazide, chlorthalidone, hydroflumethiazide, and methylchlorthiazide.

Mechanism of Action

Thiazide diuretics increase the excretion of sodium, chloride, and water by inhibiting sodium ion transport across the renal tubular epithelium. Although thiazides may have more than one action, the major mechanism responsible for diuresis is to inhibit active chloride reabsorption at the distal portion of the ascending limb or, more likely, the early part of the distal tubule (i.e., the cortical diluting segment). Exactly how chloride transport is impaired is unknown. Thiazides also increase the excretion of potassium and bicarbonate, and decrease the elimination of calcium and uric acid. By increasing the sodium load at the distal renal tubule, hydrochlorothiazide indirectly increases potassium excretion via the sodium/potassium exchange mechanism. Hypochloremia and hypokalemia can cause mild metabolic alkalosis. The diuretic efficacy of hydrochlorothiazide is not affected by the acid–base balance of the patient.

Hydrochlorothiazide is not an aldosterone antagonist, and its main action is independent of carbonic anhydrase inhibition. The antihypertensive mechanism of hydrochlorothiazide is unknown. It usually does not affect normal blood pressure. Initially, diuretics lower blood pressure by decreasing cardiac output and reducing plasma and extracellular fluid volume.

Cardiac output eventually returns to normal, plasma and extracellular fluid values return to slightly less than normal, but peripheral vascular resistance is reduced, resulting in lower blood pressure. These diuretics also decrease the glomerular filtration rate, which contributes to the drug's lower efficacy in patients with renal impairment. The changes in plasma volume induce an elevation in plasma renin activity, and aldosterone secretion is increased, contributing to the potassium loss associated with thiazide diuretic therapy.

Pharmacokinetics

Hydrochlorothiazide absorption from the GI tract varies depending on the formulation and dose. Bioavailability is approximately 50–60%. The drug crosses the placenta but not the blood-brain barrier and is distributed in breast milk. Hydrochlorothiazide is not metabolized and is excreted unchanged in the urine. The half-life of the drug ranges from 5.6 to 14.8 h. The onset of action of the drug is 2 h following oral administration, with peak effects occurring at 4 h. The duration of action ranges from 6 to 12 h.

Contraindications/Precautions

Hydrochlorothiazide-induced fluctuations in serum electrolyte concentration can occur rapidly and precipitate hepatic coma in susceptible patients. Therefore, the

drug should be used with caution in patients with hepatic disease. Hyperglycemia, impaired glucose tolerance, and glycosuria can occur during hydrochlorothiazide therapy, and blood and/or urine glucose levels should be assessed more carefully in patients with diabetes mellitus who are receiving hydrochlorothiazide. Hydrochlorothiazide should be used cautiously in patients with renal disease such as severe renal impairment because the drug decreases the glomerular filtration rate and may precipitate azotemia in these patients. Therapy should be interrupted or discontinued if renal impairment worsens, as evidenced by an increase in concentrations of BUN, serum creatinine, or nonprotein nitrogen. With the exception of metolazone, thiazide diuretics are considered ineffective when the creatinine clearance is less than 30 mL/min. Hydrochlorothiazide is contraindicated in patients with anuria.

The safety of hydrochlorothiazide administration during pregnancy has not been established, so the drug should be administered to pregnant women only when absolutely necessary. Thiazides cross the placenta, and jaundice can occur in the fetus or neonate. Hydrochlorothiazide is classified as pregnancy category D. Thiazide diuretics distribute into breast milk, and it has been recommended by some manufacturers that women should not nurse while receiving thiazide diuretics. The American Academy of Pediatrics recommends breast-feeding be avoided during the first month of lactation in patients receiving thiazide diuretics, because suppression of lactation has been reported. Thiazide diuretics, including hydrochlorothiazide, should be used with caution in patients with sulfonamide hypersensitivity or carbonic anhydrase inhibitor hypersensitivity because of the risk of cross-sensitivity. Caution should be used when hydrochlorothiazide is administered to patients with gout or hyperuricemia since thiazide diuretics have been reported to reduce the clearance of uric acid. Hydrochlorothiazide has been reported to activate or exacerbate systemic lupus erythematosus (SLE).

Patients with severe electrolyte imbalances, such as hyponatremia and hypokalemia, should have their condition corrected before hydrochlorothiazide is initiated. Initiation of thiazide diuretics under these circumstances can produce life-threatening situations such as cardiac arrhythmias, hypotension, and seizures. Hydrochlorothiazide can cause an increase in serum calcium concentrations and should be used with caution in patients with hypercalcemia. Thiazide diuretics have been associated with a slight increase in serum cholesterol and triglyceride concentrations. Data from long-term studies, however, suggest diuretic-induced cholesterol changes are not clinically significant and do not contribute to coronary heart disease risk.

Thiazides should be avoided in neonates with jaundice. Thiazide-induced hyperbilirubinemia is greater in this patient population.

Thiazide diuretics have been reported to cause pancreatitis and should be used with caution in patients with a history of pancreatitis.

Antihypertensive effects of thiazide diuretics may be enhanced in patients with a sympathectomy.

Drug Interactions

Hydrochlorothiazide can have additive effects when administered with other antihypertensive drugs or diuretics. In some patients, these effects may be desirable,

but orthostatic hypotension is possible. Dosages must be adjusted accordingly. In addition, amiloride hydrochloride, spironolactone, and triamterene can reduce the risk of developing hypokalemia because of their potassium-sparing effects; these agents have been used as therapeutic alternatives to potassium supplements.

Hydrochlorothiazide-induced electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypercalcemia) can predispose patients to digoxin toxicity, resulting in possibly fatal arrhythmias. Electrolyte balance should be corrected prior to initiating digoxin therapy.

The risk of developing severe hypokalemia can be increased when other hypokalemia-causing agents (e.g., corticosteroids, corticotropin, amphotericin B, other diuretics) are coadministered with hydrochlorothiazide. Monitoring serum potassium levels and cardiac function is advised, and potassium supplementation may be required.

Concomitant administration of hydrochlorothiazide to patients receiving nondepolarizing neuromuscular blockers can cause prolonged neuromuscular blockade due to hydrochlorothiazide-induced hypokalemia. Serum potassium concentrations should be determined and corrected (if necessary) prior to initiation of neuromuscular blockade therapy.

Thiazide diuretics reduce lithium renal clearance and can increase lithium serum concentrations. In some cases, thiazide diuretics can be used to counteract lithium-induced polyuria. Lithium dosage should be reevaluated and serum lithium concentrations monitored when a thiazide is added.

Hydrochlorothiazide can interfere with the hypoglycemic effects of oral hypoglycemics, which could lead to a loss of diabetic control. Additionally, the concurrent use of diazoxide and thiazide diuretics has resulted in enhanced hyperglycemia.

Hydrochlorothiazide-induced hypovolemia could cause an increased concentration of procoagulant factors in the blood, which could decrease the effects of concomitantly administered anticoagulants and require dosage adjustments of these agents; these effects, however, have not been reported to date.

Hydrochlorothiazide can reduce the renal clearance of amantadine, with subsequent increased serum concentrations and possible toxicity. This interaction has been reported with a combination product of hydrochlorothiazide and triamterene. Since it is unclear which component was responsible for the interaction, caution should be exercised when administering either drug concurrently with amantadine.

NSAIDs can decrease the diuretic, natriuretic, and antihypertensive actions of diuretics through inhibition of renal prostaglandin synthesis. Concomitant administration of NSAIDs with diuretics also can increase the risk for renal failure secondary to decreased renal blood flow. Patients should be monitored for changes in the effectiveness of their diuretic therapy and for signs and symptoms of renal impairment.

Cholestyramine, an anion-exchange resin, may bind to acidic drugs, such as the thiazide diuretics in the GI tract, and decrease their absorption and therapeutic effectiveness. It is recommended that thiazides be administered at least 4 h before cholestyramine. Although to a lesser extent than cholestyramine, colestipol also has been shown to inhibit the GI absorption and therapeutic response of thiazide diuretics. Administering the diuretic dose at least 2 h before colestipol has been suggested.

Adverse Reactions

Patients receiving hydrochlorothiazide should be monitored closely for signs of electrolyte imbalance including hyponatremia, hypokalemia, hypomagnesemia, and hypochloremia. Patients should be aware of the symptoms of these disturbances (e.g., lassitude, mental confusion, fatigue, faintness, dizziness, muscle cramps, tachycardia, headache, paresthesia, thirst, anorexia, nausea, or vomiting), and report these signs immediately. Thiazides also can decrease urinary calcium excretion, resulting in hypercalcemia.

Hypokalemia is one of the most common adverse effects associated with thiazide diuretic therapy and can lead to cardiac arrhythmias. This effect is especially important to consider in patients receiving cardiac glycoside therapy because potassium depletion increases the risk of cardiac toxicity. Hyperaldosteronism, secondary to cirrhosis or nephrosis, can predispose patients to hypokalemia when hydrochlorothiazide is administered. Low dietary potassium intake, potassium-wasting states, or administration of potassium-wasting drugs also can predispose patients to hydrochlorothiazide-induced hypokalemia. Patients receiving hydrochlorothiazide therapy may require supplemental potassium to prevent hypokalemia or metabolic alkalosis.

Hypochloremic alkalosis can occur with hypokalemia during hydrochlorothiazide therapy, and it is particularly likely to occur in patients with other losses of potassium and/or chloride such as through severe vomiting, diarrhea, excessive sweating, GI drainage, paracentesis, or potassium-losing renal diseases.

Patients receiving hydrochlorothiazide can develop a dilutional hyponatremia, but it usually is asymptomatic and moderate. Withdrawal of the drug, fluid restriction, and potassium or magnesium supplementation typically will return the serum sodium concentration to normal, but severe hyponatremia can occur. Geriatric patients are especially susceptible to developing hyponatremia, so care should be taken when diuretics are administered to these patients.

Hydrochlorothiazide reportedly has caused azotemia and interstitial nephritis, resulting in reversible renal failure. These effects have occurred mainly in patients with preexisting renal disease.

Hydrochlorothiazide can produce glycosuria and hyperglycemia in diabetic patients, possibly due to potassium depletion. Blood and/or urine glucose levels should be assessed more carefully in diabetic patients receiving hydrochlorothiazide.

Thiazide diuretics are well known to cause hyperuricemia. Thiazide diuretics appear to interfere with proximal tubule secretion of uric acid since thiazides are also organic acids and they compete with uric acid for binding at this site. Since thiazides reduce the clearance of uric acid, patients with gout or hyperuricemia may have exacerbations of their disease.

Hypercholesterolemia and/or hypertriglyceridemia have been associated with thiazide diuretic therapy. Although elevations in total cholesterol concentrations of 8% can negate the protection against coronary heart disease provided by a 5 mmHg reduction in blood pressure, data from long-term studies suggest diuretic-induced cholesterol changes are not clinically significant and do not contribute to coronary heart disease risk. After approximately 1 year of treatment, total serum cholesterol

concentrations will subside to baseline or lower, suggesting diuretic-induced cholesterol changes are not a significant coronary heart disease risk factor.

Orthostatic hypotension and hypotension can occur during hydrochlorothiazide therapy and can be exacerbated by alcohol, narcotics, or antihypertensive drugs.

Thiazide diuretics have been associated with cholestatic jaundice. Caution should be used when thiazides are administered to jaundiced infants due to the risk of hyperbilirubinemia.

Adverse GI effects associated with thiazide therapy include anorexia, gastric irritation, nausea/vomiting, cramps, diarrhea, constipation, sialadenitis, and pancreatitis.

Adverse CNS effects associated with thiazide therapy include dizziness, headache, paresthesias, vertigo, and xanthopsia.

While their incidence is rare, agranulocytosis, aplastic anemia, pancytopenia, hemolysis with anemia, leukopenia, and thrombocytopenia have been reported with thiazide diuretic therapy.

Other adverse effects reported with hydrochlorothiazide include blurred vision, muscle spasm, impotence, and weakness.

Adverse dermatologic reactions to hydrochlorothiazide and other thiazide diuretics are uncommon but may occur. These reactions include purpura, photosensitivity, rash, alopecia, urticaria, erythema multiforme including Stevens–Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis (TEN), and polyarteritis nodosa.

Loop Diuretics

Mechanism of Action

Loop diuretics act by inhibition of NaCl reabsorption in the thick ascending limb of the loop of Henle. They inhibit the Na/K/2Cl transport system in the luminal membrane. The reduction in sodium chloride reabsorption leads to decreases in normal lumen-positive potential (secondary to potassium recycling) and a positive lumen potential which drives divalent cationic reabsorption (calcium magnesium). Therefore, loop diuretics increase magnesium and calcium excretion. Hypomagnesemia may occur in some patients and hypocalcemia does not usually develop because calcium is reabsorbed in the distal convoluted tubule. In circumstances that result in hypercalcemia, calcium excretion can be enhanced by administration of loop diuretics with saline infusion. Since a significant percentage of filtered NaCl is absorbed by the thick ascending limb of loop of Henle, diuretics acting at this site are highly effective. Examples of loop diuretics include bumetanide, ethacrynic acid, furosemide, and torsemide.

Properties of Loop Diuretics

These drugs are rapidly absorbed following oral administration and may be administered by IV. They act rapidly and are eliminated by renal secretion and glomerular

filtration (half-life depends on renal function). Coadministration of drugs that inhibit weak acid secretion (e.g., probenecid or indomethacin) may alter loop diuretic clearance. Other effects include increased renal blood flow, blood flow redistribution within the renal cortex and decreased pulmonary congestion and the left ventricular filling pressure in congestive heart failure (CHF), which can be observed prior to an increase in urine output.

Clinical uses include acute pulmonary edema, acute hypercalcemia, management of edema, and hyperkalemia (loop diuretics increase potassium excretion; effect increased by concurrent administration of NaCl and water).

In acute renal failure, loop diuretics may increase rate of urine flow and increase potassium excretion and may convert oligouric to non-oligouric failure but renal failure duration is usually not affected.

In anion overload (e.g., bromide, chloride, iodide, that are all reabsorbed by the thick ascending loop), administration of loop diuretics may reduce systemic toxicity by decreasing reabsorption; moreover, concurrent administration of sodium chloride and fluid is required to prevent volume depletion.

Adverse Events

Hypokalemia Metabolic Alkalosis

Increased delivery of NaCl and water to the collecting duct increases potassium and proton secretion which may cause a hypokalemic metabolic alkalosis. It is managed by potassium replacement and by ensuring adequate fluid intake.

Ototoxicity

Loop diuretics may lead to dose-related hearing loss (in usually reversible). Ototoxicity is more common with decreased renal function and with concurrent administration of other ototoxic drugs such as aminoglycosides.

Hyperuricemia may cause gout. Loop diuretics may cause increased uric acid reabsorption in the proximal tubule, secondary to hypovolemic states.

Hypomagnesemia

Loop diuretics may cause a reduction in sodium chloride reabsorption, decrease normal lumen-positive potential (secondary to potassium recycling), generate positive lumen potential that drives divalent cationic reabsorption (calcium magnesium), and finally, loop diuretics increase magnesium and calcium excretion (hypomagnesemia may occur in some patients which can be reversed by oral magnesium administration)

Allergic reactions with furosemide: skin rash, eosinophilia, interstitial nephritis (less often)

Other Adverse Events

Dehydration (may be severe); hyponatremia (less common than with thiazides that may occur in patients who increased their water intake in response to a hypovolemic thirst); Hypercalcemia may occur in severe dehydration and if a hypercalcemic condition (e.g., oat cell long carcinoma) is also present.

Contraindications and Precautions

Obviously, it is best not to use this medication in a dehydrated patient if water is being restricted.

Weakness or lethargy could be an indicator that blood potassium has dropped too low.

Because of the increased calcium excretion brought on by furosemide (i.e., an increase in urinary calcium levels), there could be a problem using this medication in patients with a history of calcium oxalate bladder stone formation.

It is extremely difficult to overdose with this medication. Toxic doses reported are over 100 times a typical oral dose of medication. It is important to realize that in the treatment of heart failure (this drug's primary use), a crisis can arise at any time.

Taking ginseng may reduce the action of loop diuretics, resulting in problems with high blood pressure or water retention.

Drug Interactions

One of the most common drug interactions to be aware of is the interaction between furosemide and vasodilating heart medications (especially the angiotensin-converting enzyme inhibitors such as enalapril and captopril). Furosemide may decrease circulating blood volume as it causes a depletion in body water. Thus, water and electrolyte balance must be stable before a vasodilator is added in.

The bronchodilator theophylline may be able to reach higher blood levels when used in conjunction with furosemide. This means that the theophylline dose may need to be reduced.

Loop diuretics can increase the risk of digitalis-induced cardiac toxicity.

Furosemide may lead to displacement of plasma protein binding of warfarin and clofibrate (with elevated plasma levels of these drugs).

Loop diuretics reduce lithium renal clearance and can increase lithium serum concentrations.

Furosemide may increase renal toxicity of cephalosporin antibiotics.

Licorice may potentiate the side effects of potassium-depleting diuretics, including loop diuretics.

Furosemide is often used concurrently with digitalis. If furosemide leads to a significant drop in blood potassium levels, this can increase the risk of heart rhythms disturbances and other signs of digitalis toxicity.

Furosemide is often used in combination with prednisone to reduce serum calcium levels. It is possible for this combination of medication to lead to a reduction in potassium level significant enough to require potassium supplementation.

Aminoglycoside antibiotics (amikacin, gentamicin etc.) have properties that make them toxic to the ear and to the kidney. These properties increase with concomitant use of furosemide.

Potassium-Sparing Diuretics

Mechanism of Action

Potassium-sparing diuretics are diuretics that do not promote the excretion of potassium through the kidneys. Spironolactone and eplerenone work by antagonizing aldosterone which competitively binds to receptors at the aldosterone-dependent sodium/potassium exchange site in the distant convoluted tubule. This causes sodium and water to be excreted while retaining potassium. Amilioride and triamterene work by directly blocking sodium channels which prevents sodium resorption and potassium secretion.

Pharmacokinetics

Spironolactone is rapidly and extensively metabolized although its metabolites are inactive. Greater than 90% of spironolactone is bound to plasma proteins and is primarily excreted in the urine and secondarily in the bile. Eplerenone is metabolized through CYP34A; therefore, inhibitors of CYP34A are contraindicated in combination with this drug.

Clinical Uses

Spironolactone is used in heart failure and decreases all-cause mortality, decreases hospitalization and death from all causes. It is also effective for the treatment of essential hypertension, edema, and hypokalemia.

Drug Interactions

The combination of potassium supplements with potassium-sparing diuretics increases the risk for hyperkalemia. The combination of potassium and lithium decreases lithium clearing and increases the possibility of lithium toxicity. Potassium-sparing diuretics increase the half-life of digoxin which can lead to digoxin toxicity. Angiotensin-converting enzyme inhibitors, angiotensin II receptor

blockers, and nonsteroidal anti-inflammatory diseases have the possibility of causing hyperkalemia when combined with spironolactone; therefore, potassium monitoring needs to be increased. Rituximab and amifostine can enhance the hypotensive effect of rituximab and amifostine when taken in combination with potassium-sparing diuretics. Potassium-sparing diuretics should not be taken with other potassium-sparing diuretics due to the increased risk of hyperkalemia.

Anti-hemostatic Drugs

Warfarin has been the standard oral anticoagulants used for the prevention and treatment of venous thromboembolic events such as deep vein thrombosis, pulmonary embolism, and stroke. Warfarin use is recommended in patients with prosthetic heart valves and in patients with atrial fibrillation or atrial aflutter and risk factors.

Mechanisms of Action

The anticoagulant effect of warfarin is mediated by inhibition of the vitamin K–dependent gamma-carboxylation of coagulation factors II, VII, IX, and X. This results in the synthesis of immunologically detectable but biologically inactive forms of these coagulation proteins. Warfarin also inhibits the vitamin K–dependent gamma-carboxylation of proteins C and S. Activated protein C in the presence of protein S inhibits activated factor VIII and activated factor V activity. Thus, warfarin creates a biochemical paradox by producing an anticoagulant effect due to the inhibition of procoagulants (factors II, VII, IX, and X) and a potentially thrombogenic effect by impairing the synthesis of naturally occurring inhibitors of coagulation (proteins C and S). The anticoagulant effect of warfarin is delayed until the normal clotting factors are cleared from the circulation, and the peak effect does not occur until 36–72 h after drug administration. During the first few days of warfarin therapy, prolongation of the PT mainly reflects depression of factor VII, which has a half-life of only five to seven hours; thus, the intrinsic coagulation pathway that does not require factor VII remains intact. Equilibrium levels of factors II, IX, and X are not reached until about one week after the initiation of therapy. For this reason, heparin and warfarin treatment should overlap by four to five days when warfarin is initiated in patients with thrombotic disease.

Complications and Therapeutic Concerns

The major complication associated with the use of warfarin is bleeding. In addition, there are major concerns about its use in pregnancy. Finally, there may be a problem with skin necrosis shortly after the institution of warfarin, usually in high doses.

Bleeding

The risk of major bleeding episodes in patients treated with warfarin is directly related to the degree of anticoagulation. Studies in patients with atrial fibrillation indicate that the risk increases substantially at INR values above 4.0. High-risk patients may have bleeding episodes at lower INR values. Patients at high risk of bleeding are those who are elderly (age >75 years old), have CHF, cirrhosis, and those who are on concurrent medications that interact with warfarin significantly (e.g., Amiodarone). Therefore, in those patients, a lower initial dose of ≤5 mg/day is recommended. In order to improve the ability to predict major bleeding, other measurements have been evaluated. For example, one study of 212 outpatients followed for five years reported that the risk of hemorrhage was associated with an increased level of thrombomodulin (>56 μg/L), an endothelium-derived antithrombotic cell-surface glycoprotein that is mainly present on the luminal surface of endothelial cells. The anticoagulant properties of thrombomodulin result from its binding to thrombin and subsequent activation of protein C. However, not all bleeding episodes in anticoagulated patients are due to the anticoagulation. As an example, it should not be assumed that hematuria alone can be explained by chronic stable warfarin therapy. In one report of 243 patients prospectively followed for two years, the incidence of hematuria was similar to that in a control group not receiving warfarin. Furthermore, evaluation of patients who developed hematuria revealed a genitourinary cause in 81% of cases. Infection was most common, but papillary necrosis, renal cysts, and several malignancies of the bladder were also found.

Use in Pregnancy

Warfarin is contraindicated during pregnancy because of its teratogenic effects. However, the actual risk of embryopathy is unknown. One study, for example, found no congenital abnormalities in 46 women with prosthetic valves who took warfarin during the first trimester. However, other studies have not found such a benign outcome, primarily in patients taking warfarin between the sixth and twelfth weeks of pregnancy. Additionally, warfarin can cross the placenta and increase the risk of bleeding in fetus. Therefore, warfarin use should be avoided during pregnancy. It is recommended that patients use alternative anticoagulants such as heparin and low-molecular-weight heparin during pregnancy.

Warfarin-Induced Skin Necrosis

Warfarin-induced skin necrosis typically occurs during the first several days of warfarin therapy, often in association with the administration of large loading doses. The skin lesions occur on the extremities, breasts, trunk, and penis (in males) and marginate over a period of hours from an initial central erythematous macule. Biopsies demonstrate fibrin thrombi within cutaneous vessels with interstitial hemorrhage. Skin necrosis appears to be mediated by the reduction in protein C levels on the first day of therapy, which induces a transient hypercoagulable state.

Approximately one-third of patients have underlying protein C deficiency; however, among patients with protein C deficiency, skin necrosis is an infrequent complication of warfarin therapy. Case reports have also described this syndrome in association with an acquired functional deficiency of protein C, heterozygous protein S deficiency, and factor V Leiden.

Warfarin–Drug Interactions

A number of different drugs can interact with warfarin, leading to alterations in anticoagulation. The major mechanisms for warfarin–drug interactions are:

- Decrease warfarin absorption
- Alter warfarin metabolism
- Displace warfarin from protein-binding sites
- Alter vitamin K production
- Inhibit p-glycoprotein which is important for warfarin clearance
- Process additive antiplatelet or anticoagulation effect
- Cause gastric erosion and increase risk of gastrointestinal bleeding

Decreased Absorption

The bile acid–binding resins cholestyramine decreases warfarin absorption. These drugs also enhance warfarin elimination by interrupting its enterohepatic recirculation. As a result, higher warfarin doses are required as is careful monitoring of the prothrombin time. On the other hand, dosing requirements will fall when resin therapy is discontinued. Separation of administration time by at least two hours may reduce the interaction.

Altered Metabolism

Warfarin is mainly metabolized by the hepatic cytochrome CYP2C9 (P4502C9) isoenzyme. It is also metabolized to a lesser extent by CYP1A2, CYP3A4, and CYP2C19. Drugs that induce these hepatic cytochrome isoenzyme can interact with warfarin and result in decreasing anticoagulation effects of warfarin. Common examples are listed in Table 9.7. Coadministration of these drugs enhances warfarin clearance and reversibly increases the dose required for adequate anticoagulation.

Phenytoin interacts with warfarin by displacing warfarin from protein-binding sites, and thus increasing anticoagulation effect. However, this effect is transient and is usually overcome within 1–2 months by the CYP isoenzyme induction of warfarin metabolism by phenytoin. On the other hand, warfarin inhibits phenytoin metabolism and significantly increases phenytoin concentration. Therefore, careful monitoring is warranted when phenytoin is started or stopped in patient on warfarin, or vice versa.

Table 9.7 Common drugs that increase warfarin metabolism

Drug/dietary supplement	Mechanism
Aprepitant, fosaprepitant	CYP2C9 inducer
Nafcillin, dicloxacillin	CYP3A4 and 2C9 inducer
Lopinavir, ritonavir, darunavir	CYP2C9 inducer
Rifampin, rifabutin	CYP2C9 inducer
Phenobarbital and carbamazepine	CYP2C9 inducer
Bosentan	CYP3A4 and 2C9 inducer
Glutethimide	CYP2C9 inducer
Griseofulvin	CYP3A4 and 2C9 inducer
St. John's wort	CYP3A4 and 2C9 inducer
Peginterferon alfa-2b	CYP2C9 inducer

Table 9.8 Common drugs that inhibit warfarin metabolism

Drug/dietary supplement	Mechanism
Amiodarone	CYP2C9, CYP3A4, CYP2C19 inhibitor
Atazanavir	CYP3A4 inhibitor
Cimetidine	CYP3A4 inhibitor
Capecitabine	CYP2C9 inhibitor
Cranberry	CYP2C9 and CYP3A4 inhibitor
Corticosteroid	CYP3A4 inhibitor
Dronedarone	CYP2C9 inhibitor
Efavirenz	CYP2C9 and CYP2C19 inhibitor
Proton pump inhibitors	CYP2C19 inhibitor
Etoposide	CYP3A4 inhibitor
Fibric acid derivatives	Displace warfarin from protein-binding sites; CYP2C9 inhibitor, reduction in coagulation factor synthesis
Itraconazole, ketoconazole	CYP3A4 inhibitor
Fluconazole, miconazole, voriconazole	CYP2C9, CYP2C19, CYP3A4 inhibitor
HMG co-A reductase inhibitors (except atorvastatin)	CYP2C9 inhibitor
Leflunomide	Metabolite is CYP2C9 inhibitor
Erythromycin, telithromycin, azithromycin	CYP3A4 inhibitor
Metronidazole	CYP2C9 inhibitor
Celeboxib	CYP2C9 inhibitor
Propafenone	CYP1A2 inhibitor
Propoxyphene	CYP2C9 inhibitor
Selective serotonin reuptake inhibitors	CYP2C9 and CYP3A4 inhibitor
Sitaxsentan	CYP2C9, CYP2C19, and CYP3A4 inhibitor
Sulfamethoxazole	CYP2C9 inhibitor
Tamoxifen	CYP2C9 inhibitor (avoid combination)
Torsemide	CYP2C9 inhibitor

Warfarin metabolism can also be inhibited by numerous drugs, potentially requiring a reduction in drug dosage. Common examples are listed in Table 9.8. The coadministration of any of these drugs requires close monitoring of the prothrombin time to avoid excess anticoagulation. The magnitude of the drug interaction is highly variable depending on the CYP isoenzyme being inhibited and

potency of the inhibitor. Warfarin is a racemic mixture with S-enantiomer and R-enantiomer. S-enantiomer is 3–4 times more potent than R-enantiomer. S- and R- enantiomers are metabolized by CYP2C9 and CYP3A4 isoenzymes respectively. Therefore, drugs that inhibit CYP2C9 pathway, which metabolize the more potent enantiomer, are expected to produce a more profound interaction than drugs that inhibit CYP3A4 pathway. As an example, amiodarone, fluconazole, metronidazole, and sulfamethoxazole preferentially inhibit metabolism of the S-enantiomer via cytochrome CYP2C9 and can therefore have a profound enhancing effect on anticoagulation that often requires warfarin dose adjustment. Tamoxifen is a very potent CYP2C9 inhibitor and should not be coadministered with warfarin.

Effect on Albumin Binding

Circulating warfarin is tightly bound to albumin. It has been suggested that the coadministration of a nonsteroidal anti-inflammatory drug, which is also highly bound, might displace warfarin from its binding sites, leading sequentially to a marked elevation in the unbound and pharmacologically active warfarin concentration and an increased risk of bleeding. Though this mechanism is often cited in the drug interaction literature, it is now known that such effects are of negligible clinical importance. Displacement from protein binding leads to little or no increase in the unbound, pharmacologically active warfarin concentration because of a concurrent rise in warfarin clearance due to increased availability of unbound drug.

Altered Vitamin K Absorption

Certain antibiotics can eradicate the gastrointestinal flora that takes part in vitamin K production. This results in a decrease in vitamin K and an increase in anticoagulation effect. Common examples are tetracycline, penicillins, cephalosporins, macrolides, and quinolone antibiotics.

Ulcerogenic Agent

Agents that increase gastric irritation and erosion of the protective lining of the stomach increase the risk of a GI bleed when used concurrently with warfarin. An example is the nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, naproxen, ibuprofen, and ketoprofen.

Others

Mechanisms of several interactions with warfarin are still unknown (Table 9.9). An example is acetaminophen. Acetaminophen (paracetamol) use has been associated in epidemiologic studies with an increased risk of developing a prolonged

Table 9.9 Drugs that interact with warfarin through other mechanisms

Drug	Mechanism	Effect
Androgens	Increases in antithrombin III or protein C; decreased synthesis/increased destruction of clotting factors	Enhance anticoagulation effect
Acetaminophen	Unknown	Enhance anticoagulation effect
Aspirin, clopidogrel, ticlopidine	Antiplatelet effects; cause gastric erosion	Increase risk for gastrointestinal bleeding
Anticoagulant	Additive anticoagulation effect	Increase risk of bleeding
Drotrecogin alfa	Unknown	Increase risk for bleeding; do not use within 7 days of warfarin therapy or when INR is ≥3
Alfafa	Antiplatelet properties	Enhance anticoagulation effect
Bilberry	Antiplatelet properties	Enhance anticoagulation effect
Anise	Antiplatelet properties	Enhance anticoagulation effect
Ginkgo biloba	Inhibit platelet aggregation; increase risk for intracranial bleeding	Increase risk for bleeding; do not recommend concurrent use
Ginseng, American	May induce warfarin metabolism	Decrease anticoagulation effect
Green tea	Contains vitamin K; antiplatelet properties	Increase risk of bleeding; decreases anticoagulation effect
Fenugreek	Antiplatelet properties	Enhance anticoagulation effect
Ivermectin	Inhibit factor II and factor VII activity	Enhance anticoagulation effect
Nonsteroidal anti-inflammatory drugs	Inhibit platelet aggregation; ulcerogenic effect; displace warfarin from protein-binding site	Increase risk of bleeding
Oral contraceptives	Increase warfarin clearance; increase clotting factors	Diminish anticoagulation effect; avoid concomitant use
Orlistat	Decrease vitamin K absorption	Increase anticoagulation effect
Pentoxifylline	Decrease fibrinogen and platelet activity	Increase risk of bleeding
Phytonadione	Vitamin K activity	Diminish anticoagulation effect
Quinolone antibiotics	Displace protein-binding sites; reduction of GI flora essential for vitamin K production	Enhance anticoagulation effect
Sucralfate	Decrease warfarin absorption	Diminish anticoagulation effect; administer warfarin 2 h before or 6 h after sucralfate

(continued)

Table 9.9 (continued)

Drug	Mechanism	Effect
Tetracycline antibiotics	Reduction of GI flora essential for vitamin K production	Enhance anticoagulation effect
Thrombolytics	Interfere with normal clotting function	Increase risk of bleeding
Thyroid hormones	Increase catabolism of vitamin K–dependent clotting factors	Increase anticoagulation effect; reduce warfarin dose
Tolterodine	Anticholinergic effect causes prolonged gastric emptying and increased absorption of warfarin	Increase anticoagulation effect
Tricyclic antidepressants	Anticholinergic effect causes prolonged gastric emptying and increased absorption of warfarin	Increase anticoagulation effect
Vitamins A and E	Unknown	Enhance anticoagulation effect

international normalized ratio (INR). One case control study of 289 patients found that the odds ratio of developing an INR above 6.0 increased with greater acetaminophen intake; a statistically significant odds ratio of 3.5 was observed when weekly consumption exceeded the equivalent of more than seven regular strength tablets, and rose to 10.0 when weekly consumption exceeded the equivalent of 28 regular strength tablets. Patients taking daily acetaminophen >1.3 g/day for greater than one week may need INR to be closely monitored. The mechanism by which acetaminophen might potentiate the action of warfarin is not well understood.

Fibrinolytics

Acute myocardial infarction (MI) is a condition that results from rupture of an atheromatous plaque with subsequent thrombus formation and vessel occlusion. Currently available thrombolytic agents include alteplase (tPA), reteplase, tenecteplase, and urokinase. It has been shown that thrombolytics reduce mortality in acute MI. There has been an overall 30% reduction in mortality from 10% to 15% in the prethrombolytic era to 7–10%.

Indications

Fibrinolytics are indicated for the management of ST-elevation myocardial infarction (STEMI) and the lysis of thrombi in coronary arteries, management of acute ischemic stroke (AIS), and management of acute pulmonary embolism (Table 9.10). The efficacy of these pharmacological agents and other reperfusion procedures is dependent upon the time at which reperfusion occurs and the degree of flow obtained. The earlier reperfusion occurs, the greater the degree of myocardial salvage that can be achieved. Thus, the benefit is greatest when thrombolytic agents are administered soon after the onset of symptoms, particularly within the first four hours after a stroke. Thrombolytic therapy is not indicated in patients with unstable angina and no ST elevation because of lack of proven benefit. ST segment depression is also not an indication for thrombolytic therapy unless it represents a true posterior or dorsal MI.

Contraindications

Patients who are allergic to fibrinolytics are not candidates to the therapy. In order to be eligible for fibrinolytic therapy, the patient must not carry any exclusion criteria, see Table 9.11. Up to 40% of patients in some series are ineligible for thrombolytic therapy. Active internal bleeding is an absolute contraindications. Patients older than 75 years may get less overall benefit than younger patients, but advanced age is no longer considered a major contraindication for thrombolytic therapy.

Table 9.10 Fibrinolytics indication

Recommended criteria for treatment:
• STEMI: Chest pain ≥20 min duration, onset of chest pain within 12 h of treatment (or within prior 12–24 h in patients with continuing ischemic symptoms), and ST segment elevation >0.1 mV in at least two contiguous precordial leads or two adjacent limb leads on ECG or new or presumably new left bundle branch block (LBBB)
• AIS: Onset of stroke symptoms within 3 h of treatment
• Acute pulmonary embolism: Age ≤75 years: Documented massive pulmonary embolism by pulmonary angiography or echocardiography or high probability lung scan with clinical shock

Table 9.11 Contraindications to fibrinolytic agents

Indication	Exclusion criteria
Treatment of STEMI or PE	Active internal bleeding; history of CVA; recent intracranial or intraspinal surgery or trauma; intracranial neoplasm; arteriovenous malformation or aneurysm; known bleeding diathesis; severe uncontrolled hypertension
Treatment of acute ischemic stroke	Evidence of intracranial hemorrhage or suspicion of subarachnoid hemorrhage on pretreatment evaluation; recent (within 3 months) intracranial or intraspinal surgery; prolonged external cardiac massage; suspected aortic dissection; serious head trauma or previous stroke; history of intracranial hemorrhage; uncontrolled hypertension at time of treatment (e.g., >185 mmHg systolic or >110 mmHg diastolic); seizure at the onset of stroke; active internal bleeding; intracranial neoplasm; arteriovenous malformation or aneurysm; known bleeding diathesis including but not limited to: current use of anticoagulants or an INR >1.7, administration of heparin within 48 h preceding the onset of stroke and an elevated aPTT at presentation, platelet count <100,000/mm^3

Side Effects

Common side effects associated with fibrinolytics include bleeding. Bleeding can include major bleeding (0.5%) and minor bleeding (7%). Major bleeding are defined as bleeding that requires blood transfusion or hospitalization. Symptoms of bleeding include bruising (1%), GI hemorrhage (5%), genitourinary bleeding (4%), and bleeding at catheter site (15%). Other side effects include fever, hypotension, nausea, and vomiting.

Drug Interactions

Most drug interactions associated with fibrinolytics are related to its anticoagulation effect pharmacodynamically. For example, anticoagulants and antiplatelet agents such as warfarin and aspirin may enhance anticoagulant effect of fibrinolytics. In most cases, close monitoring of signs and symptoms of bleeding is sufficient.

Table 9.12 Drug interactions with fibrinolytics

Drug	Effect	Recommendation
Aprotinin	Diminish the therapeutic effect of thrombolytic agents	Consider therapy modification
Drotrecogin alfa	Thrombolytic agents may enhance the adverse/toxic effect of drotrecogin alfa. Bleeding may occur	Consider therapy modification
Nitroglycerin	May decrease the serum concentration of alteplase	Monitor therapy
Nonsteroidal anti-inflammatory agents	Enhance the adverse/toxic effect of thrombolytic agents. An increased risk of bleeding may occur	Monitor therapy
Salicylates	Enhance the adverse/toxic effect of thrombolytic agents. An increased risk of bleeding may occur	Monitor therapy

Herbal products that process antiplatelet properties such as alfafa, anise, and bilberry may enhance the anticoagulant effect of fibrinolytics and their concurrent uses are not recommended. Additional drug interactions are listed in Table 9.12.

Monitoring

Monitoring is very important to assess drug efficacy and detect potential side effects experienced by the patient, especially when a drug interaction existed. Patients on fibrinolytics should be monitored for signs and symptoms of bleeding. Additionally, they should be monitored for the following:

- Acute ischemic stroke: neurological assessments every 15 min during infusion and every 30 min thereafter for the next 6 h, then hourly until 24 h after treatment.
- Emergency CT scan if severe headache, acute hypertension, nausea, or vomiting occurs.
- Blood pressure every 15 min for the first 2 h then every 30 min for the next 6 h, then hourly until 24 h after initiation of drug. Increase frequency if a systolic BP is ≥180 mm Hg or if a diastolic BP is ≥105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels.
- Obtain a follow-up CT scan at 24 h before starting anticoagulants or antiplatelet agents.
- ST-elevation MI: Assess for evidence of cardiac reperfusion through resolution of chest pain, resolution of baseline ECG changes, preserved left ventricular function, cardiac enzyme washout phenomenon, and/or the appearance of reperfusion arrhythmias; assess for bleeding potential through clinical evidence of GI bleeding, hematuria, gingival bleeding, fibrinogen levels, fibrinogen degradation products, prothrombin times, and partial thromboplastin times.

Antiplatelet Drugs

Platelets play a major role in the thrombotic response to rupture of a coronary artery plaque. Cardiovascular disease, which includes myocardial infarction, stroke, and peripheral vascular disease, remains far and away the leading the cause of death in the United States and most developed countries, accounting for more than 900,000 deaths annually in the United States alone. The totality of evidence from basic research, observational epidemiologic studies, and randomized clinical trials has provided strong support for the efficacy of antiplatelet drugs in decreasing the risk of cardiovascular disease in a wide range of patient categories.

Mechanism of Action

Antiplatelet agents can interfere with a number of platelet functions including aggregation, release of granule contents, and platelet-mediated vascular constriction. They can be classified according to their mechanisms of action:

1. Class I: Aspirin and related compounds (nonsteroidal anti-inflammatory drugs and sulfinpyrazone) block "irreversible"cyclooxygenase (prostaglandin H synthase), the enzyme that mediates the first step in prostaglandin and thromboxane biosyntheses from arachidonic acid.
2. Class II: Dipyridamole inhibits phosphodiesterase-mediated breakdown of cyclic AMP which prevents platelet activation by multiple mechanisms.
3. Class III: Ticlopidine and clopidogrel achieve their antiplatelet effect by blocking the binding of ADP to a low-affinity, type 2 purinergic receptor and preventing the activation of the GP IIb/IIIa receptor complex and subsequent platelet aggregation.
4. Class IV: Anti-IIb/IIIa antibodies (abciximab) and receptor antagonists (tirofiban, eptifibatide) inhibit the final common pathway of platelet aggregation and may also prevent initial adhesion to the vessel wall.

Aspirin

Aspirin has been thoroughly evaluated as an antiplatelet drug and was found to prevent vascular death by approximately 15% and nonfatal vascular events by about 30%.

Side Effects – Aspirin

Common side effects including gastrointestinal side effects (dyspepsia, nausea, vomiting) occur in about 40% of patients (versus 30% in the placebo group) in which 10–20% of these side effects are self-limited. Gastrointestinal bleeding is seen in up to 5% per year but frank melena (1% per year) and hematemesis (0.1%)

are rare. Gout may be aggravated in some patients due to impaired urate excretion. Worsening of bronchospasm and asthma as well as rare anaphylactic reactions have also been observed.

Drug interactions with aspirin: see chapter NSAID.

Dipyridamole

Side Effects – Dipyridamole

It is possible that dipyridamole may have a deleterious effect because of its potential for inducing coronary steal, which can exacerbate the angina. For these reasons, dipyridamole is not recommended in unstable angina.

Adverse effects at therapeutic doses are usually mild and transient. Vomiting, diarrhea, and symptoms such as dizziness, nausea, headache, and myalgia have been observed. Such effects usually disappear on long-term use of dipyridamole.

As a result of its vasodilating properties, dipyridamole may cause hypotension, hot flushes, and tachycardia. In rare cases, worsening of coronary heart disease has been observed.

Hypersensitivity reactions like rash, urticaria, severe bronchospasm, and angioedema have been reported.

In very rare cases, increased bleeding during or after surgery has been observed.

Isolated cases of thrombocytopenia have been reported in conjunction with treatment with dipyridamole.

Drug Interactions – Dipyridamole

Dipyridamole increases plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should be considered.

When dipyridamole is used in combination with anticoagulants or acetylsalicylic acid, the statements on intolerance and risks for these preparations must be observed. Addition of dipyridamole to acetylsalicylic acid does not increase the incidence of bleeding events. When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.

Dipyridamole may increase the hypotensive effect of drugs which reduce blood pressure and may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.

Thienopyridines

Ticlopidine and clopidogrel are structurally related thienopyridines with platelet inhibitory activities. Both drugs selectively inhibit ADP-induced platelet aggregation with no direct effects on arachidonic acid metabolism.

Side Effects

Neutropenia, which can be quite severe and occurs in approximately 1% of patients, is the most serious side effect of ticlopidine. It usually appears during the first three months of treatment and requires immediate discontinuation of the drug. How this occurs is not well understood but direct suppression of the bone marrow may be involved. Rash (2%), diarrhea (3%), dyspepsia, hepatic dysfunction, and the development of bronchiolitis obliterans organizing pneumonia (BOOP) have also been observed.

Thrombotic thrombocytopenia purpura-hemolytic uremic syndrome (TTP-HUS) is a rare complication of ticlopidine therapy. The reported incidence when the drug is used after cardiac stenting is 1 case in 1,600 to 1 in 4,800. All cases occur within twelve weeks. Treatment includes discontinuation of the drug and plasma exchange. Ticlopidine has not yet been approved for use in unstable angina by the Food and Drug Administration, but it is recommended by the ACC/AHA Task Force in a dose of 250 mg twice per day in patients not able to take aspirin.

Ticlopidine or clopidogrel is also recommended in addition to aspirin when coronary artery stenting is performed. Neutrophil counts should be obtained at baseline, every two to three weeks during the first four months, and monthly thereafter. Platelet counts should also be obtained at baseline and every week during the first four months of therapy.

Ticlopidine therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8–10% within 1 month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged.

There were no major adverse events from clopidogrel itself in the CURE trial, although the combination of clopidogrel plus aspirin was associated with a significant increase in major (3.6% versus 2.7%) and minor bleeding (15.3% versus 8.6%). Clopidogrel appears to be associated with fewer complications (e.g., neutropenia, TTP-HUS) than ticlopidine.

Drug Interactions – Ticlopidine

Therapeutic doses of ticlopidine caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore, the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios or being given to patients with hepatic impairment may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine.

Studies of specific drug interactions of ticlopidine yielded the following results:

Aspirin and Other NSAIDs: Ticlopidine potentiates the effect of aspirin or other NSAIDs on platelet aggregation. The safety of concomitant use of ticlopidine and NSAIDs has not been established. The safety of concomitant use of ticlopidine and aspirin beyond 30 days has not been established. Aspirin did not modify the ticlopidine-mediated inhibition of ADP-induced platelet aggregation, but ticlopidine

potentiated the effect of aspirin on collagen-induced platelet aggregation. Caution should be exercised in patients who have lesions with a propensity to bleed, such as ulcers. Long-term concomitant use of aspirin and ticlopidine is not recommended.

Antacids: Administration of ticlopidine after antacids resulted in an 18% decrease in plasma levels of ticlopidine.

Cimetidine: Chronic administration of cimetidine reduced the clearance of a single dose of ticlopidine by 50%.

Digoxin: Coadministration of ticlopidine with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected.

Theophylline: In normal volunteers, concomitant administration of ticlopidine resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 h and a comparable reduction in total plasma clearance of theophylline.

Phenobarbital: In 6 normal volunteers, the inhibitory effects of ticlopidine on platelet aggregation were not altered by chronic administration of phenobarbital.

Phenytoin: In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Several cases of elevated phenytoin plasma levels with associated somnolence and lethargy have been reported following coadministration with ticlopidine. Caution should be exercised in coadministering this drug with ticlopidine, and it may be useful to remeasure phenytoin blood concentrations.

Propranolol: In vitro studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied in vivo. Caution should be exercised in coadministering this drug with ticlopidine.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, ticlopidine was used concomitantly with beta-blockers, calcium channel blockers, and diuretics without evidence of clinically significant adverse interactions.

Drug Interactions – Clopidogrel

During drug interaction studies, no clinically significant drug–drug interactions were observed with clopidogrel and aspirin (administered as 500 mg twice a day for 1 day), heparin, atenolol, nifedipine, estrogen, digoxin, or theophylline. The pharmacodynamic activity of clopidogrel was not significantly influenced by coadministration of phenobarbital or cimetidine.

Coadministration of clopidogrel with naproxen resulted in increased occult GI blood loss. There are no known drug or laboratory test interactions with clopidogrel.

Cytochrome P_{450} System

At high concentrations in vitro, clopidogrel inhibited the activity of CYP_{450} 2C9, which could result in higher plasma levels of drugs metabolized by this isozyme, such as phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many nonsteroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of such interactions.

Experience from the CAPRIE study indicated that clopidogrel can be safely administered long term (e.g., up to 3 years) with many other commonly prescribed medications without evidence of clinically significant interactions. These medications include diuretics, beta-blocking agents, angiotensin-converting enzyme inhibitors, calcium antagonists, cholesterol-lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents, and hormone replacement therapy.

Recent studies proposed that omeprazole decreases the platelet inhibitory effects of clopidogrel.

A retrospective cohort study of 8,205 patients with ACS taking clopidogrel after discharge from hospitals showed that patients on omeprazole were associated with higher risk of death and re-hospitalization. The proposed mechanism of the interaction could be due to the inhibition of CYP2C19 by omeprazole resulting in decreased clopidogrel activation.

GP IIb/IIIa Receptor Antagonists

Glycoprotein(GP) IIb/IIIa receptor antagonists work by binding to GP IIb/IIIa receptor and result in platelet inhibition. Glycoprotein(GP) IIb/IIIa receptor antagonists are indicated for the prevention of cardiac ischemic complications in patients undergoing percutaneous coronary intervention (PCI), prevention of cardiac ischemic complications in patients with unstable angina not responding to conventional therapy when PCI is scheduled within 24 h, and potentially in ST-elevation myocardial infarction. Examples of glycoprotein(GP) IIb/IIIa receptor antagonists are Abciximab, tirofiban, and eptifibatide.

Side Effects

Glycoprotein(GP) IIb/IIIa receptor antagonists can cause hypotension, bradycardia, and nausea in more than 10% of patients. One complication of GP IIb/IIIa receptor antagonist therapy is thrombocytopenia, occurring within 24 h of initiating therapy. The reported incidence is 0.8 to 1.6% (versus 0.7% for placebo). While the mechanism is unknown, platelet transfusions are effective. Another concern is excessive bleeding if emergency bypass surgery is required after the administration. A paucity of data exists, but one report suggested that routine platelet transfusions prevented major bleeding and reduced excessive blood transfusions.

Drug Interactions

Drugs that increase the risk of bleeding may interact with Anti-IIb/IIIa antibodies by potentiating the risk of bleeding. Examples are anticoagulants, other antiplatelet agents, herbs (alfafa, anise, bilberry), ibritumomab, nonsteroidial anti-inflammatory agents, and thrombolytic agents. In patients taking these agents concomitantly with Anti-IIb/IIIa antibodies, close monitoring for any signs and symptoms of bleeding is warranted.

Dextran may enhance the anticoagulant effect of Abciximab and cause excessive bleeding and the combination should be avoided.

Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. If possible, antiplatelet agents should not be used within 7 days of drotrecogin alfa.

Lipid-Lowering Drugs

Lipid-altering agents encompass several classes of drugs that include HMG-CoA reductase (hydroxymethylglutaryl CoA reductase) inhibitors or statins, fibric acid derivatives, bile acid sequestrants, nicotinic acid, probucol, ezetimibe, and omega-3-fatty acids. These drugs differ with respect to mechanism of action and to the degree and type of lipid lowering. Thus, the indications for a particular drug are influenced by the underlying lipid abnormality. The mechanisms of benefit seen with lipid-lowering are incompletely understood. Regression of atherosclerosis occurs in only a minority of patients; furthermore, the benefit of lipid lowering is seen in as little as six months, before significant regression could occur. Thus, other factors must contribute; these include plaque stabilization, reversal of endothelial dysfunction, and decreased thrombogenicity.

Statins

The HMG-CoA reductase inhibitors commonly known as “statins” represent a major therapeutic advance in lipid-regulating pharmacological therapy because of their increased efficacy, tolerability, and ease of administration. Currently available statins include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin. These agents are competitive inhibitors of HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. Fluvastatin dosed at 20–40 mg/day, lovastatin dosed at 10–80 mg/day, pravastatin dosed at 10–40 mg/day, simvastatin dosed at 5–40 mg/day, or rosuvastatin dosed at 5–40 mg/day may be expected to decrease LDL cholesterol 20–60 %.

The resultant reduction from the inhibition of HMG-CoA reductase in intracellular cholesterol in the liver stimulates the upregulation of the B/E receptor and

increases clearance of lipoproteins containing apo B or apo E from the plasma compartment. Although the predominant effect is to decrease circulating LDL cholesterol, VLDL and IDL particles are also removed. Inhibition of the synthesis of apo B–containing lipoproteins has also been postulated as a potential mechanism for these agents, but this hypothesis remains controversial. Potential beneficial nonlipid effects include a reduction in plasminogen activator inhibitor 1 (PAI-1) in patients with hypercholesterolemia, reported with lovastatin and pravastatin, which provides a hemostatic mechanism for clinical improvement with HMG-CoA reductase inhibitor therapy. Other potential actions of statins beyond lowering lipids include prevention of thrombus formation, stabilization of plaques, anti-inflammatory modulation, and increased endothelial function.

Side Effects

Adverse reactions occur less frequently with the statins than with the other classes of lipid-lowering agents. The side effects of the HMG-CoA reductase inhibitors are minimal. The major clinical problems that have been reported are hepatotoxicity and myopathy. Serum liver enzyme levels were greater than three times the upper limit of normal in less than 2% of subjects who received maximum dose lovastatin in the 1-year Expanded Clinical Evaluation of Lovastatin (EXCEL) study, and at the usual dosage, the incidence was less than 1%. Most cases of transaminase elevation appear to occur within the first 3 months of therapy. Rhabdomyolysis has been documented in approximately 0.1% of subjects receiving lovastatin monotherapy and appears to occur at about the same frequency for all the HMG-CoA reductase inhibitors. However, the exact incidence of myopathy, as defined by creatine kinase elevation, that is attributable to HMG-CoA reductase inhibitor use is difficult to establish: In subjects who continued in the EXCEL study a second year, creatine kinase elevations above the upper limit of normal were reported in 50–67% of the groups receiving various dosages of lovastatin and 54% of the placebo group.

Drug Interactions

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate)

In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. Myopathy may occur with fibrates or statins alone; therefore, combination of both may have additive myopathic effects. Gemfibrozil has a higher incidence of rhabdomyolysis compared to fenofibrate although most cases were associated with cerivastatin which has now been withdrawn from the market worldwide due to this interaction.

Niacin

It has been hypothesized that niacin may enhance the effect of HMG-CoA reductase inhibitors, thus increasing the risk of myopathy. Adverse effects associated with statin therapy when combined with niacin is similar to statin therapy alone.

CYP 34A Inducers/Inhibitors

Pravastatin and fluvastatin are not extensively metabolized by the cytochrome CYP3A4 system; as a result, they have few interactions with other drugs unlike other statins. Several studies have noted no increase in the risk of myositis when pravastatin was used in conjunction with sustained-release niacin or cyclosporine; similar considerations appear to apply to fluvastatin. In contrast, lovastatin in high dose (40–80 mg/day) is associated with an appreciable risk of myositis in patients also receiving cyclosporine. However, this combination is usually well tolerated if only low doses of lovastatin are used (10 or 20 mg/day): Muscle toxicity occurs in only zero to two percent of cases. Similar results have been reported with low-dose simvastatin.

Bile Acid Sequestrants

Patients with mild-to-moderate hypercholesterolemia: LDL-C reduction was greater when atorvastatin 10 mg and colestipol 20 g were coadministered (−45%) than when either drug was administered alone (−35% for atorvastatin and −22% for colestipol). For patients with severe hypercholesterolemia, LDL-C reduction was similar (−53%) when atorvastatin 40 mg and colestipol 20 g were coadministered when compared with that of atorvastatin 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when atorvastatin 40 mg plus colestipol 20 g were coadministered compared with atorvastatin 40 mg alone. Concomitant administration resulted in an approximately 40–50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 h before or 4 h after cholestyramine or 1 h before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. However, the combination drug therapy was less effective in lowering the triglycerides than atorvastatin monotherapy in both types of hypercholesterolemic patients. When atorvastatin is used concurrently with colestipol or any other resin, an interval of at least 2 h should be maintained between the two drugs, since the absorption of atorvastatin may be impaired by the resin.

Amiodarone

The FDA issued an alert in August 2008 to remind practitioners of the drug interaction between doses of simvastatin greater than 20 mg daily when taken in

combination with amiodarone. This interaction has been linked to an increased risk of rhabdomyolysis. It is assumed that this interaction also exists for dronedarone although no studies have been conducted to date.

Coumarin Anticoagulants

Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy. In a study involving ten healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein binding of warfarin. Concomitant dosing did increase the AUC and C_{max} of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with lovastatin, rosuvastatin, and simvastatin in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Digoxin

Coadministration of multiple doses of atorvastatin and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately. In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Oral Contraceptives

Coadministration of atorvastatin with an oral contraceptive, containing 1 mg norethindrone and 35 μg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive.

Protease Inhibitors

The combination of statins with protease inhibitors increases the serum concentrations of HMG-CoA reductase inhibitors. Pravastatin may slightly decrease the serum concentrations of protease inhibitors.

Erythromycin

In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4. This increase in statin concentrations can lead to an increased risk of rhabdomyolysis but is not an issue with azithromycin.

Cyclosporine

Caution should be exercised with concomitant use of immunosuppressive agents due to an increase in the serum concentrations of HMG-CoA inhibitors. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Azole Antifungals

Combination of HMG-CoA inhibitors with systemic azole derivatives such as fluconazole can decrease the metabolism of the statin although this effect has not been found with rosuvastatin.

Eltrombopag

Coadministration of eltrombopag with a statin and/or ezetimibe results in increased concentrations of eltrombopag which is used for patients with idiopathic thrombocytopenic purpura.

Grape Fruit Juice

Taking grape fruit juice when taking statins can decrease the metabolism of statins. So patients who are taking a statin are advised not to take grapefruit juice.

Fibrates

Two fibrates are currently available in the United States: gemfibrozil and fenofibrate. Other fibrates that are available worldwide include bezafibrate and ciprofibrate. The mechanism of action of the fibric acid derivatives is complex and has not been completely elucidated. The major effect is a decrease in VLDL secondary to increased lipoprotein lipase activity; lipoprotein lipase hydrolyzes triglyceride from VLDL to form IDL, which is either removed by the B/E receptor through apo

E–mediated recognition and binding or collect more cholesterol esters from HDL to become LDL. The fibrates may also exert a peripheral effect by decreasing plasma levels of free fatty acids.

In addition to their effects on lipoprotein levels, fibric acid derivatives may alter the composition of lipoproteins. As noted above, gemfibrozil and bezafibrate have been shown to decrease the concentration of small, dense LDL. The fibrates may thus protect against coronary atherosclerosis not only by reducing LDL cholesterol level but also by shifting LDL particles to a less atherogenic phenotype.

Additionally, the fibric acid derivatives provide nonlipid benefits, such as improvements in coagulation and fibrinolysis. A reduction in platelet aggregability and reactivity in response to epinephrine has been documented with gemfibrozil. Gemfibrozil has also been shown to decrease the activity of PAI-1, thereby potentially improving fibrinolytic efficacy. Bezafibrate has been reported to decrease circulating levels of fibrinogen; fibrinogen has been directly associated with CAD risk in epidemiological studies

Adverse Effects

The side effects of the fibric acid derivatives are generally mild and are encountered in approximately 5–10% of patients treated with these agents. The majority of complaints are of nonspecific gastrointestinal symptoms such as nausea, flatulence, bloating, and dyspepsia.

Increased lithogenicity of bile has been reported with clofibrate therapy but has not been clearly demonstrated with the other fibrates. Fibrate monotherapy rarely results in muscle toxicity, although mild elevations of creatine kinase may occasionally occur. However, the risk for myopathy is increased when a fibrate is used in combination with an HMG-CoA reductase inhibitor, as described above. Although recent studies have demonstrated that this combination may be used without severe muscle toxicity, great caution is required, and careful patient education and surveillance are prerequisites.

Drug Interactions

An important drug interaction is that fenofibrate increases the clearance of cyclosporine. In one series of 43 heart transplant recipients, for example, fenofibrate therapy led to a 30% reduction in cyclosporine levels. Five of these patients had an episode of acute rejection that was associated with decrease in cyclosporine levels on the visit before the episode. A small elevation in the plasma creatinine concentration of 0.34 mg/dL (30 μmol/L), which did not become apparent for at least six months, was also noted. Fibrates are primarily excreted by the kidneys; therefore, the dosage and dosing interval should be reduced in patients with renal insufficiency to avoid myositis. The dosing of bezafibrate, for example, should be reduced with renal insufficiency. Bezafibrate, like other fibrates, interacts with warfarin. As a result, the warfarin dose should be reduced by 30% in patients treated with this drug.

Probucol

Probucol is a complex agent that cannot be readily classified with the other lipid-regulating drugs in terms of structure or mechanism of action. It is a bisphenol derivative that is similar in structure to butylated hydroxytoluene, a compound with powerful antioxidant activity that has also been demonstrated to decrease the early microcirculatory changes induced by hypercholesterolemia in rabbits.

The mechanism of action by which probucol lowers lipid levels has not been completely elucidated. Probucol does not appear to decrease the production of lipoproteins nor does it alter plasma clearance through the B/E receptor pathway.

Probucol dosed at 1 g/day decreases LDL cholesterol 5–15% and decreases HDL cholesterol 20–30%. Triglyceride is usually not affected. The effect on HDL cholesterol appears to be greater in patients with higher pretreatment levels of HDL cholesterol and is of concern because of the inverse relation between HDL cholesterol level and CAD incidence established in epidemiological studies.

The side effects of probucol appear to be minimal. Probucol is highly lipophilic, so its absorption is enhanced after a fatty meal; therefore, administration should be separated from meals to prevent drug toxicity. Mild gastrointestinal symptoms are occasionally reported. The main clinical concern with probucol use is the possible potentiation of rhythm disorders associated with prolongation of repolarization. In experimental animals, increased incidence of sudden cardiac death with probucol administration was thought to be caused by induced ventricular arrhythmias. Although no clear correlation between probucol use and sudden cardiac death has been established in humans, the Q-T interval should be monitored, especially in patients with baseline prolongation or receiving concomitant sotalol, quinidine, procainamide, tricyclic antidepressants, phenothiazines, or other agents known to increase the Q-T interval.

Bile Acid Sequestrants

Cholestyramine is a polymeric resin, administered orally to bind bile acids. Originally, cholestyramine was used to treat pruritis secondary to cholestasis, but its main use today is to treat hypercholesterolemia with concomitant hypertriglyceridemia. Cholestyramine also has been used to treat Clostridium difficile enterocolitis, although traditional antibiotics are more effective. Colestipol hydrochloride is an oral antilipemic agent. It is a nonabsorbable bile acid sequestrant similar in action to cholestyramine. Colestipol and cholestyramine appear to be equal in their cholesterol-lowering effects. Since the development and release of HMG-CoA-reductase inhibitors, colestipol's use has declined. Colestipol, however, is not absorbed and has a safer toxicity profile than do other antilipemics, thus making it a desirable agent in children and pregnant women. Colestipol was approved by the FDA in 1977.

By releasing chloride, colestipol combines with bile acids in the intestine to form insoluble, nonabsorbable complexes that are excreted in the feces along with unchanged resin. Since cholesterol is the major precursor of bile acids, the removal of bile acids from the enterohepatic circulation increases the catabolism of

cholesterol to form bile acids. The loss of bile acids stimulates a compensatory increase in the hepatic production of cholesterol. It is postulated that the increased hepatic production of cholesterol falls short of the amount lost, leading to a net decrease in circulating cholesterol. This effect, however, has not been clearly shown. It is likely that colestipol's cholesterol-lowering effect is related to increased catabolism of low-density lipoprotein (LDL). Clinically, colestipol lowers LDL and total cholesterol, but has little effect on HDL cholesterol. Triglycerides increase with colestipol therapy. Thus, colestipol is appropriate for type II hyperlipoproteinemia in patients without hypertriglyceridemia.

Colestipol can bind to substances other than bile acids, especially if they undergo enterohepatic recirculation as does digitoxin. While colestipol has been used clinically to accelerate the clearance of digitoxin in cases of toxicity, charcoal and Fab fragments are probably preferred agents for this use. Other agents that bind readily with colestipol include chenodiol, chlorothiazide, digoxin, fat-soluble vitamins, penicillin G, and tetracycline.

Pharmacokinetics

Since colestipol is not absorbed orally, serum concentrations and half-life parameters do not apply. Colestipol is not affected by digestive enzymes. It is eliminated in the stool. Reduction of the plasma cholesterol concentration usually is seen within 24–48 h of starting therapy, and maximum effects are achieved within 1 month.

Contraindications/Precautions

Colestipol is contraindicated in patients with cholelithiasis or complete biliary obstruction. In these conditions, secretion of bile acids into the GI tract is impaired. Colestipol is also contraindicated in patients with primary biliary cirrhosis since it can further raise serum cholesterol.

Colestipol is relatively contraindicated in constipated patients because of the danger of fecal impaction. Colestipol is relatively contraindicated in patients with coronary artery disease or hemorrhoids because constipation can aggravate these conditions.

Because colestipol can bind with vitamin K, colestipol is relatively contraindicated in patients with any preexisting bleeding disorder or coagulopathy (see Interactions).

Because colestipol can bind with exogenous thyroid hormones if administered simultaneously (see Interactions), colestipol is relatively contraindicated in patients with hypothyroidism.

Colestipol is relatively contraindicated in patients with renal disease because colestipol releases chloride, which can increase the risk of developing hyperchloremic metabolic acidosis.

It is unknown whether or not cholestipol causes fetal harm if taken during pregnancy. Adequate studies have not been done. Cholestipol should only be used during pregnancy if the potential benefits justify the potential added risk to the fetus.

Drug Interactions

Colestipol can bind with and possibly decrease the oral absorption of carbamazepine, thiazide diuretics, oral furosemide, oral penicillin G, propranolol, oral tetracyclines, orally administered vancomycin, and fat-soluble vitamins including vitamin A, vitamin D, and vitamin K or orally administered phytonadione. Colestipol can bind with and delay or prevent absorption of thyroid hormones including dextrothyroxine. Colestipol also can bind with ursodiol. Staggering the doses of these agents by several hours should prevent binding with colestipol.

Cholestyramine can decrease the serum concentrations of imipramine. While it is logical to conclude that staggering the times of administration may avoid this interaction, doing so did not prevent a similar interaction between cholestyramine and doxepin even when the doses were separated by 6 h. Until more data are available, clinicians should avoid using cholestyramine in patients stabilized on doxepin or imipramine.

Colestipol may affect the hypoprothrombinemic actions of warfarin. Colestipol can bind with vitamin K in the diet, impairing vitamin K absorption, which, in turn, may increase warfarin's hypoprothrombinemic effect. Conversely, colestipol can bind with warfarin directly and impair warfarin bioavailability, although the effects of colestipol on warfarin absorption are less pronounced than the ability of cholestyramine to bind with warfarin. To avoid altering warfarin pharmacokinetics, doses of warfarin and colestipol should be staggered by at least 4–6 h.

Colestipol should be prescribed cautiously to any patient receiving warfarin, although colestipol may be an acceptable alternative to cholestyramine in a patient receiving warfarin who also requires therapy with a bile acid sequesterant.

Colestipol can bind with digitoxin and enhance digitoxin clearance. Because digitoxin undergoes enterohepatic recirculation, staggering the administration times of each agent may not prevent this drug interaction. Colestipol should be used cautiously in patients receiving digitoxin.

Patients should be observed for loss of digitalis effect if colestipol is added or for digitalis toxicity if colestipol is discontinued in a patient stabilized on cardiac glycosides. Digoxin also may be similarly affected, albeit to a lesser degree since it undergoes less enterohepatic recirculation than digitoxin.

Cholestyramine has been shown to reduce the bioavailability of glipizide but appears to have no effect on tolbutamide absorption. The effect of cholestyramine on the bioavailability of other oral sulfonylureas is unknown.

Cholestyramine enhances the clearance of methotrexate from the systemic circulation. This interaction has actually been used therapeutically in patients with methotrexate toxicity, although activated charcoal is more effective.

Adverse Reactions

The most common adverse reactions to colestipol therapy are GI related. Constipation occurs in 10% of patients. It is usually mild and transient but can produce fecal impaction, requiring medical attention. Every effort should be made to avert possible constipation; the patient should be instructed to drink plenty of water and include additional fiber in the diet. Colestipol can worsen preexisting constipation or aggravate hemorrhoids. Bleeding hemorrhoids or blood in the stool occur infrequently and may result from severe constipation.

Other adverse GI reactions include abdominal pain, eructation, flatulence, nausea/vomiting, diarrhea, or steatorrhea.

There have been rare reports of cholelithiasis, cholecystitis, GI bleeding, or peptic ulcer. A causal effect has not been established.

Because colestipol can bind with and impair the absorption of dietary vitamin K, hypoprothrombinemia can occur.

Other adverse reactions have been reported with colestipol. Cardiovascular effects are rare such as angina and tachycardia. There have been infrequent reports of a hypersensitivity rash, with urticaria and dermatitis. Reports include musculoskeletal aches and pains in the extremities, joint pain and arthritis, and backache. Neurologic effects include headache and occasional reports of dizziness or lightheadedness, and insomnia. Other infrequent effects include anorexia, shortness of breath, and swelling of the hands or feet.

Niacin

Niacin, also known as vitamin B_3, has initially been used as a natural cholesterol-lowering agent that often rivals prescription drugs in mild-to-moderate cases. Three forms of niacin supplements, each with a specific therapeutic role, are commercially available: nicotinic acid (also called nicotinate), niacinamide, and inositol hexaniacinate, a compound ofniacin and inositol (another B-family vitamin).

Normally, enough niacin from foods is absorbed to carry out basic functions, working on the cellular level to keep the digestive system, skin, and nerves healthy. This vitamin is also critical to releasing energy from carbohydrates and helping to control blood sugar levels. Interestingly, niacin is also synthesized from tryptophan, an amino acid found in eggs, milk, and poultry.

In a recent study of people with high cholesterol, niacin not only reduced LDL and triglycerides by 17% and 18%, respectively, but it also increased HDL by 16%. Although both nicotinic acid and inositol hexaniacinate have cholesterol-benefiting actions, inositol hexaniacinate is the preferred form, it does not cause skin flushing and poses much less risk of liver damage with long-term use.

Niacin improves circulation by relaxing arteries and veins, and disorders characterized by circulation difficulties may benefit as a result. In those suffering from Raynaud's disease, for example, niacin's ability to improve blood flow to the

extremities may counter the numbness and pain in the hands and feet that occur when blood vessels overreact to cold temperatures. The calf-cramping and other painful symptoms of intermittent claudication, another circulation disorder, may lessen under the vessel-relaxing influence of niacin as well. The inositol hexaniacinate form of niacin works best for circulation-related discomforts.

Niacinamide can help treat osteoarthritis and rheumatoid arthritis, insulin-dependent diabetes, insomnia, and migraine headaches.

Precautions

High doses (75 mg or more) of niacin can cause side effects. The most common side effect is called "niacin flush." It is harmless unless with concurrent asthma; so people with asthma should not take niacin supplements at high dosages. At very high doses like those used to lower cholesterol, liver damage and gastroduodenal ulcers can occur. Patients with liver disease or gastric ulceration should not take niacin supplements.

Drug Interactions

Taking aspirin before taking niacin may reduce the flushing associated with niacin. However, large doses of aspirin may prolong the length of time of action.

Niacin binds bile acid sequestrants (cholesterol-lowering medications such as colestipol and cholestyramine) and may decrease their effectiveness; therefore, niacin and these medications should be taken at different times of the day.

When niacin is taken at the same time as another class of cholesterol-lowering medications, called HMG-CoA reductase inhibitors or statins, the likelihood for serious side effects, such as muscle inflammation or liver toxicity, is increased. In severe cases, kidney failure may occur.

Doses of niacin that are high enough to reduce cholesterol levels may raise blood sugar and lead to a loss of blood sugar control. However, one study suggests that niacin may actually benefit patients with recent onset of Type I diabetes. People taking insulin, metformin, glyburide, glipizide, or other similar medications used to treat high blood sugar levels should monitor their blood sugar levels closely.

Niacin should not be taken at the same time as tetracycline, an antibiotic, because it interferes with the absorption and effectiveness of this medication. Niacin either alone or in combination with other B vitamins should be taken at different times from tetracycline.

When niacin is taken with certain blood pressure medications (such as prazosin, doxazosin, and guanabenz), the likelihood of side effects from these medications is increased.

The use of nicotine patches with niacin may increase the chances of or worsen the flushing reactions associated with these supplements.

Ezetimibe

Ezetimibe is classified as a cholesterol absorption inhibitor which works by inhibiting the absorption of cholesterol in the brush border of the small intestine. This leads to decreased delivery of cholesterol to the liver and therefore decreased hepatic stores of cholesterol and increases overall clearance of cholesterol from the blood. Ezetimibe decreases LDL by 15–20%, increases HDL by about 5%, and has a negligible effect on TGs. Ezetimibe is available commercially in combination with simvastatin giving a potential reduction in LDL of up to 50%.

Contraindications/Precautions

Ezetimibe has been shown to cause myopathy, rarely leading to elevated serum creatine kinase.

Ezetimibe is a pregnancy category C but increases to pregnancy category X when combined with a statin.

Elevations in liver function tests three times the upper limit of normal have occurred with ezetimibe however is more common when coadministered with statins.

Adverse Effects

Adverse effects seen with ezetimibe include abdominal pain, diarrhea, back pain, arthralgia, fatigue, sinusitis, coughing, and pharyngitis.

Drug Interactions

Bile acid sequestrants may decrease the absorption of ezetimibe.

Cyclosporin may increase the serum concentrations of ezetimibe and also increase the AUC of cyclosporin. Concentrations of cyclosporine should be monitored if combination therapy is warranted.

Fibric acid derivatives may increase cholesterol secretion into the bile leading to cholelithiasis. Coadministration of ezetimibe with gemfibrozil is not recommended.

Omega-3 Fatty Acids

Omega-3 fatty acids through unknown mechanisms primarily decreases triglycerides by 30–50% and mostly available over-the-counter as fish oil; however, a prescription product which is regulated by the FDA is available. It may also enhance the antiplatelet effect of antiplatelet agents. Patients have to take 4 g daily and is usually available as a 1-g capsule. Omega-3 fatty acid is contraindicated in patients with a known fish allergy. ALT has been known to increase withour concurrent increase in AST.

Adverse effects include dyspepsia and taste perversion. It can also cause flu-like symptoms and infection. Omega-3 fatty acids can increase the prolongation of bleeding time in patients who are coadministered warfarin; therefore, INR should be monitored closely.

Bibliography

Antiarrhythmics

Vaughan-Williams, EM. A classification of antiarrhythmic action reassessed after a decade of new drugs. J Clin Pharmacol 1984; 24:129.

Members of the Sicilian Gambit. Antiarrhythmic therapy: A pathophysiological approach. Futura Publishing, Armonk, NY, 1994. p. 41.

Velebit, V, Podrid, PJ, Lown, B, Cohen, BH, et al. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982; 65:886.

The Cardiac Arrhythmia Suppression Trial Investigators (CAST). Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial arrhythmia suppression after myocardial infarction. New Engl J Med 1989; 10:406.

The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992; 327:227.

Pratt, CM, Camm, AJ, Cooper, W, et al, for the SWORD Investigators. Mortality in the Survival With Oral d-Sotalol (SWORD) trial: Why did patients die? Am J Cardiol 1998; 81:869.

Julian, DG, Camm, AJ, Frangin, G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997; 349:667.

Boutitie, F, Boissel, J-P, Connolly, SJ, et al, and the EMIAT and CAMIAT Investigators. Amiodarone Interaction with ß-blockers: Analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. Circulation 1999; 99:2268.

Kowey PR, Yan G and Crijns H. Antiarrythmic Drugs. In: Fuster, V (12th ed): Hurst's the heart. New York, NY; McGraw Hill.

Mitchell Brent. Ventricular Tachycardia. Merck Manual of Diagnosis and Therapy. 2008. Accessed on July 31, 2009.

Banai S, Tzivoni D. Drug therapy for torsades de pointes [Abstract]. J Cardiovasc Electrophysiol. 1993;4:206–10.

Wyse DG., Waldo AL., DiMarco JP. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–33.

Howard P. Ibutilide: an antiarrhythmic agent for the treatment of atrial fibrillation or flutter. Annals Pharmacother. 1999;33:38–47.

Kalus J, Mauro V. Dofetilide: a class III-specific antiarrythmic agent. Annals Pharmacother 2000;34:44–56.

Hohnloser SH, Crijns HJ, Van Eickels M et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med. 2009;360:668–78.

Touboul P, Brugada J, Capucci A et al. Dronedarone for prevention of atrial fibrillation: a dose ranging study. Eur Heart J. 2003;24(16):1481–7.

Antiarrythmic Agents. DRUGDEX® Evaluation. MICROMEDEX® Healthcare Series. © 1974–2009 Thomson Reuters. Available at http://www.thomsonhc.com/home/dispatch. Accessed July 30, 2009.

Antiarrhythmic Agents. Lexi-Drugs online. Lexi-Comp Inc. 1978–2009. Available at: http://www.crlonline.com/crlsql/servlvet/crlonline. Accessed on July 30,2009.

Antihypertension

Centrally Acting Agents

MacMillan, LB, Hein, L, Smith, MS, et al. Central hypotensive effects of the alpha-2a-adrenergic receptor subtype. Science 1996; 273:801.
Link, RE, Desai, K, Hein, L, et al. Cardiovascular regulation in mice lacking alpha-2 adrenergic receptor subtypes b and c. Science 1996; 273:803.
Hardman JG, Limbird LE. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, 2005; p.215–220.

Alpha-Blockers

Kasiske, BL, Ma, JZ, Kalil, RS, Louis, TA. Effects of antihypertensive therapy on serum lipids. Ann Intern Med 1995; 122:133.
Carruthers, G, Dessain, P, Fodor, G, et al. Comparative trial of doxazosin and atenolol on cardiovascular risk reduction in systemic hypertension. Am J Cardiol 1993; 71:575.
Levy, D, Walmsley, P, Levenstein, M, for the Hypertension and Lipid Trial Study Group. Principal results of the Hypertension and Lipid Trial (HALT): A multicenter study of doxazosin in patients with hypertension. Am Heart J 1996; 131:966.
Khouri, AF, Kaplan, NM. Alpha-blocker therapy of hypertension. JAMA 1991; 266:394.
Editorial. Alpha-blockade for hypertension: Indifferent past, uncertain future. Lancet 1989; 1:1055.
Materson, BJ, Reda, DJ, Cushman, WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. N Engl J Med 1993; 328:914.
Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. JAMA 2000; 283:1967.
Lasagna, L. Diuretics versus alpha-blockers for treatment of hypertension (editorial). JAMA 2000; 283:2013.
Hardman JG, Limbird LE. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, 2005; p.232–234; 879–883
Roehrborn CG. Efficacy and safety of once-daily alfuzosin in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a randomized, placebo-controlled trial. Urology 2001 Dec;58(6):953–9
MacDonald R; Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. Urology. 2005 Oct;66(4):780–8.

Beta-Blocking Agents

Dollery, CT, Frishman, WH, Cruickshank, JM. Current cardiovascular drugs, 1st ed, Current Science, London, 1993, p. 83.
Koch-Weser, J, Frishman, WH. beta-Adrenoceptor antagonists: new drugs and new indications. N Engl J Med 1981; 305:500.
Opie, LH. Drugs and the heart. Part 1. Beta blocking agents. Lancet 1980; 1:693.
Leibowitz, D. Sotalol: A novel beta blocker with class III antiarrhythmic activity. J Clin Pharmacol 1993; 33:508.

Laßnig E, Auer J, Berent R, Mayr H, Eber B. Beta-Blockers and Heart Failure. J Clin Basic Cardiol 2001;4:11–14.
Woosley, RL, Kornhauser, D, Smith, R, et al. Suppression of chronic ventricular arrhythmias with propranolol. Circulation 1979; 60:819.
Koch-Weser, J. Drug therapy: metoprolol. N Engl J Med 1979; 301:698.
Frishman, W. Acebutolol. Cardiovasc Rev Rep 1985; 6:979.
Dobbs, JH, Skoutakis, VA, Acchardio, SR, Dobbs, BR. Effects of aluminum hydroxide on the absorption of propranolol. Curr Ther Res 1977; 21:877.
Hibbard, DM, Peters, JR, Hunninghake, DB. Effects of cholestyramine and colestipol on the plasma concentrations of propranolol. Br J Clin Pharmacol 1984; 18:337.
Somogyi, A, Muirhead, M. Pharmacokinetic interactions of cimetidine 1987. Clin Pharmacokinet 1987; 12:321.
Feely, J, Wilkinson, GR, Wood, AJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med 1981; 304:692.
Zhou, HH, Anthony, LB, Roden, DM, Wood, AJ. Quinidine reduces clearance of (+)-propranolol more than (-)-propranolol through marked reduction in 4-hydroxylation. Clin Pharmacol Ther 1990; 47:686.
Hii, JT, Duff, HJ, Burgess, ED. Clinical pharmacokinetics of propafenone. Clin Pharmacokinet 1991; 21:1.
Vestal, RE, Kornhauser, DM, Hollifield, JW, Shand, DG. Inhibition of propranolol metabolism by chlorpromazine. Clin Pharmacol Ther 1979; 25:19.
Holtzman, JL, Kvam, DC, Berry, DA, et al. The pharmacodynamic and pharmacokinetic interaction of flecainide acetate with propranolol: Effects on cardiac function and drug clearance. Eur J Clin Pharmacol 1987; 33:97.
Branch, RA, Shand, DG, Wilkinson, GR, Nies, AS. The reduction of lidocaine clearance by dl-propranolol: An example of hemodynamic drug interaction. J Pharmacol Exp Ther 1973; 184:515.
Branch, RA, Shand, DG, Wilkinson, GR, Nies, AS. The reduction of lidocaine clearance by dl-propranolol: An example of hemodynamic drug interaction. J Pharmacol Exp Ther 1973; 184:515.
Ochs, HR, Carstens, G, Greenblatt, DJ. Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. N Engl J Med 1980; 303:373.
van Harten, J, van Brummelen, P, Lodewijks, MTM, et al. Pharmacokinetics and hemodynamic effects of nisoldipine and its interaction with cimetidine. Clin Pharmacol Ther 1988; 43:332.
Kirch, W, Kleinbloesem, CH, Belz, GG. Drug interactions with calcium antagonists. Pharmacol Ther 1990; 45:109.
Hardman JG, Limbird LE. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, 2005; p.227–232.

Nitroprusside

Cohn JN, et al. Nitroprusside. Ann Intern Med 1997;91:752–57
Merillon JP, Fontenier G, Lerallut JF, et al. Aortic input impedance in heart failure: Comparison with normal subjects and its changes during vasodilator therapy. Eur Heart J 1984; 5:447–455.
Yin FC, Guzman PA, Brin KP, et al. Effect of nitroprusside on hydraulic vascular loads on the right and left ventricle of patients with heart failure. Circulation 1983; 67:1330–1339.
Pepine CJ, Nichols WW, Curry Jr RC, Conti CR. Aortic input impedance during nitroprusside infusion. J Clin Invest 1979; 64:643–654.
duCailar J, Mathier-Daude JC, Kienlen J, Chardon P. Blood and urinary cyanide concentrations during long-term sodium nitroprusside infusions. Anesthesiology 1979; 51:363–364.
Ca-channel-blockers

Somogyi, A, Muirhead, M. Pharmacokinetic interactions of cimetidine 1987. Clin Pharmacokinet 1987; 12:321.
Bailey, DG, Arnold, MO, Munoz, C, Spence, JD. Grapefruit juice-felodipine interaction: Mechanism, predicability, and effect of naringin. Clin Pharmacol Ther 1993; 53:637.
Kirch, W, Kleinbloesem, CH, Belz, GG. Drug interactions with calcium antagonists. Pharmacol Ther 1990; 45:109.
Capewell, S, Freestone, S, Critchley, JAJH, et al. Reduced felodipine bioavailability in patients taking anticonvulsants. Lancet 1988; 2:480.
Dunselman, PH, Edgar, B. Felodipine clinical pharmacokinetics. Clin Pharmacokinet 1991; 21:418.
Lown, KS, Bailey, DG, Fontana, RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997; 99:2545.
Schwartz, JB, Upton, RA, Lin, ET, et al. Effect of cimetidine or ranitidine administration on nifedipine pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 1988; 43:673.
Howden, CW. Clinical pharmacology of omeprazole. Clin Pharmacokinet 1991; 20:38.
Soons, PA, van den Berg, G, Danhof, M, et al. Influence of single-and multiple-dose omeprazole treatment on nifedipine pharmacokinetics and effects in healthy subjects. Eur J Clin Pharmacol 1992; 42:319.
Muck, W, Wingender, W, Seiberling, M, et al. Influence of the H2-receptor antagonists cimetidine and ranitidine on the pharmacokinetics or nimodipine in healthy volunteers. Eur J Clin Pharmacol 1992; 42:325.
Friedel, HA, Sorkin, EM. Nisoldipine. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of angina pectoris, hypertension and related cardiovascular disorders. Drugs 1988; 36:682.
van Harten, J, van Brummelen, P, Lodewijks, MTM, et al. Pharmacokinetics and hemodynamic effects of nisoldipine and its interaction with cimetidine. Clin Pharmacol Ther 1988; 43:332.
Rutledge, DR, Pieper, JA, Mirvis, DM. Effects of chronic phenobarbital on verapamil disposition in humans. J Pharmacol Exp Ther 1988; 246:7.
Venkatesan, K. Pharmacokinetic drug interactions with rifampicin. Clin Pharmacokinet 1992; 22:47.
Lai, WT, Lee, CS, Wu, JC, et al. Effects of verapamil, propranolol, and procainamide on adenosine-induced negative dromotropism in human beings. Am Heart J 1996; 132:768.
Hardman JG, Limbird LE. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, 2005; p. 889–890.

ACE Inhibitors

Croog, SH, Levine, S, Testa, MA, et al. The effects of antihypertensive therapy on the quality of life. N Engl J Med 1986; 314:1657.
Boissel, JP, Collet, JP, Lion, L, et al. A randomized comparison of the effect of four antihypertensive monotherapies on the subjective quality of life in previously untreated asymptomatic patients: Field trial in general practice. J Hypertens 1995; 13:1059.
Kostis, JB, Shelton, B, Gosselin, G, et al. Adverse effects of enalapril in the studies of left ventricular dysfunction (SOLVD). Am Heart J 1996; 131:350.
Auer J, Berent R, Eber B. Long term ACE inhibitor therapy in patients with heart failure or left ventricular dysfunction. J Evidence–Based Healthcare 2001; 5:22–23.
Toto, RD, Mitchell, HC, Lee, H-C, et al. Reversible renal insufficiency due to angiotensin converting enzyme inhibitors in hypertensive nephrosclerosis. Ann Intern Med 1991; 115:513.
Rose, BD. Clinical Physiology of Acid-Base and Electrolyte Disorders, 4th ed, McGraw Hill, New York 1994.
Reardon, LS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. Arch Intern Med 1998; 158:26.

Textor, SC, Bravo, EL, Fouad, FM, Tarazi, RC. Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. Am J Med 1982; 73:719.
Israili, ZH, Hall, WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 1992; 117:234.
Brown, NJ, Snowden, RN, Griffin, MR. Recurrent angiotensin-converting enzyme inhibitor associated angioedema. JAMA 1997; 278:232.
Lip, GYH, Ferner, RE. Poisoning with anti-hypertensive drugs: Angiotensin converting enzyme inhibitors. J Hum Hypertens 1995; 9:711.
Hardman JG, Limbird LE. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, 2005; p. 893–95

AT-1-Antagonists

Burnier, M, Brunner, HR. Angiotensin II receptor antagonists. Lancet 2000; 35:637.
Grossman, E, Peleg, E, Carroll, J, et al. Hemodynamic and humoral effects of the angiotensin II Antagonist losartan in essential hypertension. Am J Hypertens 1994; 7:1041.
Kassler-Taub, K, Littlejohn, T, Elliott, W, et al, for the Irbesartan/Losartan Study Investigators. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. Am J Hypertens 1998; 11:445.
Andersson, OK, Neldam, S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan [see comments]. Blood Press 1998; 7:53.
Bakris, GL, Siomos, M, DeJuran, R, et al. ACE inhibition or angiotensin receptor blockade: Impact on potassium in renal failure. Kidney Int 2000; 58:2084.
Pitt, B, Poole-Wilson, PA, Segal, R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial the Losartan Heart Failure Survival Study ELITE II. Lancet 2000; 355:1582.
Goldberg, AI, Dunlay, MC, Sweet, CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. Am J Cardiol 1995; 75:793.
Faison, EP, Snavely, DB, Thiyagarajan, B, Nelson, EB. The incidence of cough with the angiotensin II receptor antagonist, losartan, is significantly less than with angiotensin converting enzyme inhibitors and is similar to that of placebo (abstract). Am J Hypertens 1994; 7:34A.
van Rijnsoever, EW, Kwee-Zuiderwijk, WJ, Feenstra, J. Angioneurotic edema attributed to the use of losartan. Arch Intern Med 1998; 158:2063.
Heeringa, M, Van Puijenbroek, EP. Reversible dysgeusia attributed to losartan (letter). Ann Intern Med 1998; 129:72.

Nitrates

DePace, NL, Herling, IH, Kotler, ML, et al. Intravenous nitroglycerin for rest angina. Potential pathophysiologic mechanisms of action. Arch Intern Med 1982; 142:1806.
Kaplan, K, Divison, R, Parker, M, et al. Intravenous nitroglycerin for treatment of unstable angina unresponsive to standard nitrate therapy. Am J Cardiol 1983; 51:694.
Karlberg KE, Saldeen T, Wallin R, et al. Intravenous nitroglycerin reduces ischaemia in unstable angina pectoris: a double-blind placebo-controlled study. J Intern Med 1998; 243:25.

Curfman, GD, Heinsimes, JA, Lozner, EC, Fung, HL. Intravenous nitroglycerin in the treatment of spontaneous angina pectoris: A prospective randomized trial. Circulation 1983; 67:276.
Horowitz, JD. Role of nitrates in unstable angina pectoris. Am J Cardiol 1992; 70:64B.
Winniford, MD, Kennedy, PL, Wells, PJ, Hillis, LD. Potentiation of nitroglycerin-induced coronary dilation by N-acetylcysteine. Circulation 1986; 73:138.
Packer, M, Lee, WH, Kessler, PD, et al. Prevention and reversal of nitrate tolerance in patients with congestive heart failure. N Engl J Med 1987; 317:799.
May, DC, Popma, JJ, Black, WH, et al. In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. N Engl J Med 1987; 317:805.
Horowitz, JD, Henry, CA, Syrjanen, ML, et al. Combined use of nitroglycerin and N-acetylcysteine in the management of unstable angina pectoris. Circulation 1988; 77:787.
Ardissino, D, Merlini, PA, Savonitto, S, et al. Effect of transdermal nitroglycerin or N-acetylcysteine, or both, in the long-term treatment of unstable angina pectoris. J Am Coll Cardiol 1997; 29:941
Jackson G. Erectile dysfunction and cardiovascular disease. Int J Clin Pract. 1999;53:363–8
DeBusk R, Drory Y, Goldstein I, Jackson G, Kaul S, Kimmel SE, Kostis JB, Kloner RA, Lakin M, Meston CM, Mittleman M, Muller JE, Padma-Nathan H, Rosen RC, Stein RA, Zusman R. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of The Princeton Consensus Panel. Am J Cardiol 2000;86:175–81.
Abrams, Jonathan. Chronic stable angina. N Engl J Med. 2005;352:2524–33.
Finh, Stephan D.; Williams, Sankey V.; Daley, Jennifer; et al. Guidelines for the managements of patients with chronic stable angina: treatment. Ann Intern Med. 2001;135:616–632.
Jain A, Wadehra V, Timmis AD. Management of stable angina. Postgrad Med J. 2003;79:332–6.
Nitroglycerine. Lexi-Drugs online. Lexi-Comp Inc. 1978–2009. Available at: http://www.crlonline.com/crlsql/servlvet/crlonline. Accessed July 30, 2009.
Parker JD, Parker JO . Nitrate therapy for stable angina pectoris. N Engl J Med. 1998;338:520–31.
Sander, GE; Giles, TD. Medical management of myocardial ischemia. Am J Geriatr Cardiol. 2005;14:205–9.
Watanabe H, Kakihana M, Ohtsuka S et al. Randomized, double-blind, placebo-controlled study of supplemental vitamin E on attenuation of the development of nitrate tolerance. Circulation. 1997;96:2545–50.

Diuretics

Bronner, F. Renal calcium transport: Mechanisms and regulation An overview. Am J Physiol 1989; 257:F707.
Batlle, DC, von Riotte, AB, Gaviria, M, Grupp, M. Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med 1985; 312:408.
Leaf, A, Schwartz, WB, Relman, AS. Oral administration of a potent carbonic anhydrase inhibitor ("Diamox"). I. Changes in electrolyte and acid-base balance. N Engl J Med 1954; 250:759.
Padilla MCA, Armas_Hernandez MJ, Hernandez RH et al. Update of diuretics on the treatment of hypertension. Am J Ther 2007; (2) 154–60
Rose, BD. Diuretics. Kidney Int 1991; 39:336.

Anti-Hemostatic Drugs

Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA. 2009;301(9):937–44.
Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs. Chest. 2008;133:199 S-233 S.

Dyslipidemia

Athyros, VG, Papageorgiou, AA, Hatzikonstandinou, HA, et al. Safety and efficacy of long-term statin-fibrate combination in patients with refractory familial combined hyperlipidemia. Am J Cardiol 1997; 80:608.

Auer J, Berent R, Eber B. Focus on statins: Lipid lowering mechanisms and beyond. Preventive Cardiol 2001;4:89–92.

Auer J, Berent R, Eber B. Lessons learned from trials with statins. Clin Card 2001;24:277–280.

Auer J, Eber B. Current aspects of statins. J Clin Basic Cardiol 1999;2:203–8.

Bakker-Arkema, RG, Davidson, MH, Goldstein, RJ, et al. Efficacy and safety of a new HMG CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. JAMA 1996; 276:128.

Boissonnat, P, Salen, P, Guidollet, J, et al. The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. Transplantation 1994; 58:245.

Borders-Hemphill, Vicky. Concurrent use of statins and amiodarone. Consult. Pharm 2009;24(5) 372–9

Brown, AS, Bakker-Arkema, RG, Yellen, L, et al. Treating patients with documented atherosclerosis to National Cholesterol Education Program-recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin. J Am Coll Cardiol 1998; 32:665.

Brown, G, Albers, JJ, Fisher, LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990; 323:1289.

Dart, A, Jerums, G, Nicholson, G, et al. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. Am J Cardiol 1997; 80:39.

Frishman WH, Horn J. Statin-drug interactions: not a class effect. Cardiol Rev. 2008 (16);205–212

Grundy, SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. N Engl J Med 1988; 319:24.

Larsen, ML, Illingworth, DR. Drug treatment of dyslipoproteinemia. Med Clin North Am 1994; 78:225.

Monk, JP, Todd, JP. Bezafibrate: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hyperlipidaemia. Drugs 1987; 33:539.

Pierce, LR, Wysowski, DK, Gross, TP. Myopathy and rhabdomyolysis with lovastatin-gemfibrozil combination therapy. JAMA 1990; 264:71.

Ray GM. Antiretroviral and statin drug-drug interactions. Cardiol Rev. 2009(17)1;44–7

Rosenson, RS, Frauenheim, WA. Safety of combined pravastatin-gemfibrozil therapy. Am J Cardiol 1994; 74:499.

Schmassmann-Suhijar, D, Bullingham, R, Gasser, R, et al. Rhabdomyolysis due to interaction of simvastatin with mibefradil. Lancet 1998; 351:1929.

Part IV
Antibiotics

Chapter 10
Antimicrobial Drugs

Amanda J. Jenkins and Jimmie L. Valentine

Abstract Infectious disease may be defined as a disease that is transmissible or likely to spread [1]. In industrial Europe, diseases such as tuberculosis (TB) were scourges, and doctors and scientists of the day concentrated their efforts to treat and understand these illnesses. In modern times, the types of infectious disease affecting the human population may have changed due to the eradication of diseases such as small pox, but these diseases still result in significant morbidity and mortality worldwide [2]. In this chapter, we describe most infectious diseases affecting the Western world, with current treatment and antimicrobial options. Thereafter, we discuss the classification, pharmacokinetics, metabolism, drug and herbal interactions, assays, and forensic implications of the antimicrobials.

Keywords Meningitis • Antimicrobial • *Escherichia coli*

Bacterial and Viral Meningitis

Meningitis is an infection of the arachnoid matter in the brain and cerebrospinal fluid (CSF) present in the subarachnoid space [3]. Once the infection has broken through the protective meninges membranes, it may be rapidly spread throughout the brain by the CSF. If the infection spreads into the brain it may result in a condition known as meningoencephalitis. Meningitis is generally classified into bacterial or viral, although a third category, chronic meningitis, may also be used. Bacterial meningitis or acute pyogenic meningitis is usually caused by bacteria such as *Escherichia coli*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *pneumococcus*. *E. coli* is usually the cause of the infection in the neonate, with *H. influenzae* the

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culprit in infants and young children. *N. meningitidis* is often the cause of disease in teenagers and young adults and is most often responsible for the spread of the disease since it may be transmitted through the air. Clinically, patients present with fever, headache, sensitivity to light, stiff neck, and irritability. Approximately 10–15% of cases are fatal [4]. A spinal tap yields cloudy CSF. Determination of lactic acid in CSF may help in differentiating bacterial from viral meningitis since lactic acid is increased in bacterial but not viral meningitis [5]. Diagnosis of bacterial meningitis is also aided by proper lumbar puncture and laboratory evaluations of glucose (blood: CSF <4), WBC count >500/μL, and lactate level >32 mg/dL [6]. Treatment is with antibiotics such as aminoglycosides, cephalosporins, chloramphenicol, penicillins, and tetracyclines. Many bacteria associated with meningitis produce beta-lactamase and thereby inactivate most penicillins and cephalosporins. The carbapenem class of drugs can be uniquely utilized for such bacteria [7]. Appropriate antibiotic therapy reduces the risk of death to less than 15%. However, even with treatment, a possible complication of recovery may be hydrocephalus. This development is most common with pneumococcal meningitis. In the immunosuppressed patient, diagnosis may be more difficult as other bacteria may cause the disease, and the patient may present with atypical CSF findings.

The causative agent in viral or lymphatic meningitis may not be identified, but approximately 90% of cases are caused by enteroviruses such as coxsackieviruses. Common viruses include herpes simplex type II, mumps, and Epstein-Barr virus. Clinical presentation is similar to bacterial meningitis but the course is generally less severe. Acute viral meningitis is the most common infection of the central nervous system (CNS), and most cases occur in young adults and children due to enteroviruses [8].

Chronic Meningitis

This form of meningitis is usually defined as persistence of clinical symptoms and signs of meningitis with or without abnormal CSF that occur for more than 4 weeks [9]. One cause of chronic meningitis may be *Mycobacterium tuberculosis*. In these cases, the meninges are filled with a gelatin- or fibrous-like substance. Clinically, an individual may present with symptoms of lethargy, headache, vomiting, and mental confusion. One complication of this form of meningitis is that the long-term inflammatory reaction in the subarachnoid space may produce endarteritis which may result in an infarction.

Escherichia coli

Escherichia coli (*E. coli*) is a bacterium with many strains. The majority of strains pose little danger to humans, but one strain, *E. coli* serotype O157:H7, is a major cause of foodborne illness [10]. It is a Gram-negative rod-shaped bacterium producing Shiga toxin. Diagnosis is by detection of the bacterium in the feces. There are

approximately 73,000 cases annually in the USA. The major source of the bacterium in industrialized countries is ground beef, but other sources include unpasteurized milk and juice. The bacterium is waterborne, with transmission occurring by drinking contaminated water or contact with contaminated lakes, ponds, and swimming pools. Clinically, *E. coli* produces bloody diarrhea and abdominal cramps with little fever. Occasionally no symptoms result from the infection. Resolution may take 5–10 days. In some individuals infection with this strain may cause a hemolytic uremic syndrome resulting in destruction of red blood cells and kidney failure. This complication occurs at a frequency of 2–7%.

Most people do not require treatment, and there is no evidence that antibiotic treatment improves the course of the illness. If antibiotic treatment is provided, common antibiotics include aminoglycosides, fluoroquinolones, penicillins, sulfonamides, and trimethoprim-sulfamethoxazole.

Hemolytic uremic syndrome is life threatening and requires intensive medical care. Long-term consequences of *E. coli* infection are related to the severe uremic complication. Approximately 30% of individuals who develop this syndrome will have kidney disease in later years.

Other strains of *E. coli* also produce disease and are referred to as diarrheagenic or non-Shiga toxin producing *E. coli*. These serotypes are classified into four groups, namely enterotoxigenic (ETEC), enteropathogenic, enteroinvasive, and enteroaggregative [11]. The incidence of these strains causing disease is unknown since most laboratories do not have the ability to identify the organisms, although some technologies such as gene ontologies [12], selection reaction monitoring (SRM) mass spectrometry [13], sequential peptide affinity (SPF) [14], and other molecular biology-based techniques hold some promise. Clinical symptoms include watery or bloody diarrhea, abdominal cramps with or without fever, chills, loss of appetite, and muscle aches. ETEC is the main cause of traveler's diarrhea. It is also transmitted by contaminated food or water. As with Shiga toxin *E. coli*, treatment is usually supportive. ETEC may be resistant to antibiotics such as trimethoprim/sulfamethoxazole and ampicillin. Fluoroquinolones may be effective treatment.

Streptococcal Disease (Group A and B)

Group A *streptococcus* is a bacterium found in the throat and skin. Infections are known as "strep throat." Although a relatively mild disease, these microorganisms may cause more severe illness to spread through direct contact with mucous of an infected person. Treatment with antibiotics such as macrolides, penicillins, quinolones, quinupristin/dalfopristin, teicoplanin, and tetracyclines is effective. Symptoms range from no illness to severe with necrotizing faciitis and toxic shock syndrome (TSS). These latter conditions are known as invasive Group A streptococcal disease. There were approximately 9,400 cases of invasive disease in the USA in 1999 [15]. Invasive disease results when bacteria enter areas of the body where they are usually absent. Necrotizing faciitis describes the destruction of muscle and skin tissue.

Early symptoms include fever, pain, and redness. Treatment may involve surgery to remove necrosed tissue. Streptococcal toxic shock syndrome results in a rapid decrease in blood pressure and organ failure. Signs include shock, fever, dizziness, and confusion. Approximately 20% of individuals with necrotizing faciitis and more than 50% of toxic shock syndrome patients die [16].

If an individual becomes sensitized to streptococcal antigens, rheumatic fever may result. This is a systemic, nonsuppurative inflammatory disease [3]. This disease affects the joints, lungs, blood vessels, and the heart. Although an individual may acquire this disease at any age, more than 90% of cases occur between the ages of 5 and 15 years [3]. Treatment with antibiotics has reduced the death rate significantly over the last 50 years. Deaths caused by this disease are due to heart damage with involvement of the heart valves.

Group B *streptococcus* (GBS) is a bacterium that may cause illness especially in the young and elderly. It is the cause of the most common life-threatening infections in newborn babies, such as sepsis, meningitis, and pneumonia. In pregnant women the most common infections include sepsis, amnionitis, and urinary tract infections [17]. In other adults, blood, skin or soft tissue infections, and pneumonia result from exposure to this bacterium. The bacteria may be transmitted from the gastrointestinal and genital tracts intrapartum. The mode of transmission in nonpregnant adults is not known. The United States Center for Disease Control (CDC) and Prevention found a total of 19,512 cases of GBS in nonpregnant adults between 1990 and 2007 and diabetes was an underlying finding in 44% of these patients [18]. Approximately 17,000 cases occur annually in the USA [19]. About 16% of adults and 5% of infants with the infection die. Long-term effects may include children with learning problems and hearing and sight loss due to meningitis. Elderly adults are particularly susceptible to the disease and have a high rate of mortality [20]. Treatment is with antibiotics such as penicillin or ampicillin which may be administered intravenously.

Haemophilus influenzae

Haemophilus influenzae is a Gram-negative coccobacillus. The bacterium enters the human body through the nasopharynx. The bacteria may colonize and remain for months without causing any symptoms. In some individuals, however, the organism causes an invasive infection. The mode of transmission to the blood is unknown but may result in meningitis, epiglottitis, pneumonia, arthritis, and cellulitis [21]. Between 2% and 5% of people die with invasive *Haemophilus influenzae* disease. Diagnosis should include serotyping a culture since type b is the only form preventable by vaccine. Antimicrobial therapy usually involves 10–14 days of treatment with chloramphenicol or a cephalosporin such as cefotaxime [22]. Other drugs which have been utilized in therapy include bacitracin, penicillins, chloramphenicol, macrolides, quinolones, rifampin, sulfonamides, tetracyclines, and trimethoprim/sulfamethoxazole. Strains of *Haemophilus influenzae* resistant to ampicillin are common throughout the USA, and therefore this medication should be avoided.

Hepatitis

Several hepatitis-causing viruses are known, including A, B, C, D, and E. Clinically, patients present with symptoms such as fever, lethargy, nausea, loss of appetite, abdominal pain, and jaundice. The course of disease caused by viral infection of the liver is categorized into several clinical syndromes, namely, the carrier state, acute hepatitis, chronic hepatitis, and fulminant hepatitis [3]. The latter results in massive necrosis of the liver and is primarily associated with hepatitis B virus (HBV).

Hepatitis A virus (HAV) is an RNA picornavirus which may result in infection in humans after an incubation period of 15–50 days [23]. The probability of symptoms is age dependent with >70% of infections in young children being asymptomatic. Jaundice is a frequent symptom in adults. Illness may last for about 2 months, although some individuals have prolonged or relapsing illness up to 6 months. The virus replicates in the liver and is excreted in the feces of an infected individual. A person is most likely to transmit the disease in the 2-week period before the onset of jaundice. The disease is transmitted by the fecal–oral route and more rarely by transfusion with blood collected from an infected person. Hepatitis A is diagnosed by identification of IgM-anti-Hepatitis A antibody, as it cannot be clinically differentiated from other types of viral hepatitis. Approximately 100 people die per year in the USA as a result of liver failure from hepatitis A. A vaccine is available for prophylaxis and may also be administered within 2 weeks after contact with an HAV infected person.

Hepatitis B virus (HBV), the most well-known hepatitis-causing virus has a core of double-stranded DNA. It is estimated that more than one million people in the USA who have chronic HBV infection are potentially infectious [24]. Immunization is the most effective prevention. Transmission is typically by the percutaneous route, blood and blood products, hypodermic needles, dental, and surgical instruments [3]. The virus is present in semen, menstrual blood, urine, and feces [3]. Like HAV, diagnosis is made by identification of specific serum markers. The incubation period of HBV ranges from 1 to 6 months and the individual antigen and antibody titers vary throughout the course of the disease. For example, when the patient is asymptomatic, markers such as HbsAg are detected but as symptoms appear anti-Hbe and anti-HBs are measured.

Hepatitis C virus (HCV) is an RNA virus which has infected an estimated four million Americans [25]. HCV is diagnosed by identification of anti-HCV, typically by immunoassay followed by specific confirmation by immunoblot assay. Alternatively RNA gene amplification techniques may be utilized. Many people with acute HCV are asymptomatic. Less than 30% develop jaundice. Progression to chronic liver disease may take many years after exposure. Cirrhosis may occur in 10–20% of individuals with chronic HCV. Standard of care for patients with chronic HCV is pegylated interferon (peg-IFN) combined with weight-based dosing of ribavirin [26]. An emerging therapy for chronic HCV is using the prodrug of ribavirin, viramidine, that is taken up by hepatocytes and converted into ribavirin in situ [27].

Hepatitis D virus (HDV) is a single-stranded RNA virus that requires the presence of HBV to replicate. Infection may be acquired with HBV or as a superinfection in individuals with chronic HBV infection [28]. The former category of individuals generally develop more severe acute disease and are at greater risk of developing fulminant hepatitis than the latter. Transmission of HDV is similar to the other viruses, although sexual transmission appears to be less efficient than for HBV. The type of antibodies detected in the serum of infected individuals is dependent on whether the virus has been acquired as a co-infection with HBV. In people who are co-infected, both IgM anti-HDV and IgG anti-HDV are detected. Hepatitis Delta antigen can be detected in serum in only about 25% of patients with HDV–HBV infection. Although not always effective, interferon-alfa and peg-IFN are the current method of treatment [29, 30].

Hepatitis E virus (HEV) is a spherical single-stranded RNA virus that is the major cause of non-A, non-B hepatitis. HEV is now established as a major cause for sporadic cases as well as epidemics of hepatitis and has become the most frequently isolated hepatitis virus transmitted through food and water [31]. The incubation period is 15–60 days after HEV exposure. Although symptoms of HEV exposure are similar to other types of viral hepatitis, less common symptoms include diarrhea and an urticarial rash. There is no evidence of chronic infection with HEV. IgM and IgG anti-HEV are produced after HEV infection. Currently there are no commercially available tests to identify HEV in the USA, although serologic tests using enzyme immunoassays and Western Blot techniques as well as viral genotyping are utilized in research laboratories. Transmission of this virus is mainly by the fecal–oral route. Person-to-person transmission is relatively rare with this hepatitis virus [32].

Herpes

Herpes simplex virus (*HSV*) type I causes an oral infection, known as "fever blisters" [33]. Herpes simplex type II is commonly associated with herpes genitalis and is one of the most common sexually transmitted diseases (STD) in the world [34] and is caused by *HSV* II in approximately 80% of cases. Two forms are recognized clinically (primary and recurrent), but both forms result in vesicular and ulcerative lesions. The initial infection is associated with more numerous painful lesions, fever, and headache due to lack of immunity. Recurrent lesions tend to be less severe and less far-reaching with little systemic illness [35]. Transmission to neonates is possible in infected pregnant women. If a woman is infected near the time of delivery, there is a 1:2 likelihood of the newborn developing neonatal herpes [3]. This disease is potentially fatal due to the resulting generalized severe encephalitis. Other diseases caused by the *HSV* include HSV I encephalitis resulting in hemorrhagic necrosis, and herpetic viral meningitis (HSV II). A commercial ELISA test is available to screen for both HSV I and II, and confirmation is performed by viral cultures using monoclonal antibodies and/or PCR for HSV II DNA.

There is no cure for genital herpes, but antimicrobial treatments such as acyclovir, dicofovir, docosanol, famiciclovir, fomivirsen, foscarnet, ganciclovir, idoxuridine, penciclovir, trifuridine, valacyclovir, valganciclovir, and vidarabine can prevent and shorten recurrent episodes.

Legionnaires' Disease

Legionellosis is a disease caused by the bacterium *Legionella pneumophilia* which is found in water systems. The infection may present as Legionnaires' disease (LD) or Pontiac fever (PF). The former is the more severe form that is characterized by pneumonia, fever, chills, and cough, whereas Pontiac fever presents as an acute flu-like illness with fever and muscle aches. Other Legionella species may also cause these conditions, but in the USA more than 90% of cases are caused by *L. pneumophilia* [36]. Less than 20,000 cases of Legionnaires' disease and Pontiac fever occur each year in the USA, but 5–15% of LD cases are fatal. Person-to-person transmission does not occur and infection is caused by inhalation of contaminated aerosols. Pontiac fever generally does not require treatment as individuals usually recover in a few days. LD may be effectively treated with erythromycin. Rifampin may be co-administered in severe cases. Preferred drugs for LD are doxycycline, second-generation macrolides, telithromycin, or quinolones [37].

Salmonellosis

The estimated incidence of salmonellosis is about 1.4 million cases per year in the USA, with about 500 fatalities [38]. Salmonellosis is an infection caused by the Gram-negative bacterium Salmonella. This bacterium includes three species, *S. typhi*, *S. cholerae-suis*, and *S. enteriditis*. The bacteria are transmitted to humans by eating food contaminated with the organism, usually from animal feces. There are several distinct clinical syndromes caused by this bacterium. The most severe is typhoid fever which is caused exclusively by *S. typhi*. Other conditions include gastroenteritis; bacteremia; enteric fevers; localized infections in bones, joints, etc.; and asymptomatic carriers. Gastroenteritis is the most common form of infection and involves fever, diarrhea, and abdominal cramps. The illness resolves in 4–7 days and most individuals recover without treatment, providing dehydration is prevented. Antibiotics are not usually necessary unless the infection extends beyond the intestinal tract. Ampicillin, gentamicin, trimethoprim/sulfamethoxazole, or ciprofloxacin may be administered. Other medications include aminopenicillins, chloramphenicol, fluoroquinolones, polymixin B, and the tetracyclines. Clinical signs of typhoid fever include lethargy, fever with bacteremic chills, and abdominal pain. By the second week the spleen enlarges and a rash may appear. The fever is now persistent. If untreated, the fever is accompanied by confusion and delirium by the third week of the disease. Complications include infective endocarditis and intestinal hemorrhage and perforation [3].

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is caused by a bacterium, *Staphylococcus aureus*. In the USA, the incidence of this illness is 1–2/100,000 women 15–44 years of age [39]. This organism flourishes in skin and mucous membranes. It has been associated with the use of tampons and barrier contraceptive devices. It may also occur as a complication of surgery or abscesses. Symptoms include rash, fever, diarrhea, and muscle pains. More serious symptoms include hypotension and multisystem failure. Approximately 5% of TSS cases result in death. Treatment includes an antibiotic regimen using drugs such as the macrolides, penicillin G, quinolones, quinupristin/dalfopristin, teicoplanin, or the tetracyclines.

Tuberculosis

In 2000, there were at least 16,000 reported TB cases in the USA [40]. Tuberculosis (TB) is a chronic granulomatous disease caused by the bacterium *Mycobacterium tuberculosis* [3]. The bacteria may infect any part of the body but typically involves the lungs. Most infections are acquired by direct transmission of airborne droplets of organisms from an individual with active TB by inhalation to another. After exposure, most people are able to resist disease and the bacteria become inactive, but viable organisms may remain dormant in the lungs for many years. This is called latent TB infection [3]. These individuals have no symptoms, do not have active disease, and therefore cannot transmit the organisms to other people. However, they may develop disease if untreated. TB disease occurs when the immune system is unable to prevent the bacteria from multiplying. People with weak immune systems are susceptible to development of the disease. These include individuals with HIV, diabetes mellitus, silicosis, substance abuse, severe kidney disease, or leukemia. Symptoms depend on the area of the body where the bacteria are growing. In the lungs, the individual may develop cough (and may cough up blood) and pain in the chest. Other symptoms include weight loss, weakness or fatigue, chills, fever, and night sweats. TB may be treated with several drugs including amikacin, aminosalicylic acid, capreomycin, cycloserine, ethambutol, ethionamide, isoniazid, kanamycin, pyrazinamide, rifampin, and streptomycin. The most common drugs used to treat this communicable disease are isoniazid (INH), rifampin, ethambutol, pyrazinamide, and streptomycin. Treatment usually involves taking multiple medications.

Classification of Antimicrobials

There have been a number of attempts to classify antibiotics or antivirals based upon both chemical structure [41] and mechanism of action [42, 43]. The former method fails with regard to many of the newer antibiotics and antivirals, whereas the latter

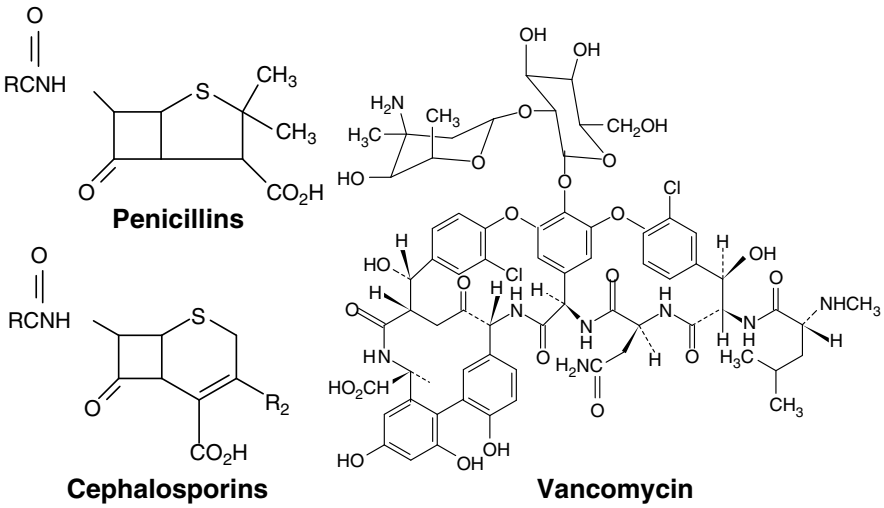

Fig. 10.1

type of classification system based on mechanism of action is sometimes deficient because the mechanism of action of all antibiotics is not clearly elucidated. The antivirals are different, but like the antibiotics their purpose is to disrupt the normal physiological status of the parasitic organism (a virus, in the case of antivirals). Thus, the best method for classifying antimicrobials (a term used here to include both antibiotics and antivirals) combines elements of both types of classification. This can be illustrated in Fig. 10.1 that shows antibiotics that inhibit bacterial cell wall synthesis (the mechanism of action) may have both similar and dissimilar chemical structures. For example, the penicillins and cephalosporins, with their common beta-lactam ring, have similar chemical structures while vancomycin is dissimilar, yet all have a mode of action that involves inhibition of bacterial cell wall synthesis. Table 10.1 lists the major classifications of antimicrobials with regard to chemical structure and/or mechanism of action.

Pharmacokinetics of Antimicrobials

Classical pharmacokinetics of therapeutic drugs describes the rate of absorption, distribution, and elimination following drug administration. Antimicrobials, however, must be considered differently than most therapeutic drugs since, although the host is administered the drug, the microbe must also absorb, distribute, and eliminate the drug, at a rate that is usually independent of the host. For many therapeutic drugs where absorption is comparable, the observed pharmacological effects can be correlated with the rate drug is removed from the central compartment

Table 10.1 Classification of antimicrobial agents

Classification – mechanism of action	Classification – chemical structure	Examples
Inhibit bacterial cell wall synthesis	Beta-lactams; azoles	Penicillins, cephalosporins, vancomycin, cycloserine, bacitracin, azole antifungals (clotrimazole, fluconazole, itraconazole, ketoconazole)
Affect permeability of bacterial cell membrane and lead to leakage of intracellular compounds	Detergents, polyenes	Polymyxin, polyene antifungals (nystatin, amphotericin B)
Affect the function of 30-S and 50-S ribosomal subunits causing a reversible inhibition of protein synthesis	Macrolides, tetracyclines	Chloramphenicol, tetracyclines, macrolides (erythromycin, clarithromycin, azithromycin) clindamycin, pristinamycins (quinupristin/dalfopristin)
Binding to 30-S ribosomal subunit altering protein synthesis leading to bacterial cell death	Aminoglycosides	Aminoglycosides (gentamicin, tobramycin, kanamycin, streptomycin), spectinomycin
Inhibit bacterial nucleic acid metabolism via inhibition of polymerase (*rifamycins*) or topoisomerases (*quinolones*)	Rifamycins, quinolones	Rifamycins (rifampin, rifabutin, rifapentine), quinolones
Antimetabolites – blocking essential enzymes of bacterial folate metabolism	Sulfonamides	Trimethoprim/sulfameth-oxazole, sulfonamides
Antivirals –	Pyridine nucleosides	
Type 1 – Nucleic acid analogs that inhibit viral DNA		
(a) Polymerase		Acyclovir, ganciclovir
(b) Reverse transcriptase		Zidovudine, lamivudine
Type 2 – Nonnucleoside reverse transcriptase inhibitors		Nevirapine, efavirenz, delavirdine
Type 3 – Inhibitors of essential viral enzymes, e.g.		
(a) HIV protease		Saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir
(b fluenza neuraminidase		Amantadine, rimantadine, zanamivir

(systemic circulation) through processes of metabolism, re-distribution, or elimination. This is the basis for performing therapeutic monitoring and adjusting a patient's dose based upon a determination of the drug or a metabolite in a physiological fluid that can describe what is happening in the central compartment. An example is digoxin, whose blood level can be measured and a therapeutic range established that should produce the desired effect, i.e., increase the strength of contractility in the failing heart, without producing the toxic effect of arrhythmia. In contrast, the observed pharmacological effect with an antimicrobial depends upon the parasite

(microbe) suffering a toxic effect such as inhibition of growth or cellular disruption without concurrent toxic effects to the host, not just disappearance from the central compartment of the host. Thus, it often becomes difficult to equate the experimentally determined pharmacokinetics of an antibiotic with a therapeutic response. Rather, therapeutic monitoring of antimicrobials is more often done to prevent a toxic response in the host. For example, monitoring the peak and trough levels of aminoglycosides to prevent oto- or nephro-toxicity in the host. A typical clinical protocol utilizes two serum concentrations to define the therapeutic range to prevent the known toxicities. A so-called peak level is obtained 30 min following dosing and a "trough" level determined 30 min prior to the next dose. For gentamicin, these levels should be in the range of 6–10 μg/mL for the peak level and 0.5–2 μg/mL for the trough level. For such levels to be meaningful, they should be drawn when the drug is near a steady-state concentration, usually after three or more doses.

Host–Parasite Considerations

Coupled with the host–parasite pharmacokinetic descriptions, the phagocytic complex produced by the immune response of the patient (host) toward the parasite must also be considered. That is, once an immune response is mobilized by the host in response to a parasitic invasion, will the antimicrobial agent be absorbed by the phagocytic complex and will its typical mechanism of action be operative within the complex? In short, the answer to this question is that antimicrobial agents work in concert with the immune system as evidenced by the fact that a person that is immune compromised will often not respond in the desired manner to antimicrobial therapy. This is indirect evidence that antimicrobials penetrate phagocytes and augment destruction of the microorganism. Some direct evidence also exists that antibiotics are absorbed into phagocytes. Tulkens [44] discussed evidence that beta-lactams diffuse into but do not accumulate in phagocytes because of their acidic character and aminoglycosides being too polar to readily cross membranes are taken up slowly by endocytosis resulting exclusively in lysosomal localization. This investigator also discussed licosaminides, macrolides, and fluoroquinolones that accumulate in phagocytes, with the two former antibiotics exhibiting accumulation in both cytosolic and lysosomal localization, whereas the fluoroquinolones appear to be entirely soluble in bacterial cells. Using a Staphylococcus aureus-infected line of macrophages the author was able to demonstrate that the macrolides and to a greater extent the fluoroquinolones reduced the original inoculum.

Another factor that must be considered is the presentation of the antimicrobial agent to the loci of infection. Such sites of infection might occur in soft tissues, joints, or bones that have limited blood perfusion. Similarly, the central nervous system (CNS) has limited availability to most antimicrobials due to the blood–brain barrier. Some of the antimicrobials exist as anions at physiological pH and are actively transported out of the CNS following passive diffusion into the CNS. Thus

the net concentration gradient favors passage of the antibiotic out of the CNS. With an inflamed meninges passive diffusion of many antimicrobials into the CNS occurs at an increased rate shifting the net concentration gradient in favor of agent into the CNS. But as the CNS infection is arrested, the gradient in the opposite direction is restored. With such inaccessible sites, successful therapy will depend upon achieving what is referred to as the minimum inhibitory concentration, the so-called MIC. The concept of MIC relates to the lowest concentration of antibiotic that will prevent visible growth of bacteria in serially diluted concentrations of the bacteria in either agar or broth. Passive diffusion of the antibiotic to the site of infection at or above the MIC would be expected to produce inhibition of bacterial growth. Evidence has been reported that a sub-MIC level might enhance phagocytosis by macrophages. Nosanchuk et al. [45] demonstrated that the major antifungal drugs used in the treatment of cryptococcosis, amphotericin B, and fluconazole would enhance phagocytosis of macrophages at subinhibitory concentration. The results suggest that the normal mechanism of action, altering cell wall permeability or inhibiting cell wall synthesis, respectively (Table 10.1), can cooperate with humoral and cellular immune defense systems in controlling fungal infection even at sub-MIC concentrations. Thus, as emphasized above, a functional immune system is important to the therapeutic effectiveness of the antimicrobial agent.

Antimicrobial Absorption

In general, enteral, parentral, and topical administration can be used with most classes of antimicrobials, although there are exceptions based upon physicochemical properties of the specific agent. All routes of administration, with the exception of intravenous, will have a distinct absorption phase, that is, a lag time until the antimicrobial reaches its maximum concentration in blood plasma, often referred to as C_{pmax}, following administration.

The enteral route of administration offers the most complex set of physiological barriers to absorption. One of the most formidable barriers is pH found in various segments of the gastrointestinal tract. The effect of pH is basically twofold. First, the antimicrobial drug may be labile to acid or base hydrolysis. Typically, pH in the stomach is acidic (approximately 2) and that of the intestine is basic (approximately 8). For example, penicillin G is rapidly hydrolyzed by stomach acid and less than one-third of it would be absorbed. Converting penicillin G to the potassium salt forms penicillin VK that is acid resistant and permits adequate oral bioavailability. The second factor related to pH is the relationship that exists between it and the acid dissociation constant (pK_a) of the antimicrobial drug. Depending upon the pK_a of an antimicrobial, the possibility exists that the antimicrobial will become ionized. Since the unionized form generally is required for passive diffusion across the lipoidal membranes that constitute the gastrointestinal tract, bioavailability of the dosage form can be limited. Sulfonamides illustrate this principle since most members

of the class have a pK_a value in the range of 4.9–7.7 [41]. Applying the principles of the Henderson–Hasselbach equation, viz.,

$$pK_a - pH = \log(\text{ionized drug} / \text{unionized drug})$$

it is apparent that at the intestinal pH of approximately 8, it would be anticipated that the sulfonamides would exist mainly as the unionized form and be absorbed *via* passive diffusion. This is in fact the case for all the sulfonamides which are absorbed well when given orally, the exception being sulfasalazine which is a prodrug designed to be metabolized in the distal portion of the small intestine and colon for a local action. Once the sulfonamide is absorbed into the systemic circulation where the pH is 7.4, it exists mainly in the unionized form and can cross other membrane barriers in the body as well as penetrate the microbial organism *via* passive diffusion as described in the subsequent section.

pK_a of the antimicrobial agent may also determine whether it can form complexes with other co-administered drugs. For example, fluorquinolones such as ofloxacin, lomefloxacin, norfloxacin, and ciprofloxacin have ionizable groups with pK_a values close to neutrality [42]. The optimum pH for complexation with iron (III) was found to be 3.8 [43]. Thus, it would be expected that concurrent administration of iron with a fluoroquinone would reduce the bioavailability of both drugs due to complexation in the acid environment of the stomach.

Oral absorption of tetracyclines can be inhibited by virtue of the fact that because of their chemical structure, sites for chelation are present. Thus concurrent administration of over-the-counter antacids containing calcium, aluminum, zinc, silicate, or bismuth subsalicylate [44], or formulations of iron or vitamins containing iron [45] will form chelated complexes that are not absorbed across gastric mucosa. In a similar manner, calcium contained in dairy products will form chelation complexes that will inhibit absorption of the tetracyclines [46].

Another barrier to antimicrobial absorption is metabolism of the administered drug by isozymes found in the wall and clefts of the gastrointestinal tract. Such metabolism would convert the nonpolar, lipid-soluble antimicrobial into a polar, more water-soluble metabolite. Because of the change in physicochemical properties, the metabolite would not be available for passive diffusion across the lipoidal membranes of the gastrointestinal tract. Specific examples of this barrier to absorption are given in the subsequent section on Antimicrobial Metabolism.

Antimicrobial Distribution

Following the absorptive process, the antimicrobial agent is transported throughout the body *via* systemic circulation. The blood pH 7.4 and the inherent pK_a of the antimicrobial drug will determine the unionized to ionized ratio. That portion of the antimicrobial drug that is ionized can be bound to blood proteins, the most notable

being albumin, through electrostatic interactions. That portion that is unionized or often termed the "free drug" is available to diffuse across cellular membranes. This "free drug" is also referred to as the "pharmacologically active" portion of the absorbed drug since in order to interact with a receptor to produce an effect, the drug has to transverse the protective cellular membrane. As noted above, with antimicrobial drugs it is advantageous for no host pharmacological action to occur, rather it is hoped that the microbe will be the recipient of the toxic effects of the antimicrobial agent. In *Escherichia coli* it has been shown that the intracellular pH and the pK_a of the sulfonamide determine the passive diffusion rate across the bacteria membrane [47].

Antimicrobial agents must reach deep-seated parts of the body that harbinger microbes if they are to be effective. Some examples will illustrate this principle. First, antimicrobial agents must penetrate into the gastric mucus and crypts of the gastrointestinal tract to eradicate *Campylobacter pylori*. Such penetration by the antimicrobial agent has been determined by physicochemical properties of the antimicrobial, such as pK_a, stability and activity over a wide range of pH, and lipid solubility [48]. A second example is penetration of antimicrobials into infections involving cysts in patients with autosomal-dominant polycystic kidney disease [49]. In ten patients with this disease, blood, urine, and cyst fluid were analyzed either at surgery or autopsy for antibiotic concentrations. Drugs active against anaerobes, such as metronidazole and clindamycin, were present in therapeutic concentrations in the cysts. Ampicillin, trimetoprim-sulfamethoxazole, erythromycin, vancomycin, and cefotaxime were likewise found in the cysts but not aminoglycosides. These authors suggested that this was due to the favorable physicochemical properties of the penetrating drugs, viz., pK_a, and lipid solubility. A third example will illustrate how a concomitantly administered drug can enhance the bioavailability of an antimicrobial agent into a deep-seated area of the body. Patients undergoing cataract surgery were given an intravenous infusion of either eftazidime, cefotaxime, aztreonam, or ceftriaxone along with or without oral acetazolamine [50]. Difference in aqueous humor concentration with concurrent administration of acetazolamide was statistically significant demonstrating that trans-membrane penetration of antimicrobials into a deep-seated compartment like the eye can be accomplished. A fourth example illustrates that antimicrobial agents can penetrate into bone that has limited vascular circulation [51]. Two groups of patients each containing four persons received either 1 g oxacillin or 1 g cefazolin pre-operatively then had cervical discs removed and concentration of antibiotic measured. Two other groups of four persons each received 2 g of drug instead of the 1 g given to the other groups. Antibiotic levels were detected in all discs but were only quantifiable in the 2-g dosed groups. This study demonstrated that larger doses of an antimicrobial agent would be required to treat a bone infection.

Host Metabolism of Antimicrobials

Metabolism of antimicrobial agents in the host (human patient) occurs by either Phase I (oxidative) and/or Phase II (conjugation) mechanisms. Metabolism of the

Table 10.2 Cytochrome isoforms metabolizing antimicrobials

Antimicrobial chemical structure	Cytochrome (CYP) isoform responsible for metabolism
Azoles	2C9, 2C19 (fluconazole)
Macrolides	3A4
Rifamycins	2C9, 2C19, 3A4 (rifampicin an inducer)
Quinolones	1A2
Sulfonamides	2C9
Pyridine nucleotides	1A2, 3A4 (zidovudine)
	3A4 (nevirapine, saquinavir, indinavir, ritonavir, nelfinavir)
	3A4 (efavirenz, an inducer)

β-lactam antimicrobials occurs mainly as a result of parasite enzymes as discussed in a subsequent section. Most Phase I metabolism of antimicrobials in humans occurs through a super-family of mixed-function monooxygenase enzymes termed the cytochromes P450 or abbreviated CPY [52]. The different cytochromes are divided into families based upon their protein and DNA homology [53]. Six of these enzyme families mediate the oxidative metabolism of most drugs, viz., CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [54]. These families of isoenzymes are well known for many clinically relevant drug–drug interactions [55–59] and most have rather specific drug substrates. Many antimicrobials discussed in the present context are metabolized either by CYP1A2, CYP2C9, CYP2C19, and/or CYP3A4. Table 10.2 shows a current listing of those antimicrobials known to be metabolized by these isoforms. Phase II metabolism of some antimicrobials is accomplished by glucuronide conjugation with the uridine 5′-diphospho-glucuronosyltransferase (UGT) family of enzymes. Various isoforms exist for the UGT family, with each isoform exhibiting substrate specificity for different drugs [60, 61]. The multigene superfamily of human UGT includes more than 24 genes and cDNAs, 16 of which are functional and encode full-length proteins [62, 63], eight are encoded by the UGT1A locus (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, and 1A10) [64, 65], and eight are encoded by UGT2 genes (2A1, 2B4, 2B7, 2B10, 2B11, 2B15, 2B17, and 2B28) [66]. At the present time, those antimicrobials that are known to form glucuronides have not been characterized for the specific UGT isoform responsible for the transformation. For example, zidovudine (AZT) is metabolized to its inactive glucuronide by UGT, and this conversion can be inhibited by fluconazole [67], presumably by competitive inhibition. Two other types of Phase II metabolism have been reported but not fully examined to date, viz., glutathione conjugation with activated sulfonamides [68, 69] and *N*-acetylation of amantadine [70, 71].

From a number of studies, information is available on which CYP family a particular therapeutic drug is a substrate. For example, tolbutamide, an oral hypoglycemic drug, which is structurally similar to the sulfonamides, is known to be a substrate for CYP2C9 producing hydroxytolbutamide as the metabolite [72]. Thus, it would

be reasonable to expect that co-administration of a sulfonamide and tolbutamide might alter the metabolic degradation of the latter due to competitive inhibition of CYP2C9. This has been demonstrated both in vivo [73] and in vitro [74]. In the former study, the area under the curve (AUC) for tolbutamide was increased fivefold when co-administered with sulfaphenazole, a sulfonamide used in TB. In the latter study, sulfaphenazole was shown to possess the greatest inhibition of tolbutamide in human liver CYP2C9 followed by sulfadiazine, sulfamethizole, sulfisoxazole, and sulfamethoxazole.

CYP2C9 is involved mostly in the metabolism of polar acidic drugs [75] and is competitively inhibited by the sulfonamides listed above, tolbutamide, nonsteroidal anti-inflammatory drugs [76, 77] COX-2 inhibitors [78, 79], phenytoin, selective serotonin reuptake inhibitors (SSRIs) [80], and warfarin [81]. The other major cytochrome family responsible for antimicrobial metabolism, CYP3A4, is responsible for the metabolism of about 50% of all therapeutic agents [82]. Both CYP2C9 and CYP3A4 are found in human liver and intestine [83] but evidence to date indicates that CYP3A4 is the predominant form present in intestine and is inducible with rifampin [84]. Because each cytochrome family has many different therapeutic drugs as substrates, there exists the potential for administration of an antimicrobial to affect the metabolism of a concurrently administered therapeutic agent by competitive inhibition that may result in one of the following:

1. Increasing therapeutic drug concentration
2. Decreasing therapeutic drug concentration
3. Increasing antimicrobial concentration
4. Decreasing antimicrobial concentration

In instances 1 and 2, the severity of the observed effect will depend upon the therapeutic index of the drug. For example, if the therapeutic drug has a very small therapeutic to toxic ratio, the co-administration of an antimicrobial drug may have a deleterious effect if both are metabolized by the same cytochrome isoenzyme system. This narrow range of toxic to therapeutic ratio was brought to light with the prokinetic agent, cisapride, used for the treatment of gastrointestinal disorders, particularly gastro-esophageal reflux in adults and children. Cisapride is metabolized by CYP3A4 [85]. Co-administration with the macrolide antibiotics produced potentially fatal arrhythmias [86–88]. This was shown to be due to an increase of unmetabolized cisapride due to competition between the macrolide antibiotic and cisapride for the CYP3A4 isozyme.

A similar situation was discovered when the antifungal drug, ketoconazole, was ingested concurrently with the nonsedating antihistamine, terfenadine. Fatal cardiac arrhythmias occurred [89] and were found to be due to a competition for CYP3A4 metabolism wherein terfenadine's metabolism was blocked [90]. This increase in terfenadine concentration unmasked its ability to block fast potassium channels in the heart resulting in cardiac conduction delays [91].

While many examples could be cited concerning alterations of a therapeutic drug's effect when co-administered with an antimicrobial agent, examination of cyclosporine will be instructive and illustrate the clinical problem [92]. Cyclosporine,

a common immunosuppressive drug, is administered after human organ transplants. Rifampicin decreases cyclosporine blood concentrations below the limit of detection of many assays, whereas erythromycin and ketoconazole increase its concentration. Similarly, sulfadimidine and trimethoprim have been reported to increase cyclosporine levels. Other macrolide antibiotics and azole antifungal agents, and fluoroquinolones, increase cyclosporine levels. Obviously, concomitant use of these antimicrobial agents with cyclosporine would require adjustment of the cyclosporine dose to achieve optimal immunosuppression.

In some cases, two different classes of antimicrobial agents might be concurrently administered. For example, in the treatment of tuberculosis sometimes two different rifamycins may be co-administered with a macrolide. This can be illustrated by rifampicin and rifabutin, both of which are inducers of CYP3A4, decreasing the blood level of clarithromycin (a macrolide antibiotic), which is also metabolized by CPY3A4 [93].

Erythromycin has been suggested as a probe to determine the extent of CYP3A4 activity in an individual. The underlying concept is that a person's CYP3A4 activity could be determined and used as a predictor of potential drug interactions, since CYP3A4 has such a prominent role in the metabolism of drugs. In the so-called erythromycin breath test [94], a subject is administered ^{14}C-*N*-methyl-erythromycin (3 μCi) intravenously. The radiolabeled CO_2 from *N*-demethylation mediated by CYP3A4 is determined in subsequent breath samples. While this test has been widely explored, it has been found that oral probes will augment the information obtained by intravenous labeled erythromycin since CYP3A4 is also found in intestinal epithelium. The benzodiazepine, midazolam, is often used for this test [95, 96]. An interesting use of the erythromycin breath test has been to investigate variations in CYP3A4 metabolism in HIV patients [97]. This study suggested that HIV patients had greater variability in hepatic activity of CYP3A4, and this may explain the variations often seen in the plasma concentrations of protease inhibitors like indinavir.

Elimination of Antimicrobials

Antimicrobials are eliminated from the body by a variety of pathways including excretion into the urine, bile, sweat, milk, and feces depending upon their physicochemical properties. Renal elimination occurs for many of the antimicrobials by several mechanisms, viz., glomerular or tubular, but there also exists a possibility of passive reabsorption occurring in the proximal tubule. If the antimicrobial is not bound to blood proteins, it can be effectively removed by glomerular filtration that is facilitated using passive diffusion of the unionized drug with a molecular size less than that of proteins. In general, the rate of clearance of the glomerulus is about 120 mL/min, and therefore, if the observed clearance of the antimicrobial is greater than 120 mL/min, a combination of glomeruli and tubular excretion must be occurring. If the antimicrobial is ionized at physiological pH, it could be excreted by an

active transport system in either the proximal or distal tubule (loop of Henle). Examples of antimicrobials excreted both by passive glomerulus and active proximal tubular secretion are the penicillins and cephalosporins. For example, penicillin G has a renal clearance rate of >200 mL/min and approximates that of plasma flow since both passive and active renal transport is occurring. Probenecid will effectively compete with penicillin G for active transport in the tubule and results in an increased blood level of penicillin G and a prolonged half-life. In a similar way, many of the pyridine nucleotides antimicrobials, such as acyclovir, ganciclovir, and zidovudine are actively transported in the renal tubule [98]. As an example, valaciclovir, a prodrug form of acyclovir, has its renal excretion altered by a co-administration of either cimetidine or probenecid, the former most likely due to inhibition of liver CYP3A4 and the latter due to competition for active tubular excretion [99].

Antimicrobial Metabolism in the Microbe

Metabolism of antimicrobials, as noted above, may occur in both host (patient) and microorganism. The microbial metabolism may be beneficial to the microorganism by rendering the toxic drug harmless to the microorganism or detrimental by incorporating the drug into the respiratory, metabolic, or structural pathways of the microorganism, so bringing about its ultimate demise. An example of the former is the production of beta-lactamase by bacteria that opens the beta-lactam ring of penicillins and cephalosporins and produces an inactive antibiotic. The latter type of microbial metabolism is summarized in Table 10.1 where antimicrobial agents cause inhibition of growth or antimicrobial cell death by a variety of incorporation mechanisms.

To prevent the microorganism from metabolizing the β-lactam antimicrobial, a β-lactamase inhibitor, such as clavulanic acid, sulbactam, or tazobactam, can be co-administered. In general, the observed antimicrobial action is greater than if the β-lactam antimicrobial was given as a single agent. Some examples are ampicillin-sulbactam, ticarcillin-clavulanate, amoxicillin-clavulanate, and piperacillin-tazobactam [100].

Drug Interactions

Psychotropic drugs are known to have many varied interactions with antimicrobial agents [101, 102]. Several examples with the antifungal agent, itraconazole, a known inhibitor of CYP3A4, will be utilized as an example. Haloperidol plasma concentrations were increased in schizophrenic patients concurrently treated with itraconazole [103]. The resultant increase in plasma concentrations produced significant

neurological side effects. The increase in plasma concentration of alprazolam, during concurrent administration of itraconazole, produced significantly depressed psychomotor function in test subjects [104].

Psychotropic drugs are often used in the pharmacological treatment of emotional disorders of HIV-infected patients. Such patients may also be receiving antidepressants, antifungal, antiviral, and protease inhibitor drugs. For example, in vitro CYP3A4 metabolism of the antidepressant trazodone suggested that biotransformation to its major metabolite, meta-chlorophenylpiperazine, was inhibited by the antifungal, ketoconazole, as well as the protease inhibitors ritonavir and indinavir [105].

Multidrug antiviral regimens are typically used to treat HIV-infected patients in addition to the antibiotics and therapeutic drugs discussed above. For example, a patient is often treated with one or more nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, zalcitabine, lamivudine, or abacavir) and a protease inhibitor (saquinavir, ritonavir, indinavir, nelfinavir, or amprenavir) or alternately with two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (nevirapine, delavirdine, or efavirenz) [106]. The protease inhibitors are metabolized by CYP3A4 and several of the reverse transcriptase inhibitors are inducers of various cytochromes, including CYP3A4. Therefore, combinations of antiviral drugs have the potential for drug interactions. Inhibition of CYP3A4 may sometimes be an advantage. For example, higher plasma levels of the HIV protease inhibitor, saquinavir, which is metabolized by CYP3A4, can be achieved by combining the drug with CYP3A4 inhibitors like ritonavir or ketoconazole [107]. But, conversely, it cannot be co-administered with therapeutic agents that are likewise metabolized by CYP3A4, such as terfenadine or cisapride.

The widespread use of drugs for gastrointestinal disorders, such as antacids and H_2 histamine receptor blocking agents such as ranitidine, has been reported to alter the bioavailability of many antimicrobials [108, 109]. The prokinetic agent cisapride is an example of a therapeutic drug used to treat gastrointestinal disorders. Due to competition for CYP3A4 with other concomitantly administered drugs, toxic effects could be unmasked. Such interactions are potentially harmful to the patient. In one study, interaction between erythromycin and cisapride produced prolongation of the QT interval and clinically cardiac arrhythmias were observed. Other antimicrobials such as fluconazole or miconazole did not produce QT elongation when administered with cisapride [110]. Because the azole antifungal agents are inhibitors of CYP3A4, their concurrent use with cisapride is not recommended [91].

The HMG-CoA reductase inhibitors commonly used to block cholesterol biosynthesis are metabolized by CYP3A4. Therefore, their concurrent use with the antimicrobials that are also metabolized by CYP3A4 should be avoided [111].

Information is now being published that the drug sildenafil (viagra) is predominately metabolized by CYP3A4 [112]. Therefore, any other drug that is metabolized by CYP3A4, including the antimicrobials discussed above, has the potential to impair sildenafil biotransformation.

Herbal and Natural Product Interactions

Many patients using antimicrobials may also use over-the-counter herbal preparations to augment their health needs. Even though the use of herbal products has become widespread in recent years, there is little scientific information available on how these substances affect prescribed and over-the-counter drugs. Early reports indicate that the herbal products may either induce CYP3A4 or be metabolized by this isoenzyme and hence have the potential to inhibit the metabolism of drugs. For example, the naphthodiantrons found in St John's wort appear to induce CYP3A4 and would therefore have the potential to decrease the blood concentrations of any antimicrobial also metabolized by CYP3A4. However, this flavonoid constitutes only about 0.1–0.5% of the St John's wort [113]. Thus the contribution to clinical inhibition would be questionable but not unexpected depending upon the method of manufacturing the herbal preparation. Using midazolam as the probe for CYP3A4, one group has suggested that this herb when ingested in the dose recommended for depression is unlikely to inhibit CYP3A4 activity [114]. However, another study has demonstrated that using only one probe for CYP3A4 activity may not give a true picture of metabolism in a patient [115].

Recently, it has been found that garlic supplements interact with some antiretroviral medications. In one study [116], the area under the serum concentration curve for saquinavir was decreased approximately 51% when concurrently used with a garlic supplement. Such a drop in serum levels was sufficient to cause treatment failures.

A common natural product interference is between endogenous constituents of grapefruit juice and antimicrobials. A number of flavones have been demonstrated to be present in grapefruit juice. For example, kaempferol, naringenin, and quercetin are three such flavones and all are metabolized by CYP3A4 [117, 118]. The bioavailability of erythromycin has been shown to increase as a result of the inhibitor effect of grapefruit juice on intestinal CYP3A4 [60]. Similar results have been demonstrated with saquinavir and amprenavir [61]. Several investigators have shown that the inhibitor effect of grapefruit juice occurs only with the oral dose and not an intravenous dose of the therapeutic drug [63, 64, 87]. Such information suggests that the inhibition of CYP3A4 occurs in the gastrointestinal tract as opposed to the liver. Thus the increase in the observed bioavailability of the studied antimicrobials apparently is due to reduced metabolism of the parent drugs in the gastrointestinal tract. Similar results would be anticipated with any orally administered microbial that is metabolized by CYP3A4 and to a lesser extent by those metabolized by CYP2C9. This is because the flavonoids found in grapefruit juice seem to be more selective to inhibiting CYP3A4 than CYP2C9 [90]. There may also be some selectivity of inhibition based upon the particular flavones studied. For example, Obach has examined some individual flavones found in grapefruit juice, viz., hyperforin, I3,II8-biapigenin, hypericin, and quercetin for their inhibition of CYP2C9, CYP3A4, and several other cytochromes. The biflavone, I3,II-8-biapigenin demonstrated the greatest potency toward CYP2C9 and CYP3A4.

Assays for Antimicrobials

A variety of assays are available for determining both the sensitivity of a strain of bacteria to antibiotic susceptibility as well as for determining the level of the antimicrobial in a physiological fluid. The earliest antibiotic assays evolved from attempts to qualitatively demonstrate antimicrobial activity in biological fluids [119]. For clinical purposes there are two distinct requirements. First, there is a need to know if a bacterium is sensitive or resistant to the proposed antibiotic treatment. This type of assay has been a mainstay of clinical laboratories for a number of years. The patient's blood or urine is cultured on agar plates along with various antibiotic standards and controls. Replication of the bacteria would be an indication of resistance to the proposed antibiotic treatment, whereas inhibition of growth would indicate sensitivity [120]. For those antimicrobials with a narrow therapeutic index, blood level monitoring is advisable.

Commercially available immunoassays exist for some antimicrobials, such as the aminoglycosides. The aminoglycosides have also been analyzed by chromatographic methods [121–125]. The macrolide antibiotics, because of their large molecular size, lend themselves to analysis with high-performance liquid chromatography (HPLC) with either electrochemical or ultra-violet detection. Erythromycin propionyl ester and its free base [126–129], clarithromycin [130], and its biologically active hydroxy metabolite may all be determined in biological fluids using high-performance liquid chromatography. Chromatographic methods have been utilized for analysis of many of the antivirals [131–136].

Implications for Toxicological and Forensic Investigations

Antimicrobials are inherently nontoxic agents. However, as the foregoing discussion indicates, when combined with a variety of therapeutic drugs, some potentially toxic and even fatal effects are possible. This is largely due to the fact that most antimicrobials are metabolized by CYP3A4 isoenzymes that also metabolize over 50% of all therapeutic drugs. When competition for the saturable CYP3A4 occurs, toxic effects of the therapeutic drug, the effects not usually seen when given alone, are unmasked. Most toxicology and forensic laboratories do not normally analyze for the antimicrobial drugs in general toxicology screens. The main reason is that separate and distinct assays are required for most members of this group. Many antimicrobials have their origin from natural sources and hence are large complex molecules not readily lending themselves to most toxicological and forensic analytical methods. However, when investigative or medical records indicate that a toxic or presumed toxic event followed a combination of a therapeutic and antimicrobial drug, there must be careful consideration of the toxic effect of the therapeutic agent due to competition by the antimicrobial for CYP3A4. Some suspicion may already be raised with an elevation of the concentration of the therapeutic drug in

the biological fluid. However, the interpretation of the reason for the elevated level might be incorrect if it is assumed a priori that the patient or decedent has taken an overdose of the therapeutic drug.

References

1. *The Little Oxford Dictionary*, 4th edition, compiled by George Ostler, Oxford University Press, Great Britain, 1970.
2. *Casarett and Doull's Toxicology The Basic Science of Poisons*, fourth edition, Amdur, M.O., Doull, J., and Klaassen, C.D.eds. Pergamon Press, Inc. Elmsford, NY, 1991.
3. Robbins, S.L., and Kumar, V. *Basic Pathology 4th Edition*. W.B. Saunders Company, Philadelphia, PA, 1987.
4. www.cdc.gov/ncidod/dbmd/diseaseinfo/meningococcal_t.htm. 11/30/01
5. De Almeida SM, Faria FL, de Goes Fontes K, Buczenko GM, Berto DB, Raboni SM, Vidal LR, Noqueria MB. Quantitation of Cerebral spinal fluid lactic acid in infectious and non-infectious diseases. *Clin Chem Lab Med* **47:**755–61, 2009.
6. Straus SE, Thrope KE, Holroyd-Leduc J. How do I perform a lumbar puncture and analyze the results to diagnose bacterial meningitis? *JAMA* **296:**2012–22, 2006.
7. Zhanel GC, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, Norredin AM, Karlowsky JA. Comparative Review of the carbapenums. *Drugs* **67:**1027–52, 2007.
8. Davis LE. Acute and recurrent viral meningitis. *Curr Treat Options Neurol* **10:**168–77, 2008.
9. Ginsberg L, Kidd D. Chronic and recurring meningitis. *Pract Neurol* **8:**348–61, 2008.
10. Mead P.S., and Griffin, P.M. *Escherichia coli* O157:H7. *Lancet* **352:** 1207–1212 . (1998).
11. www.cdc.gov/ncidod/dbmd/diseaseinfo/diarrecoli_t.htm. 11/30/01
12. Beissbarth T. Interpreting experimental results using gene ontologies. *Methods Enzymol* **411:**340–52, 2006.
13. Sherman J, McKay MJ, Ashman K, Molloy MP. Unique ion signature mass spectrometry: a deterministic method to assign peptide identity. *Mol Cell Proteomics* published June 25, 2009.
14. Babu M, Butl G, Poquotse O, Li J, Greenblatt JF, Emili A. Sequential peptide affinity purification system for the systematic isolation and identification of protein complexes from Escherichia coli. *Methods Mol Biol* **564:**373–400, 2009.
15. www.cdc.gov/ncidod/dbmd/diseaseinfo/groupastreptococcal_t.htm. 11/30/01
16. www.cdc.gov/ncidod/dbmd/diseaseinfo/groupastreptococcal_g.htm. 11/30/01
17. Schuchat, A. Group B streptococcus. *Lancet*. **353**: 51–56 (1999).
18. Skoff TH, Farley MM, Petis S, Craig AS, Schaffner W, Gersham K, Harrison LH, Lynfield R, Mohle-Boetani J, Zansky, S, Albanese BA, Stefonek K, Zell ER, Jackson D, Thompson T, Schraq SJ. Increasing burden of invasive group B strepoccocal disease in non-pregnant adults, 1990–2007. *Clin Infect Dis* **49:**85–92, 2009.
19. www.cdc.gov/ncidod/dbmd/diseaseinfo/groupbstrep_t.htm. 11/30/01
20. Edwards MS, Baker CJ. Group B streptococcus infections in elderly adults. *Clin Infect Dis* **41:**839–47, 2005.
21. Shapiro, ED, and Ward J.I. The epidemiology and prevention of disease caused by Haemophilus influenzae type b. *Epidemiol Rev* **13**: 113–142 (1991)
22. Peltola H.H. *H. influenzae* in the post-vaccination era. *Lancet* **341**: 864–865 (1993).
23. www.cdc.gov/mmwr/preview/mmwrhtml/rr4812a1.htm 11/30/01
24. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the immunization practices advisory committee. *MMWR* November 22, 1991 **40** (RR-13): 1–19.
25. Recommendations for prevention and control of Hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR* October 16, 1998 **47** (RR19): 1–39.

26. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C. June 10–12, 2002. *Hepatology* **36**(Suppl. 1):S3–20, 2002.
27. Lin CC, Philips L, Xu C, Yeh LT. Pharmacokinetics and safety of viramidine, a prodrug of ribavirin, in healthy volunteers. *J Clin Pharmacol* **44**:265–275, 2004.
28. www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_d/slide_1.htm. 11/30/01
29. Yurdaydin C, Bozkaya H, Karaaslan H, Onder FO, Erkan OE, Yalc_in K, et al. A pilot study of 2 years of interferon treatment in patients with chronic delta hepatitis. *J Viral Hepat*;**14:**812–816, 2007.
30. Erhardt A, Gerlich W, Starke C, Wend U, Donner A, Sagir A, et al. Treatment of chronic hepatitis delta with pegylated interferon-alpha2b. *Liver Int* **26:**805–810, 2006.
31. FitzSimons D, et al. Hepatitis A and E: Update on prevention and epidemiology. *Vaccine*, doi:10.1016/j.vaccine.2009.10.136 (in press).
32. Labrique, A.B., Thomas, D.L., Stoszek, S.K., and Nelson K.E. Hepatitis E: an emerging infectious disease. *Epidemiol Rev* **21**: 162–179 (1999).
33. www.cdc.gov/nchst/dstd/Fact_Sheets/facts_Genital_Herpes.htm 11/30/01
34. L. Corey and H. H. Handsfield, "Genital herpes and public health: addressing a global problem," *JAMA* **283:**, 791–794, 2000.
35. Mertz, G. and Corey, L.: Genital herpes simplex virus infections in adults. *Urol. Clin. North Am*. **11** :103 (1984).
36. www.cdc.gov/ncidod/dbmd/diseaseinfo/legionellosis_g.htm 11/30/01
37. Cunha BA. Atypical pneumonias; Current clinical concepts focusing on Legionnaire's Disease. Curr Opin Pulm Med **14:**183**–**94, 2008.
38. CDC. Multidrug-resistant *Salmonella* serotype enteritidis infection associated with consumption of raw shell eggs-United States, 1994–1995. *MMWR* **45**: 737–742 (1996).
39. Hajjeh, R.A., Reingold, a., Weil, A. et al. Toxic shock syndrome in the United States: surveillance update, 1979–1996. *Emerg Infect Dis J*. **5**:6 (1999).
40. www.cdc.gov/nchstp/tb/faqs/qa.htm 11/30/01
41. Berdy J. Recent developments of antibiotic research and classification of antibiotics according to chemical structure. *Adv Appl Microbiol* **18:**309**–**406, 1974.
42. Cuddy PG. Antibiotic classification: implications for drug selection. *Crit Care Nur Quart* **20:**89**–**102, 1997.
43. Fish DN, Piscitelli SC, Danziger LH. Development of resistance during antimicrobial therapy: A review of antibiotic classes and patient characteristics in 173 studies. *Pharmacother* **15:**279**–**91, 1995.
44. Tulkens PM. Intracellular distribution and activity of antibiotics. *Eur J Clinic Microbiol Infect Dis* **10:**100**–**6, 1991.
45. Nosanchuk JD, Cleare W, Franzot SP, Casadevall A. Amphotericin B and fluconazole affect cellular charge, macrophage phagocytosis, and cellular morphology of Cryptococcus neoformans at subinhibitory concentrations. *Antimicro Agents Chemother* **43:**233**–**9, 1999.
46. Mengeles Mengelers MJ, Hougee PE, Jannsen LH, Van Miert AS. Structure-activity relationships between antibacterial activities and physicochemical properties of sulfonamides. *J Vet Pharmacol Ther* **20:**276**–**83, 1997.
47. Ouedraogo G, Morliere P, Santus R, Miranda-Castell JV. Damage to mitochondria of cultured human skin fibroblasts photosensitized by fluoroquinolones. *J Photochem Photobiol. B- Biology* **58:**20**–**5, 2000.
48. Lee DS, Han HJ, Kim K, Park WB, Cho JK, Kim JH. *J Pharm Biomed Anal* **12:**157**–**64, 1994.
49. Neuvonen PJ. Interactions with absorption of tetracyclines. *Drugs* **11:**45**–**54, 1976.
50. Venho VMK, Salonen RO, Mattila MJ. Modification of the pharmacokinetics of doxycycline in man by ferrous sulfate or tissues. *Chemother* **21:**8**–**18, 1975.
51. Jung H, Peregrina AA, Rodriguez JM, Moreno-Esparza R. The influence of coffee with milk and tea with milk on the bioavailability of tetracycline. *Biopharm Drug Dis* **18:**459**–**63, 1997.
52. Buttner D, Buttner H. pH dependency in uptake of sulfonamides by bacteria. *Chemother* **26:**153**–**63, 1980.

53. McNulty CA, Dent JC, Ford GA, Wilkinson SP. Inhibitory antimicrobial concentrations against Campylobacter pylori in gastric mucosa. *J Antimicro Chemother* **22:**729–38, 1988.
54. Bennett WM, Elzinga L, Pulliam JP, Rashad AL, Barry JM. Cyst fluid antibiotic concentrations in autosomal-dominant polycystic kidney disease. *Am J Kidney Dis* **6:**400–4, 1985.
55. Voutsinas P, Kavouklis E, Voutsinas D, Kontoghiorgi K, Giamarellou H. The effect of acetazolamide on the kinetics of four newer beta-lactams in the aqueous humor. *Clin Microbiol Infect* **7:**70–4, 2001.
56. Rhoten RL, Murphy MA, Kalfas IH, Hahn JF, Washington JA. Antibiotic penetration into cervical discs. *Neurosurg* **37:**418–21, 1995.
57. Gonzalez FJ. Human cytochrome P450: Problems and prospects. *Trends Pharmacol Sci* **13:**346–52, 1992.
58. Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Fyereisen R, Waxman PJ, Waterman MR, Gotoh O, Coon MJ, Estabrook RW, Gunsalus IC, Nebert DW. P450 superfamily: Update on new sequences, gene mapping, accession numbers and nomenclature. *Pharmacogenet* **6:**1–42, 1996.
59. Caraco Y. Genetic determinants of drug responsiveness and drug interactions. *Ther Drug Monitor* **20:**517–24, 1998.
60. Wienkers LC. Problems associated with in vitro assessment of drug inhibition of CYP3A4 and other P-450 enzymes and its impact on drug discovery. *J Pharmacol Toxicol Meth* **45:**79–84, 2001.
61. Guengerich FP. Uncommon P450-catalyzed reactions. *Curr Drug Metab* **2:**93–115, 2001.
62. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* **38:**41–57, 2000.
63. Wood MJ. Interactions of antibiotics with other drugs. *J Antimicro Chemother* **20:**628–30, 1987.
64. O'Reilly RA. Warfarin metabolism and drug-drug interactions. *Adv Exp Med Biol* **214:** 205–12, 1987.
65. Burchell B, Brierley CH, Rance D. Specificity of human UDP-glucuronosyltransfereases and xenobiotic glucuronidation. *Life Sci* **57:**1819–31, 1995.
66. Clarke DJ, Burchell B. "The uridine diphosphate glucuronosyltransferase multigene family: Function and regulation." *In* Kauffman FC (ed), *Handbook of experimental pharmacology. Conjugation-deconjugation reactions in drug metabolism and toxicity.* Springer-Verlag, Berlin, Germany, 1994, pp. 3–43.
67. Gagné, J-F, Montminy V, Belanger P, Journaut K, Gaucher G, Guillemette C. Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). *Mol Pharmacol* **62:**608–17, 2002.
68. Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: Metabolism, expression and disease. *Annu Rev Pharmacol Toxicol* **40:**581–616, 2000.
69. Ritter JK, Chen F, Sheen YY, Tran HM, Kimura S, Yeatman MT, Owens IS. A novel complex locus UGT1 encodes human bilirubin, phenol and other UDP-glucuronosyltransferase isozymes with identical carboxyl termini. *J Biol Chem* **267:**3257–61, 1992.
70. Gong QH, Cho JW, Hang T, Potter C, Gholami N, Basu NK, Kubota S, Carvalho S, Pennington MW, Owens IS, Popescu NC. Thirteen UDPglucuronosyltransferase genes are encoded at the human UGT1 gene complex locus. *Pharmacogenetics* **11:**357–682, 2001.
71. Tukey RH, Strassburg CP, Mackenzie PI. Pharmacogenomics of human UDP-glucuronosyltransferases and irinotecan toxicity. *Mol Pharmacol* **62:**446–50, 2002.
72. Trapnell CB, Kelecker RW, Jamis-Dow C, Collins JM. *Antimicro Agents Chemother* **42:**1592–6, 1998.
73. Zhao Z, Koeplinger KA, Peterson T, Conradi RA, Burton PS, Suarato A, Heinrikson RL, Tomasselli AG. Mechanism, structure-activity studies, and potential applications of burch glutathione S-transferase-catalyzed cleavage of sulfonamides. *Drug Met Disp* **27:**992–8, 1999.
74. Koeplinger KA, Zhao Z, Peterson T, Leone JW, Schwende FS, Heinrikson RL, Tomasselli AG. Activated sulfonamides are cleaved by glutathione-S-transferases. *Drug Met Disp* **27:**986–91, 1999.
75. Bras AP, Hoff HR, Aoki FY, Sitar DS. Amantadine acetylation may be effected by acetyltransferases other than NAT1 or NAT2. *Can J Physiol Pharmacol* **76:**701–6, 1998.

76. Bras APM, Jänne J, Porter CW, Sitar DS. Spermidine/spermine N^1-acetyltransferase catalyzes amantadine acetylation. *Drug Met Dis* **29:**676–80, 2001.
77. Thomas RC, Ikeda GJ. The metabolic fate of tolbutamide in man and in the rat. *J Med Chem* **9:**507–10, 1966.
78. Veronese ME, Miners JO, Randles D, Gregov D, Birkett DJ. Validation of the tolbutamide metabolic ratio for population screening with use of sulfaphenazole to produce model phenotypic poor metabolizers. *Clin Pharmacol Ther* **47:**403–11, 1990.
79. Komatsu K, Ito K, Nakajima Y, Kanamitsu S-I, Imaoka S, Funae Y, Green CE, Tyson CA, Shimada N, Sugiyama Y. Prediction of in vivo drug-drug interactions between tolbutamide and various sulfonamides in humans based on in vitro experiments. *Drug Metab Disp* **28:** 475–81, 2000.
80. Miners JO, Birkett DJ. Cytochrome P4502C9: An enzyme of major importance in human drug metabolism. *Brit J Clin Pharmacol* **45:**525–38, 1998.
81. Leeman T, Transon C, Dayer P. Cytochrome P450TB (CYP2C): A major monooxygenase catalyzing diclofenac 4'-hydroxylation in human liver. *Life Sci* **52:**29–34, 1992.
82. Newlands AJ, Smith DA, Jones BC, Hawksworth GM. Metabolism of non-steroidal anti-inflammatory drugs by cytochrome P450 2C. *Brit J Clin Pharmacol* **34:**152P, 1992.
83. Tang c, Shou M, Rushmore TH, Mei Q, Sandhu P, Woolf EJ, Rose MJ, Gelmann A, Greenberg HE, De Lepeleire I, Van Hecken A, De Schepper PJ, Ebel DL, Schwartz JI, Rodrigues AD. In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: Correlation with CYP2C9 genotype and in-vivo pharmacokinetics. *Pharmacogenet* **11:**223–35, 2001.
84. Tang C, Shou M, Mei Q, Rushmore TH, Rodrigues AD. Major role of human liver microsomal cytochrome P450 2C9 (CYP2C9) in the oxidative metabolism of celecoxib, a novel cyclooxygenase-II inhibitor. *J Pharmacol Ther* **293:**453–9, 2000.
85. Schmider J, Greenblatt DJ, von Moltke LL, Karsov D, Shader RI. Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: Studies of phenytoin p0hydroxylation. *Br J Clin Pharmacol* **44:**495–8, 1997.
86. Steward DJ, Haining RL, Henne KR, Davis G, Rushmore TH, Trager WF, Rettie AE. Genetic association between sensitivity to warfarin and expression of CYP2C9*3. *Pharmcogenetics* **7:**361–7, 1997.tang.
87. Tang W, Stearns RA. Heterotropic cooperativity of cytochrome P450 3A4 and potential drug-drug interactions. *Current Drug Metab* **2:**185–98, 2001.
88. Obach RS, Zhang Q-Y, Dunbar D, Kaminsky LS. Metabolic characterization of the major human small intestinal cytochrome P450s. *Drug Met Disp* **29:**347–352, 2001.
89. Kolars JC, Schmiedlin-Ren P, Schuetz JD, Fang C, Watkins PB. Indentification of rafampin-inducible P450IIIA4 (CYP 3A4) in human small bowel enterocytes. *J Clin Invest* **90:**1871–1878, 1992.
90. Desta Z, Soukhova N, Mahal SK, Flockhart DA. Interaction of cisapride with the human cytochrome P450 system: Metabolism and inhibition studies. *Drug Metabol Disp* **28:**789–800, 2000.
91. Michalets EL, Williams CR. Drug interactions with cisapride: Clinical implications. *Clin Pharmacokinet* **39:**49–75, 2000.
92. Piquette RK. Torsade de pointes induced by cisapride/clarithromycin interaction. *Ann Pharmacother* **33:**22–6, 1999.
93. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med* **335:**290–1, 1996.
94. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr. Torsades de pointes occurring in association with terfenadine use. *J Am Med Assoc* **264:**2788–90, 1990.
95. Woolsey RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *J Am Med Assoc* **269:**1532–6, 1993.
96. Honig PK, Wortham DC, Zamani K, Conner DP Mullin JC, Cantilena LR. Terfenadine-ketoconazole interaction: Pharmacokinetic and electrocardiographic consequences. *J Am Med Assoc* **269:**1513–8, 1993.
97. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporine (Part I). *Clin Pharmacokinet* **19:**319–32, 1990.

98. Rodvold KA. Clinical pharmacokinetics of clarithromycin. *Clin Pharmackinet* **37:**385–98, 1999.
99. Rivory LP, Slaviero KA, Hoskins JM, Clarke SJ. The erythromycin breath test for the prediction of drug clearance. *Clin Pharmacokinet* **40:**151–8, 2001.
100. McCrea J, Prueksaritanont T, Gertz BJ, Carides A, Gillen L, Antonello S, Brucker MJ, Miller-Stein C, Osborne B, Waldman S. Concurrent administration of the erythromycin breath test (EBT) and oral midazolam as in vivo probes for CYP3A4 activity. *J Clin Pharmacol* **39:**1212–20, 1999.
101. Ananth J, Johnson K. Psychotropic and medical drug interactions. *Psychother Psychosomat* **58:** 178–196, 1992.
102. Shader RI, von Moltke LL, Schmider J, Harmatz JS, Greenblatt DJ. The clinician and drug interactions- An update. *J Clin Psychopharmacol* **16:**197–201, 1996.
103. Yasui N, Kondo T, Otani K, Furukori H, Mihara K, Suzuki A, Kaneko S, Inoue Y. Effects of itraconazole on the steady-state plasma concentrations of haloperidol and its reduced metabolite in schizophrenic patients: In vivo evidence of the involvement of CYP3A4 for haloperidol metabolism. *J Clin Psychopharmacol* **19:**149–54, 1999.
104. Yasui N, Kondo T, Otani K, Furukori H, Kaneko S, Ohkubo T, Nagasaki T, Sugawara K. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacol* **139:**269–73, 1998.
105. Zalma A, von Moltke LL, Granda BW, Harmatz JS, Shader RI, Greenblatt DJ. In vitro metabolism of trazodone by CYP3A4: Inhibition by ketoconazole and human immunodeficiency viral protease inhibitors. *Biol Psychiatr* **47:**655–61, 2000.
106. Barry M, Mulcahy F. Merry C. Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. *Clin Pharmacokinet* **36:**289–304, 1999.
107. Vella S, Florida M. Saquinavir. Clinical pharmacology and efficacy. *Clin Pharmacokinet* **34:**189–201, 1998.
108. Deppermann KM, Lode H, Hoffken G. Tschink G, Kalz C, Koeppe P. Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and amoxicillin-calvulanic acid. *Antimicro Agents Chemother* **33:**1901–7, 1989.
109. Lode H. Drug interactions with quinolones. *Rev Infect Dis* **10:**S132-6, 1988.
110. Laine K, Forsstrom J, Gronroos P, Irjala K, Kailajarvi M, Scheinin M. Frequency and clinical outcome of potentially harmful drug metabolic interactions in patients hospitalized on internal and pulmonary medicine wards: Focus on warfarin and cisapride. *Ther Drug Monitor* **22:**503–9, 2000.
111. Ucar M, Mjorndal T, Dahlqvist R. HNG-CoA reductase inhibitors and myotoxicity. *Drug Safety* **22:**441–57, 2000.
112. Warrington JS, Shader RI, von Moltke LL, Greenblatt DJ. In vitro biotransformation of sildenafil (Viagra): Identification of human cytochromes and potential drug interactions. *Drug Metab Disp* **28:**392–7, 2000.
113. Kinirons MT, O'Shea D, Kim RB, Groopman JD, Thummel KE, Wood AJ, Wilkinson GR. Failure of erythromycin breath test to correlate with midazolam clearance as a probe of cytochrome P4503A. *Clin Pharmacol Ther* **66:**224–31, 1999.
114. Slain D, Pakyz A, Israel DS, Monroe S, Polk RE. Variability in activity of hepatic CYP3A4 in patients infected with HIV. *Pharmacother* **20:**898–907, 2000.
115. Takeda M, Khamdang S, Naridawa S, Kimura H, Kobayashi Y, Yamamoto T, Cha SH, Sekine T, Endou H. Human organic anion transporters and human organic cation transporters mediate renal antiviral transport. *J Pharmacol Exp Ther* **300:**918–24, 2002.
116. Piscitelli SC. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis* **34:**234–8, 2002.
117. De Bony F, Tod M, Bidault R, On NT, Posner J, Rolan P. Multiple interactions of cimetidine and probenecid with valaciclovir and its metabolite acyclovir. *Antimicro Agents Chemother* **46:**458–63, 2000.

118. Lister PD, Prevan AM, Sanders CC. Importance of β-lactamase inhibitor pharmacokinetics in the pharmacodynamics of inhibitor-drug combinations: Studies with piperacillin-tazobactam and piperacillin-sulbactam. *Antimicro Agents Chemother* **41:**721–7, 1997.
119. Sabath LD. The assay of antimicrobial compounds. *Human Pathol* **7:**287–95, 1976.
120. Edberg SC, Chu A. Determining antibiotic levels in the blood. *Am J Med Technol* **41:**99–105, 1975.
121. Isoherranen N, Soback S. Chromatographic methods for analysis of aminoglycoside antibiotics. *J AOAC Internatl* **82:**1017–45, 1999.
122. Soltes L. Aminoglycoside antibiotics – two decades of their HPLC bioanalysis. *Biomed Chromatog* **13:**3–10, 1999.
123. Adams E, Van Vaerenbergh G, Roets E, Hoogmartens J. Analysis of amikacin by liquid chromatography with pulsed electrochemical detection. *J Chromatog* **819:**93–7, 1998.
124. Preu M, Guyot D, Petz M. Development of a gas chromatography-mass spectrometry method for the analysis of aminoglycoside antibiotics using experimental design for the optimisation of the derivatisation reactions. *J Chromatog* **818:**95–108, 1998.
125. Tawa R, Matsunaga H, Fujimoto T. High-performance liquid chromatographic analysis of aminoglycoside antibiotics. *J Chromatog* **812:**141–50, 1998.
126. Stubbs C, Kanfer I. High-performance liquid chromatography of erythromycin propionyl ester and erythromycin base in biological fluids. *J Chromatog* **427:**93–101, 1988.
127. Croteau D, Vallee F, Bergeron MG, LeBel M. High-performance liquid chromatographic assay of erythromycin and its esters using electrochemical detection. *J Chromatog* **419:**205–12, 1987.
128. Stubbs C, Haigh JM, Kanfer I. Determination of erythromycin in serum and urine by high-performance liquid chromatography with ultra-violet detection. *J Pharm Sci* **74:**1126–8, 1985.
129. Chen ML, Chiou WL. Analysis of erythromycin in biological fluids by high-performance liquid chromatography with electrochemical detection. *J Chromatog* **278:**91–100, 1983.
130. Chu SY, Sennello LT, Sonders RC. Simultaneous determination of clarithromycin and 14®-hydroxyclarithromycin in plasma and urine using high-performance liquid chromatography with electrochemical detection. *J Chromatog* **571:**199–208, 1991.
131. Zhang S, Yuan Z, Liu H, Zou H, Xiong H, Wu Y. *Electophoresis* **21:**2995–8, 2000.
132. Merodio M, Campanero MA, Mirshahi T, Mirshahi M, Irache JM. Development of a sensitive method for the determination of ganciclovir by reversed-phase high-performance liquid chromatography. *J Chromatog* **870:**159–67, 2000.
133. Pham-Huy C, Stathoulopoulou F, Sandouk P, Scherrmann JM, Palombo S, Girre C. Rapid determination of valaciclovir and acyclovir in human biological fluids by high-performance liquid chromatography using isocratic elution. *J Chromatog B Biomed Sci Appl* **732:**47–53, 1999.
134. Eisenberg EJ, Cundy KC. High-performance liquid chromatographic determination of cytosine-containing compounds by precolumn fluorescence derivatization with phenacyl bromide: Application to antiviral nucleosides and nucleotides. *J Chromatog B Biomed Appl* **679:**119–27, 1996.
135. Frijus-Plessen N, Michaelis HC, Foth H, Kahl GF. Determination of 3'-azido-3'-deoxythymidine, 2',3'-dideoxycytidine, 3'fluoro-3'-deoxythymidine and 2',3'-dideoxyinosine in biological samples by high-performance liquid chromatography. *J Chromatog* **534:**101–7, 1990.
136. Unadkat JD, Crosby SS, Wang JP, Hertel CC. Simple and rapid high-performance liquid chromatographic assay for zidovudine (azidothymidine) in plasma and urine. *J Chromatog* **430:**420–3, 1988.

Part V
Nonsteroidal Anti-inflammatory Drugs

Chapter 11
Nonsteroidal Anti-inflammatory Drugs, Disease-Modifying Antirheumatic Drugs, and Agents Used in Gout

Imad K. Abukhalaf, Daniel A. von Deutsch, Naser A. Ansari, and Asma Alsharif

Abstract Inflammation and the immune response are the body's mechanisms to respond to harmful stimuli. They are designed to remove the insult and resolve tissue damage. Without these response/protective mechanisms, wounds and infections would never heal and progressive tissue destruction would persist and perhaps compromise our survival. On the other hand, if they were allowed to go unchecked, they can lead to a host of serious and debilitating diseases. Fortunately, these mechanisms are highly regulated in our bodies.

This chapter discusses various aspects of the pharmacology of therapeutic agents used in patients with inflammatory diseases, specifically, nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and the agents used in gout.

Keywords Anti-inflammatory • Analgesic • Antipyretic • Antirheumatic • NSAID • Cyclooxygenase inhibitors • Gout • COX 2 selective inhibitors • COX 2 preferential inhibitors • DMARD • Cytokines • Eicosanoids • Arachidonic acid • Uricosuric • Xanthine oxidase inhibitors

Introduction

Inflammation can be categorized into two categories; acute and chronic. Acute inflammation is the body's initial response to insults. It is characterized by redness, heat, swelling, pain, and loss of function. It is the result of an intricate network of molecular and cellular interactions induced by responses to a variety of stimuli such as infectious agents, trauma, and/or antibody reactions. The inflammatory cascade

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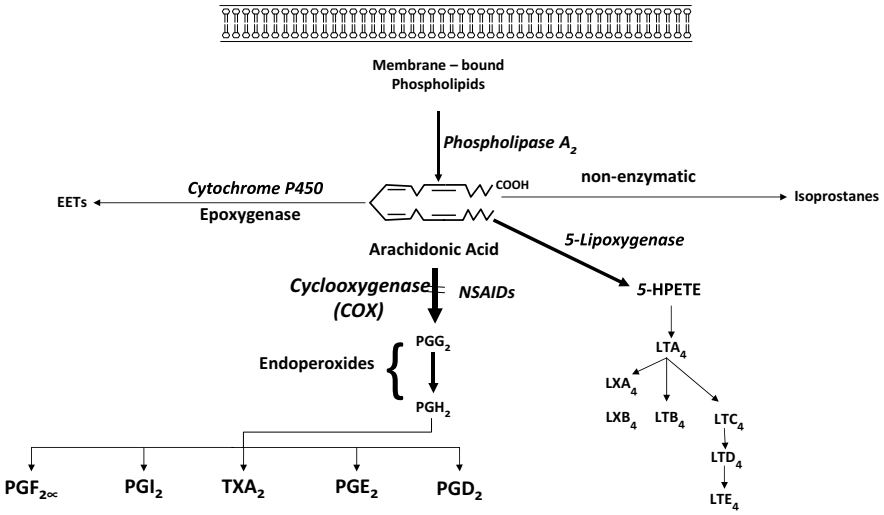

Fig. 11.1 Arachidonic acid metabolic pathways and eicosanoids synthesis. *NSAIDs* Nonsteroidal Anti-inflammatory Drugs, *PGs* Prostaglandins, *TXA2* Thromboxane A_2, *LT* Leukotriene (e.g. LTA_4), *LX* Lipoxin (e.g. LXB_4), *HPETE* Hydroperoxyeicosatetraenoic acid, *EETs* Epoxyeicosatetraenoic acids.The tissue and cell distribution of specific ecosanoids depends on the expression pattern of the enzymes involved in their synthesis. $PGF_2\alpha$ is a vasoconstrictor and bronchoconstrictor. PGI_2 is a vasodilator and inhibits platelet aggregation. TXA_2 is a vasoconstrictor and promotes platelet activation, PGE_2 is an immunomodulator, vasodilator, and plays a role in hyperalgesia and fever. PGD_2 inhibits platelet activation. LTB_4 is a chemotactic agent produced by neutrophils, it is a neutophil activator, recruits additional neutrophils and lymphocytes to the inflammation site, it is a vasodilator and plays a role in hyperalgesia. LTC_4, LTD_4, and LTE_4 are produced by macrophages and mast cells, they are vasoconstrictors, and modulate vascular permeability. Isoprostanes have anti-inflammatory role. LXA_4 and LXB_4 are counter-regulators of LK actions, they modulate the actions of cytokines and are important in the resolution of inflammation [1]

is initiated when cells are exposed to a foreign substance or are damaged. The insult stimulates a local cytokine cascade which facilitates the production of ecosanoids from arachidonic acid via the actions of cyclooxygenase (COX) and 5-lipoxygenase (Fig. 11.1). These ecosanoids are responsible for the cardinal signs of acute inflammation. They play numerous functions at different stages of the inflammatory process including chemotaxis, vasodilation, vasoconstriction, modulating vascular permeability, and hyperalgesia (Table 11.1). The acute inflammatory response requires constant stimulation to be sustained. As ecosanoid and cytokine inflammatory mediators have short half-lives and are rapidly degraded in the tissue, acute inflammation ceases to exist once the harmful stimulus is removed.

Sometimes, the response mechanism itself can be deleterious especially when it causes local tissue damage without resolving the underlying insult, thereby leading to chronic inflammation. Often, there are no distinctive boundaries in space or time among acute inflammation, chronic inflammation, and the repair process. Chronic inflammation, however, is characterized by a progressive shift in the type of cells which are present at the site of inflammation from polymorpho-

Table 11.1 Contributory roles of ecosanoids in inflammatory events

Ecosanoids	Chemotaxis and leukocyte adhesion	Increased vascular permeability	Vasodilation (erythema)	Vasoconstriction	Edema	Local heat and systemic fever	Hyperalgesia and pain
Prostaglandins, prostacyclins, and thromboxanes			PGD_2		PGE_2		
			PGE_1	TxA_2		PGE_2	PGE_2
			PGE_2	$PGF_{2\alpha}$		PGI_2	PGI_2
			PGI_2				
Leukotrienes	LTB_4		LTB_4		LTB_4		LTB_4
		LTC_4		LTC_4	LTC_4		
		LTD_4		LTD_4	LTD_4		
		LTE_4		LTE_4	LTE_4		
Lipoxins	LXA_4		LXA_4			LXA_4	
	LXB_4		LXB_4				

nuclear neutrophil leukocytes (present mainly during acute inflammation) towards mononuclear leukocytes (macrophages, monocytes, lymphocytes, and plasma cells). In addition, unlike acute inflammation, chronic inflammation has an insidious onset, and lasts for a relatively long time (weeks to years). The outcome of chronic inflammation is tissue destruction which can sometimes lead to a host of serious and debilitating diseases such as rheumatoid arthritis.

Collectively, leukotrienes, thromboxanes, prostacyclins, and cytokines such as interleukins (IL), tumor necrosis factor alpha (TNF-α) play key roles in generating, mediating, and maintaining the inflammatory process [1]. Distinctively, however, lipoxins (Fig. 11.1) have anti-inflammatory role [1]. They modulate the actions of cytokines and LK and are important in the resolution of inflammation [1]. It has been suggested that an imbalance in the leukotriene–lipoxin homeostasis may be a key factor in the pathogenesis of inflammatory diseases [1]. Table 11.1 summarizes the contributory roles of ecosanoids in the inflammatory responses.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Other Non-opioid Analgesics

In the literature, NSAIDs are sometimes referred to as antipyretic analgesics, non-opioid analgesics, anti-inflammatory analgesics, and to a lesser extent nonnarcotic analgesics. This is chiefly because most of these agents exert not only anti-inflammatory effect, but antipyretic and analgesic effects as well.

Generally, NSAIDs provide only symptomatic relief and do not slow the progression of the underlying disease. They are among the most widely used over-the-counter (OTC) therapeutic agents in the world and are commonly taken for minor to moderate pain, elevated body temperature, arthritis and other inflammatory disorders, as well as gout and hyperuricemia. For the most part, NSAIDs exert their effects by inhibiting COX, thereby preventing the conversion of arachidonic acid to prostaglandins (PGs).

Although not all NSAIDs are approved by the Federal Drug Administration (FDA) for the treatment of rheumatic diseases, most of them, however, are effective in rheumatoid arthritis, osteoarthritis, and localized musculoskeletal sprains and strains.

Most NSAIDs possess chiral centers. However, the pharmacological activities of NSAIDs appear to be due largely to the (S)- enantiomer. With the exception of naproxen, all commercial preparations available in the United States are racemic mixtures.

Biochemical Classification of NSAIDs

COX occurs in two isoforms, COX-1 and COX-2 [2]. COX-1 is a constitutive enzyme expressed in most tissues and in blood platelets. COX-2 is an inducible

enzyme (induced by cytokines, growth factors, and tumor promoters) and present mainly in inflammatory cells. Both enzymes catalyze the conversion of arachidonic acid to PGs which along with other ecosanoids play major roles in the inflammatory process (Fig. 11.1).

The anti-inflammatory effect of NSAIDs is usually the result of their inhibition of COX-2, whereas their unwanted adverse effects (mainly gastrointestinal (GI) irritation) are primarily the result of their inhibition of COX-1. Generally NSAIDs can be divided into three categories depending on their ability to inhibit COX 1 and COX 2 [3, 4]; NSAIDs that inhibit both COX-1 and COX-2 are referred to as non-selective COX inhibitors, NSAIDs that inhibit COX-2 to a higher extent than COX-1 are referred to as COX-2 preferential inhibitors, and the new-generation NSAIDs that selectively inhibit COX-2 are referred to as COX-2 selective inhibitors (Table 11.2).

Non-selective COX inhibitors block the hydrophobic channel located in juxtaposition to the active site of these enzymes resulting in inhibiting the catalytic activities of these enzymes. COX-2 selective inhibitors are hydrophobic sulfonic acid derivatives, hence, their large molecular size does not allow them to gain access to the hydrophobic channel of COX-1. These drugs selectively inhibit COX-2 because the hydrophobic channel of COX-2 is larger than that of COX-1 and thus can be blocked by these agents.

Chemistry

With the exception of nabumetone, which is a ketone prodrug, all non-selective COX inhibitors that are available in the United States are weak organic acids. As shown in Table 11.2, they are categorized into several classes of compounds. These are: salicylic acids, acetic acid derivatives, propionic acid derivatives, fenamic acid derivatives, oxicams, paraphenolic acid derivatives, and pyrazolones. This dissimilarity in the chemical structure of NSAIDs results in a protean spectrum of pharmacokinetic properties.

Pharmacokinetics

The fact that NSAIDs possess wide range of pharmacokinetic properties does not mean that they do not share common characteristics. For instance, most of these drugs are well absorbed, and food does not substantially change their bioavailability. Additionally, most of these agents are highly protein-bound usually to albumin. Most NSAIDs are extensively metabolized, some by both phase I and phase II biotransformation reactions, whereas others by phase II conjugation reactions only. CYP3A or CYP2C are the main cytochrome P450 enzyme families responsible for

Table 11.2 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Non-selective COX inhibitors									
Salicylates								COX-2 preferential inhibitors	COX-2 selective inhibitors
Acetylated salicylates	Nonacetylated salicylates	Acetic acid derivatives	Propionic acid derivatives	Fenamic acid derivatives	Pyrazolone derivatives[a]	Oxicam derivatives	*Para*- aminophenol derivatives		
Aspirin	Sodium salicylate	Indomethacin	Ibuprofen	Mefenamic acid	Phenylbutazone	Piroxicam	Acetaminophen	Nabumetone[b]	Celecoxib
Diflunisal	Calcium salicylate	Sulindac	Naproxen	Meclofenamate	Oxyphenbutazone	Tenoxicam[b]	Phenacetin[a]	Meloxicam	Rofecoxib[a]
	Choline magnesium salicylate	Tolmetin	Fenoprofen	Flufenamic acid[a]	Metamizol			Etodolac	Valdecoxib[a]
	Salicyl salicylate	Diclofenac	Ketoprofen		Propiphenazone			Nimesulide[a]	
		Ketorolac	Flurbiprofen						
		Bromfenac sodium	Oxaprozin						
			Suprofen						

[a]Not available or no longer available in the United States
[b]Prodrug

most of phase I biotransformation reactions involving NSAIDs. Although some NSAIDS (and their metabolites) undergo enterohepatic circulation, generally, elimination of NSAIDs occurs primarily by renal excretion.

Pharmacodynamics

To varying degrees all NSAIDs possess anti-inflammatory, analgesic, antipyretic properties and all except COX-2 selective inhibitors inhibit platelet aggregation. Among all non-selective COX inhibitors, aspirin has been shown to be the most effective inhibitor of platelet aggregation.

The main adverse effect of NSAIDs is GI irritability. Although the efficacy of COX-2 selective inhibitors is equal to that of non-selective inhibitors, their GI adverse effects are significantly less. In addition to hepatotoxicity, nephrotoxicity has been observed in patients taking NSAIDs chronically. This is, in part, due to the NSAIDs ability to inhibit the production of PGs, the main modulators of renal blood flow. Details of the pharmacologic and adverse effects of NSAIDs are described below.

Anti-inflammatory Effects

As mentioned earlier, ecosanoids, particularly PGs, are important chemical mediators that play major roles in the inflammatory process. Inhibiting the biosynthesis of these eicosanoids results in the disruption of the biochemical events of the inflammatory process. The main anti-inflammatory effect of NSAIDs is mediated primarily by the inhibition of PG synthesis. Specifically, NSAIDs inhibit COX, the enzyme that catalyzes the formation of prostaglandin endoperoxides PGG_2 and PGH_2 from arachidonic acid. As a result, the synthesis of all PGs and thromboxanes derived from these endoperoxides is inhibited (Fig. 11.1). This does not mean, however, that COX inhibition is NSAIDs' only anti-inflammatory mechanism of action; other mechanisms of action do contribute to the overall anti-inflammatory activity of some NSAIDs such as down-regulation of IL-1 synthesis, inhibition of chemotaxis, and decreased production of superoxides and free radicals [5].

Antipyretic Effects of NSAIDs

Control of the body's temperature occurs in the thermoregulatory center in the hypothalamus. This center regulates the balance between the loss of body heat and heat production. Fever occurs when this balance is altered in favor of heat production. The inflammatory process and/or bacterial endotoxins cause(s) the release of IL-1 from macrophage cells which, in turn, induce the biosynthesis of E-type prostaglandins (PGE_n) in the hypothalamus, causing an increase in the body's temperature (fever) by

raising the "thermostatic set-point." NSAIDs can reset the body's "thermostatic set-point" through the inhibition of COX, hence PGE_n biosynthesis. This action results in dilating superficial blood vessels and increased sweating, followed by a drop in temperature. NSAIDs have no effect on normal body temperature.

Analgesic Effects of NSAIDs

Tissue damage and inflammation result in the production of PGs. Some of these PGs, e.g., PGE_2, sensitize nociceptors to the actions of bradykinin, histamine, 5-hydroxytryptamine, and other chemical mediators [6]. Thus, pain associated with inflammatory diseases such as arthritis, bursitis, and with some forms of cancer (metastatic cancer of bone) can effectively be alleviated with NSAIDs. Additionally, by inhibiting COX, NSAIDs are very effective in alleviating headaches resulting from the vasodilatory effects of PGE_2. NSAIDs can also be used in combination with opioids resulting in a reduction of the required effective dose of opiates by 30%.

In addition to the effects that NSAIDs exert locally in alleviating pain, there is growing evidence that NSAIDs act, in part, through a centrally mediated mechanism(s) [7]. Hitherto, however, the mechanism(s) by which NSAIDs act centrally remain(s) unclear. It is believed, however, that in addition to NSAIDs' ability to inhibit COX, they may act through monoaminergic control system. PGs such as PGE_2 have been shown to augment the action of excitatory neural mediators such as calcitonin gene-related peptides through mediating their release. By inhibiting the action of COX centrally, NSAIDs block PGE_2-mediated interference with the down-regulation of nociception, thereby reducing the magnitude and duration of pain.

Anti-platelet Effects of NSAIDs

Most NSAIDs (non-selective COX inhibitors) inhibit the synthesis of thromboxane A_2 (TXA_2) in the platelet resulting in inhibiting platelet aggregation. Because aspirin is the only irreversible inhibitor of COX-1, it is the most effective anti-platelet aggregation agent of all NSAIDs.

Common Adverse Effects of NSAIDs

Adverse effects of NSAIDs are common especially in individuals taking high doses over long periods of time [8]. Common adverse effects are often encountered in the GI tract, skin, kidney, and to a lesser extent in liver, spleen, blood, and bone marrow. The severity and frequency of occurrence of these effects vary greatly among NSAIDs.

On the Gastrointestinal Tract

The most common adverse effects associated with the use of NSAIDs are GI tract disturbances that include dyspepsia, diarrhea or constipation, nausea, and vomiting [9]. The extent of gastric damage in chronic users may go unnoticed, potentially leading to erosive gastritis, peptic ulceration, and serious hemorrhage. The risk of such damage in chronic users has been estimated to be approximately one out of five. The risk of gastric bleeding from commonly prescribed NSAIDs varies greatly. Due to the seriousness and frequency of GI irritation associated with NSAIDs, warnings regarding the risks of serious GI injury are now included with the NSAID package inserts as required by the FDA.

The mechanism by which NSAIDs cause GI tract damage is a result of its inhibition of COX-1, thereby inhibiting the production of PGE_2, which is responsible for regulating gastric acid secretion and mucosal protection. The effect of NSAIDs on gastric damage can be reduced by oral administration of PG analogs such as misoprostol which is approved for the prophylaxis against NSAID-induced ulcers.

On the Skin

The second most common adverse effect associated with the use of NSAIDs is skin reactions, which can range from mild rashes, photosensitivity, and urticaria to more serious conditions. Fortunately, potentially fatal skin-related adverse reactions are rare. Sulindac and mefenamic acid have particularly high incidences of skin reactions, with frequencies of occurrence of 5–10% and 10–15%, respectively.

On the Renal System

Generally, normal use of NSAIDs has little impact on kidney function. However, some individuals suffer acute reversible renal insufficiency, which usually ends when drug administration is stopped. The basis behind these renal effects is that PGE_2 and PGI_2 influence renal vasodilation and inhibit the actions of the antidiuretic hormone (ADH). This results in decreased water reabsorption, and thus enhanced water excretion. Inhibiting PG biosynthesis by NSAIDs results in renal vasoconstriction, increased water reabsorption, hence increased water retention. Unlike normal usage, chronic treatment with NSAIDs can result in more serious adverse effects such as chronic nephritis and renal papillary necrosis. The combination of these two conditions may lead to “analgesic nephropathy.”

On the Cardiovascular System

COX-2 selective inhibitors have been associated with increased cardiovascular risk. This will be discussed in detail under “COX-2 Selective Inhibitors.”

Common Drug Interactions

NSAIDs interact with several therapeutic agents and with themselves [10]. For example, aspirin has been known to dissociate other NSAIDs from the plasma protein-binding sites. The most important drug interactions involving NSAIDs are those with heparin and oral anticoagulants. The concomitant administration of NSAIDs with heparin or oral anticoagulants such as warfarin has been known to increase the risk of bleeding. This is because of the NSAIDs ability to inhibit platelet aggregation and displace these agents (anticoagulants) from their plasma protein-binding sites, thus potentiating their effect(s). Other drug interactions include sulfonamides, which can also be displaced from their plasma protein-binding sites by salicylates resulting in increased blood concentrations of free sulfonamides and therefore increased toxicity associated with these agents. Likewise, the combination of NSAIDs with lithium or methotrexate can lead to increased toxicity associated with these agents as their rate of excretion is reduced, thus increasing their plasma levels. Additionally, the co-administration of any of the NSAIDs and probenecid results in potentiation of the NSAID effect. Patients who combine NSAIDs with these agents should be monitored closely for titration of dosage.

Other drug interactions involving NSAIDs are those with loop diuretics and antihypertensive drugs. The concomitant administration of NSAID and a diuretic or an antihypertensive agent leads to decreased efficacies of these agents. In such cases, patients should be monitored closely for drug effectiveness.

Non-selective COX Inhibitors

Salicylates

Available salicylate preparations include acetyl salicylic acid, sodium salicylate, salicylic acid, magnesium salicylate, methylsalicylate, salicylamide, 5-aminosalicylate, and diflunisal. The most frequently used members of this class of drugs are acetyl salicylic acid (aspirin) and sodium salicylate [11, 12]. Until the advent of ibuprofen, aspirin was the standard against which all NSAIDs were measured. Like other NSAIDs, the analgesic, antipyretic, and anti-inflammatory actions of salicylates are primarily attributed to their ability to inhibit COX. The action of salicylates is exerted both in the periphery and at the thermoregulatory center in the brain.

Acetylated Salicylates

Aspirin (Acetyl Salicylic Acid)

Absorption, Distribution, and Metabolism As with all acidic drugs, aspirin (and other salicylates) absorption is influenced by pH. Aspirin is rapidly absorbed in the stomach and upper small intestine in the nonionized form. Alkalinization of the

Table 11.3 Half-lives of nonsteroidal anti-inflammatory drugs

Non-selective COX inhibitors		COX-2 preferential inhibitors		COX-2 selective inhibitors	
Drug	Half-life (h)	Drug	Half-life (h)	Drug	Half-life (h)
Aspirin	0.25	Nabumetone[c]	26	Celecoxib	11
Salicylate[a]	2–19	Meloxicam	20		
Diclofenac	1.1	Etodolac	6.5		
Diflunisal	13				
Fenoprofen	2.5				
Flurbiprofen	3.8				
Ibuprofen	2				
Indomethacin	4–5				
Ketoprofen	1.8				
Ketorolac	4–10				
Meclofenamate	3				
Naproxen	14				
Oxaprozin	58				
Piroxicam	57				
Sulindac	8				
Tolmetin	1				
Suprofen	2				
Bromfenac[b] Sodium	1.4				

[a]Major anti-inflammatory metabolite of aspirin
[b]Half-life in the vitreous humor
[c]Nabumetone is a prodrug; the half-life is for its active metabolite

gastric juice and the use of enteric-coated or buffered aspirin preparations result in reduced gastric irritation and decreased rate (not extent) of absorption without reducing its clinical effectiveness. Aspirin, like most NSAIDs, is transported bound to albumin (90%). It is distributed across membranes by passive diffusion. It crosses the placenta and can be detected in milk, other bodily fluids, and tissues.

Once absorbed, aspirin undergoes rapid hydrolysis of its components, salicylate and acetic acid, by the actions of tissue and plasma esterases. This accounts for its short (15 min) plasma half-life. Half-lives of salicylates and other NSAIDs are shown in Table 11.3. Most of aspirin's therapeutic effects are attributed to its salicylate metabolite. Approximately, 13% of a given salicylate therapeutic dose is eliminated in the urine, and the rest undergoes several routes of biotransformation reactions before elimination, of which 50% is conjugated to glycine, 20% is glucuronated at the hydroxyl-group site, 12% is glucuronated at the carboxyl-group site, and the rest (less than 5%) is oxidized into gentisic acid.

When plasma concentration of salicylate exceeds 300 μg/mL (total body load of 600 mg), the metabolic enzyme system responsible for salicylate metabolism becomes saturated resulting in a longer half-life for the drug. At this point, elimination of salicylate conjugates by the kidney changes from first-order to zero-order kinetics. This means that any additional amount of salicylate beyond this point will result in a disproportionate increase in salicylate concentration. Consequently,

salicylate half-life increases from 3 to 5 h at the lower analgesic doses to 12–15 h at the higher anti-inflammatory doses.

Pharmacologic Actions and Therapeutic Indications Aspirin possesses anti-inflammatory, analgesic, antipyretic, and anti-platelet properties. Among all NSAIDs, aspirin is the only agent that irreversibly inhibits COX by acetylating the serine residue(s) at or near the active site of the enzyme [13]. In addition, it interferes with the functions of inflammatory chemical mediators resulting in inhibiting granulocyte adherence to damaged vasculature, stabilizing lysosomal membranes, and inhibiting the migration of polymorphonuclear leukocytes to the inflammation site [14].

As an analgesic, aspirin is indicated for reducing pain of mild to moderate intensity. It is ineffective in cases of severe visceral pain. By inhibiting PG synthesis, PGE_2 will not be available to sensitize the nerve endings to the actions of bradykinin, histamine, and other chemical mediators of inflammation, and thus sensation of pain is inhibited.

As an antipyretic, aspirin is indicated for reducing elevated body temperature. It has virtually no effect on normal body temperature. This effect is mediated by COX inhibition in the thermoregulatory center in the hypothalamus. This results in the inhibition of PGE_2 biosynthesis which is normally released by leukocytes in response to inflammation or infection. Additionally, aspirin inhibits IL-1 (a cytokine released from macrophages during inflammation). Such actions culminate in vasodilation of superficial blood vessels and therefore, increased heat dissipation.

In significantly lower doses, aspirin is a very effective antithrombotic agent indicated in the prophylaxis of myocardial infarction, stroke, and other thromboembolic disorders [15]. It is well documented that the PG TXA2 enhances platelet aggregation, a primary event in thrombus formation. At low doses, aspirin inhibits the production of TXA_2 in platelets (by irreversibly inhibiting COX) resulting in reduced platelet aggregation [16].

Aspirin has also been shown to reduce the incidence of colon cancer when taken chronically by approximately 50%.

Preparations and Dosage Aspirin is commercially available in many forms such as tablets, chewable tablets, chewing gum, controlled-release tablets, enteric-coated tablets, and solutions. Generally, the dosage of aspirin needed to inhibit platelet aggregation is significantly less than that needed for analgesic or antipyretic effect, which in turn, is less than the dose needed to relieve inflammation caused by arthritic and other inflammatory disorders. For the relief of mild pain or fever, the optimal dose for adults and adolescents ranges from 325 to 650 mg every 4 h, or 500 mg every 3 h, or 1,000 mg every 6 h. For children ages 2–14, the optimal dose ranges from 10 to 15 mg/kg every 4 h, up to 80 mg/kg/day.

For the relief of mild to moderate pain associated with inflammation, as in osteoarthritis or rheumatoid arthritis, the maximum dosage for adults should not exceed 6 g/day. For children, the dose ranges from 10 to 80 mg/kg/day, in divided doses every 4–6 h. On the other hand, if indicated for the treatment of juvenile

Table 11.4 Pharmacologic and adverse/toxic effects of salicylates

Dose (g)	Plasma concentration (mg/dL)	Pharmacologic	Adverse/toxic effects
0.08–0.16	0–5	Anti-platelet	Impaired hemostasis, hypersensitivity reactions, gastric intolerance, bleeding
0.65–0.975	5–10	Antipyretic, analgesic	
3–6	10–50	Uricosuric, anti-inflammatory	Tinnitus
6–10	50–80	Salicylism	Hyperventilation, respiratory alkalosis
10–20	80–110	Salicylism	Fever, dehydration, metabolic acidosis
20–30	>110	Salicylism	Shock, coma, respiratory and renal failure, death

rheumatoid arthritis, the dose ranges from 60 to 110 mg/kg/day in divided doses every 6–8 h. For the treatment of acute rheumatic fever, however, the dose for adult ranges from 5 to 8 g/d in divided doses. As for children, the initial dose should not exceed 100 mg/kg/day in divided doses for the first 2 weeks, then a maintenance dose of 75 mg/kg/day in divided doses for the next 4–6 weeks.

To reduce the severity of, or prevent acute myocardial infarction, aspirin is indicated in a dose of 160 mg/day. To reduce the risk of myocardial infarction for patients with unstable angina or previous myocardial infarction, aspirin should be administered in a dose of 325 mg/day. As discussed previously, when aspirin is taken in anti-inflammatory doses, the half-life of its primary active metabolite, salicylic acid, changes to 12 h or more. In this case, frequent dosing may not be necessary. It is clinically acceptable for patients who are on high-dose regimen to divide their total daily dosage of aspirin into only three portions taken after meals.

Contraindications Aspirin is contraindicated in patients who are allergic to aspirin or its derivatives and components, to tartrazine dye, and in people with asthma, or bleeding disorders such as hemophilia and peptic ulcers. Aspirin is also contraindicated in children with flu symptoms or chickenpox, because aspirin may increase the risk of Reye's syndrome. There has been no evidence that aspirin exerts any harmful effects on the unborn fetus.

Adverse Effects Adverse effects associated with aspirin are dose-dependent. At therapeutic doses, aspirin can cause GI distress and ulceration. High anti-inflammatory doses can cause tinnitis. Regular use of large doses can cause decreased blood iron levels (from bleeding), leukopenia, thrombocytopenia, ecchymosis, rash, urticaria, angioedema, and salicylism, which is characterized by dizziness, tinnitus, vomiting, diarrhea, confusion, central nervous system (CNS) depression, diaphoresis, headache, hyperventilation, and lassitude. As mentioned above, treatment with aspirin should be avoided with children to eliminate the risk of Reye's syndrome. Table 11.4 illustrates the toxic effects associated with various doses of aspirin.

Treatment of Aspirin Toxicity and Salicylism Treatment should start with measuring plasma salicylate levels and urine pH. As shown in Table 11.4, serious toxicity becomes imminent if the amount ingested exceeds 150 mg/kg. If ingestion is recent, gastric lavage is recommended. In serious cases, intravenous administration of fluid to maintain high urine volume is necessary. Infusion of sodium bicarbonate to alkalinize the urine, ventilatory assistance, correction of acid–base and electrolyte imbalance is of utmost importance.

Drug Interactions Administering aspirin concomitantly with other drugs/drug classes may produce undesirable adverse effects [17]. These drugs/drug classes include:

- *Heparin or other anticoagulants*: It is well documented that the combination of aspirin and heparin, coumarin, or any other anticoagulant results in increased risk of bleeding and prolongation of bleeding time.
- *Antacids and activated charcoal*: They have been shown to reduce the rate of aspirin absorption.
- *Urine acidifiers*: Urine acidifiers such as ascorbic acid, sodium phosphate, and ammonium chloride decrease the rate of excretion of salicylic acid by increasing the rate of its reabsorption.
- *Urine alkalinizers (i.e., methotrexate)*: They increase the rate of aspirin excretion.
- *Alcohol*: Concomitant administration of alcohol and aspirin results in increased risk of bleeding.
- *Penicillin*: Aspirin increases the half-life of penicillin because it competes with penicillin on the active secretory transporters in the renal tubules.
- *Vancomycin*: Co-administration of aspirin and vancomycin results in increased risk of ototoxicity.
- *ACE (angiotensin-converting enzyme) inhibitors (i.e., enalapril)*: Concomitant administration of aspirin and ACE inhibitors results in decreased antihypertensive effect.
- *Corticosteroids*: They increase the rate of excretion of aspirin resulting in reduced plasma levels.
- *Carbonic anhydrase inhibitors (i.e., acetazolamide)*: Although they increase excretion of aspirin, they also potentiate its toxicity by inducing metabolic acidosis and enhancing its penetration into the tissues.
- *Nizatidine*: Results in increased plasma levels of aspirin.
- *Methotrexate*: Aspirin has been shown to decrease the rate of excretion of methotrexate resulting in higher plasma levels and increased methotrexate toxicity.
- *Sulfonylureas (i.e., toblutamide)*: Large doses of aspirin may enhance the effects of sulfonylureas.

Diflunisal

Diflunisal is a difluorophenyl derivative of salicylic acid that is not metabolized into salicylic acid. It is more potent than aspirin as an anti-inflammatory and analgesic agent. On the other hand, unlike aspirin, it does not exert antipyretic effect. Diflunisal

undergoes enterohepatic circulation and is also found in the milk of lactating women. Additionally, its adverse effects are similar to other NSAIDs but to a lesser extent. Diflunisal metabolism is subject to saturation kinetics. Because its clearance is dependent on renal function, it is contraindicated in patients with compromised renal function. Additionally, it is contraindicated in patients with asthma attacks, rhinitis, NSAID-precipitated urticaria, and in patients sensitive to diflunisal.

Preparations and Dosage Diflunisal is available in 250- and 500-mg tablets. For the relief of mild to moderate pain, diflunisal is started with a 1-g dose followed by 0.5 g every 8–12 h. Maximum dosage should not exceed 1.5 g/day. As an anti-inflammatory agent for patients with osteoarthritis or rheumatoid arthritis, diflunisal is initiated as 0.5 or 1 g/day in divided doses twice a day provided that the daily dosage does not exceed 1.5 g.

Drug Interactions Diflunisal interacts with several drug/drug classes, which include:

- *Antacids*: Concomitant administration of diflunisal and antacids results in decreased plasma levels of diflunisal.
- *NSAIDs*: Diflunisal should not be taken with other NSAIDs for this may result in increased risk of GI irritation and bleeding.
- *Acetaminophen*: Long-term use of both diflunisal and acetaminophen may increase the risk of adverse renal effects.
- *Beta-blockers*: Diflunisal has been shown to impair the antihypertensive effects of beta-blockers and other antihypertensive agents.
- Concomitant use of diflunisal with cefamandole, cefoperazone, cefotetan, valproic acid, or plicamycin may result in increased risk of hypoprothrombinemia.
- The use of diflunisal with colchicine, glucocorticoids, potassium supplements, alcohol, or the long-term use of corticotropin has been shown to increase the risk of GI irritation and bleeding.
- *Cyclosporine and gold compounds*: Co-administration of either compound with diflunisal increases the risk of nephrotoxicity.
- *Digoxin, methotrexate, phenytoin, insulin, oral antidiabetic agents, and loop diuretics*: The administration of any of these agents with diflunisal results in increased plasma concentration of these drugs, which may lead to increased toxicity associated with these agents.
- *Heparin, oral anticoagulants, thrombolytic agents*: Diflunisal administration with any of these drugs/drug classes may result in prolonged prothrombin time, and increased risk of bleeding.
- *Probenecid*: It increases plasma concentrations of diflunisal.

Nonacetylated Salicylates

Nonacetylated salicylates agents include salicylsalicylate (salsalate), magnesium salicylate, sodium salicylate, calcium salicylate, choline salicylate, and choline

magnesium salicylate. These agents possess anti-inflammatory activity. As analgesics, however, they are less effective than aspirin. Because they are less effective inhibitors of COX, their side effects regarding GI irritation and peptic ulceration are attenuated rendering them suitable for patients with asthma and with individuals who are prone to bleeding and/or GI disorders.

Acetic Acid Derivatives

Indomethacin

Indomethacin is an indole acetic acid derivative. It is 20–30 times more potent than aspirin in its anti-inflammatory, analgesic, and antipyretic effects. This is attributable not only to COX inhibition, but also to its ability to reduce polymorphonuclear leukocytes migration and decrease T- and B-cell proliferation, which are key events in the inflammatory process. It is also believed to inhibit the production of arachidonic acid (primary precursor of eicosanoids) by inhibiting phospholipases A and C [18]. It also influences the intracellular cyclic-AMP (adenosine monophosphate) concentrations by inhibiting phosphodiesterase.

Like most other NSAIDs, indomethacin is well absorbed. It is metabolized in the liver and undergoes extensive enterohepatic circulation. It appears in the breast milk of lactating women. Indomethacin and its inactive metabolites are excreted unchanged in bile and urine. It is indicated for the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is also very effective in the management of acute gouty arthritis. It is the drug of choice for the treatment of patent ductus arteriosus, which is maintained by continual synthesis of prostacyclin and PGE_2 [19]. It is also used in the management of Bartter's syndrome, which involves a deficiency in renal chloride reabsorption and overproduction of PGs, and Sweet's syndrome, which is acute febrile neurophilic dermatosis.

Preparations and Dosage

Indomethacin is available in 25- and 50-mg capsules, 75-mg sustained-release capsules, and 25-mg/5 mL suspension also for oral use. Additionally, 50-mg suppositories and 1-mg indomethacin per vial for intravenous use (after suspension) are also available.

For the symptomatic relief of osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis in adults, indomethacin is administered in 25- to 50-mg tablets (or oral suspension) twice to four times a day. The dosage can be increased by 25 or 50 mg/day every week as long as the total dose does not exceed 200 mg/day. After clinically acceptable response is achieved, the dose should be reduced to the minimum required to maintain the same response. Suppositories can be given in 50-mg doses up to four times a day.

For the symptomatic relief of juvenile arthritis, indomethacin is administered 1.5–2.5 mg/kg/day in divided doses (three to four times per day) not to exceed 4 mg/kg/day or 150–200 mg/day. When a clinically acceptable response is achieved, the dose is reduced to the minimum dose needed to maintain that response.

For the symptomatic relief of acute gouty arthritis in adults, the usual loading dose is 100 mg followed by 50 mg three times a day. Maximum dosage should not exceed 200 mg/day. When a clinically acceptable response is achieved, dosage should be tapered until the drug is discontinued. If suppositories are used, 50 mg four times a day is the recommended regimen. Suppository use should be avoided when possible to avoid rectal irritation and bleeding.

For the treatment of patent ductus arteriosus in premature infants weighing 500–1,750 g, initial loading dose of 0.2 mg/kg over 5–10 s, followed by 0.25 mg/kg given at 12- to 24-h intervals, if needed. For neonates who are less than 7 days old, the follow-up dosage is reduced to 0.2 mg/kg. For neonates under 2 days old, the follow-up dosage is reduced to 0.1 mg/kg, if needed.

Contraindications and Adverse Effects

Indomethacin is strictly contraindicated in pregnancy, especially during the third trimester to prevent indomethacin-induced premature closure of the ductus arteriosus. It is also contraindicated in patients allergic to indomethacin, iodides, other NSAIDs, or their components. Adverse effects associated with indomethacin include abdominal pain, diarrhea, vomiting, pancreatitis, and GI bleeding. Headaches (in some cases associated with dizziness and confusion) have been reported in 15–25% of patients. Hematinic adverse effects were reported including agranulocytosis, aplastic anemia, bone marrow depression, hemolytic anemia, and iron-deficiency anemia. Hyperkalemia and hypoglycemia were also reported. Because it can be excreted in the breast milk of lactating mothers, it may cause seizures in infants.

Drug Interactions

The agents that interact with diflunisal (listed earlier), also interact with indomethacin. Other drugs/drug classes that interact with indomethacin include:

- *Aminoglycosides*: the co-administration of aminoglycosides and indomethacin results in increased risk of aminoglycoside toxicity as a result of its increased concentration in the plasma.
- *Bone marrow depressants*: may result in increased leukopenic and thrombocytopenic effects of these agents.
- *Probenecid*: significantly prolongs indomethacin's half-life resulting in increased indomethacin toxicity.
- *Zidovudine*: the co-administration of zidovudine and indomethacin results in increased toxicity of both drugs.
- *Lithium*: the co-administration of indomethacin and lithium results in increased plasma lithium concentration which may lead to increased lithium toxicity.
- *Platelet aggregation inhibitors*: may result in increased risk of GI irritation and hemorrhage.
- *Diflunisal*: increases plasma indomethacin concentration resulting in increased toxicity.

Diclofenac

Diclofenac is a phenylacetic acid derivative that possesses anti-inflammatory, analgesic, and antipyretic properties with potency equal to that of indomethacin. This is attributable not only to its effectiveness in inhibiting COX but its ability to decrease the bioavailability of arachidonic acid by enhancing its conversion to triglycerides. Like most other NSAIDs, diclofenac is rapidly absorbed following oral administration, and undergoes extensive first-pass metabolism resulting in a systemic bioavailability of approximately 50%. It is one of the few NSAIDs that accumulates in the synovial fluid with half-life in this compartment double that of the plasma. It is metabolized in the liver principally by CYP3A4 and its inactive metabolites are excreted primarily in urine and to a lesser extent in the bile. Its side effects are those common to NSAIDs, which include GI distress, hemorrhage, and to a lesser extent peptic ulceration. This drug is more commonly associated with increased plasma aminotransferase levels than any other NSAID. Other adverse effects such as dizziness, drowsiness, headache, bradycardia, glaucoma, tinnitis, and leukocytosis have been reported although to a lesser extent.

Preparations, Therapeutic Indications, and Contraindications

Diclofenac sodium is available in 25-, 50-, and 75-mg enteric-coated tablets. Extended-release tablets and rectal suppositories are available for adults. Diclofenac is indicated primarily as an anti-inflammatory agent in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis [20]. Additionally, it is used as an analgesic in the management of patients with dysminorrhea and/or chronic lower back pain. In Europe, it is also available as an oral mouthwash. Diclofenac is contraindicated in patients with active bleeding or ulcers, asthma attacks, rhinitis, NSAID-induced urticaria, or allergy to diclofenac or other NSAIDs.

Dosages

For the relief of pain and inflammation in rheumatoid arthritis, 75 or 100 mg of diclofenac sodium, as extended-release tablets, is administered daily (or 75 mg twice a day). If regular tablets are used, the loading dose should be 150–200 mg/day in divided doses. The maintenance dose is 75–100 mg/day in divided doses. The maximum dose should not exceed 225 mg/day. For the last dose, sometimes rectal suppositories are used in place of tablets. In such case, 50–100 mg of diclofenac is given.

For the relief of pain and inflammation of osteoarthritis, diclofenac tablets are given in the amount of 100–150 mg/day in divided doses. The maximum dose should not exceed 150 mg/day. To relieve pain in ankylosing spondylitis, diclofenac tablets are given in the amount of 100–125 mg/day in four or five divided doses.

For the relief of pain associated with dysmenorrhea, diclofenac tablets (50 mg) are given twice a day; if necessary, 100 mg can be given as a loading dose only.

If the patients are elderly or have serious renal dysfunction, dosage may be reduced.

Drug Interactions

Plasma levels of diclofenac are increased by the co-administration of cimetidine. Cimetidine, a histamine receptor antagonist, also binds to cytochrome P450 and diminishes the activity of hepatic microsomal mixed-function oxidases. Diclofenac also interacts with the drug/drug classes that interact with indomethacin (detailed previously).

Bromfenac

It is a phenylacetic acid derivative. It was withdrawn from the market following reports of severe and sometimes fatal hepatic failure. Currently, bromfenac sodium is available as an ophthalmic preparation and is indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

Sulindac

Sulindac is a pyrroleacetic acid derivative. It is a prodrug that is metabolized into an active sulfide metabolite that possesses significant anti-inflammatory activity. It is very well absorbed when administered orally. Because the metabolite undergoes extensive enterohepatic circulation, it has a relatively long half-life (Table 11.3). It occurs in two enantiomers with the S (−) enantiomer being more active as COX inhibitor than the R (+) enantiomer.

As with other NSAIDs the use of sulindac is associated with GI distress although to a lesser extent than indomethacin or aspirin. However, like diclofenac, it is associated with increased plasma levels of aminotransferases. Additionally, among all NSAIDs, it is the most commonly associated with cholestatic liver damage. Other less common adverse effects observed with sulindac include thrombocytopenia, agranulocytosis, and nephrotic syndrome.

Preparations, Therapeutic Indications, and Contraindications

Sulindac is available in 100- and 200-mg tablets. Sulindac is indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, tendinitis, and brusitis. It has also been shown to reduce the growth of polyps and precancerous lesions in the colon especially those associated with familial intestinal polyposis. In addition, it is an effective tocolytic agent and may be used in the treatment of pre-term labor. Sulindac is contraindicated in patients with angioadema, asthma, bronchospasm, nasal polyps, rhinitis, or NSAID-induced urticaria.

Dosage

To decrease pain and inflammation in ankylosing spondylitis, bursitis, osteoarthritis, and rheumatoid arthritis, sulindac is administered in a dose of 150–200 mg twice a day. This dosage is to be adjusted based on the patient's response up to a maximum of 200 mg twice a day. For the relief of symptoms of acute gouty arthritis and tendinitis, sulindac is given as 200 mg twice a day for 7–14 days. This dosage should be decreased to the lowest effective dosage after obtaining a clinically satisfactory response. In elderly patients, if necessary, the dosage can be reduced to half of the usual adult dosage.

Drug Interactions

Like diclofenac and other NSAIDs, sulindac interacts with several therapeutic agents. In addition to the interactions shown with diflunisal, diclofenac, and other NSAIDs, sulindac interacts with the following drugs/drug classes:

- *Ranitidine and cimetidine*: Co-administration of sulindac with either of these agents leads to increased bioavailability of these agents.
- *Dimethyl sulfoxide (DMSO)*: Co-administration of DMSO and sulindac leads to decreased effectiveness of the latter.

Tolmetin

Tolmetin is a pyrroleacetic acid derivative. It is more potent anti-inflammatory agent than aspirin but less than endomethacin [21]. Due to its short half-life (Table 11.3) and thus the need for frequent dosing, it fell into disfavor. Adverse effects associated with tolmetin are similar to those with other NSAIDs. These include GI distress, nausea, abdominal pain, diarrhea, headache, drowsiness, hypertension, dysuria, hematuria, and less frequently hepatitis.

Unlike most other NSAIDs, it does not displace anticoagulants such as warfarin from plasma protein-binding sites. However, it does prolong bleeding time presumably by prolonging prothrombin time and inhibiting the production of TXA_2 in the platelets.

Preparations, Therapeutic Indications, and Contraindications

Tolmetin is available in 200- and 600-mg capsules. As with most other NSAIDs, tolmetin is indicated in patients with rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. It is ineffective in the treatment of acute gout. It is contraindicated in patients with angioadema, asthma, bronchospasm, nasal polyps, rhinitis, or NSAID-induced urticharia.

Dosage

For the relief of pain associated with rheumatoid arthritis and osteoarthritis, tolmetin is administered in a dosage of 400 mg three times a day. The total daily maintenance dosage ranges from 600 to 1,800 mg administered in divided doses either three or four times a day. The maximum dosage for rheumatoid arthritis is 2,000 mg/day, whereas that for osteoarthritis is 1,600 mg/day.

For the relief of juvenile rheumatoid arthritis in children over 2 years of age, tolmetin is initially given in the amount of 20 mg/kg/day in divided doses three or four times a day. The maintenance dose is 15–30 mg/kg/day in divided doses. The maximum dose is 30 mg/kg/day.

Drug Interactions

Drug interactions involving tolmetin are similar to those of other NSAIDs detailed above. Tolmetin also interacts with the drug/drug classes shown below:

- *ACE inhibitors*: Concomitant administration of ACE inhibitors and tolmetin may result in decreased efficacy of the former and possibly reduced renal function.
- *Alendronate*: It may increase the GI distress associated with tolmetin.
- *Antineoplastics, antithymocyte globulin, and strontium-89 chloride*: Co-administration of any of these agents with tolmetin may increase the risk of bleeding.
- *Cidofovir*: It may contribute to increased risk of nephrotoxicity.

Ketorolac

Ketorolac possesses anti-inflammatory, analgesic, and antipyretic properties. It is used, however, for systemic analgesia mainly in the management of short-term acute postoperative pain. The adverse effects associated with ketorolac, its drug interactions profile, and contraindications are similar to those of other NSAIDs. It has been reported, however, that the use of ketorolac for more than 5 days is associated with a significant increase in renal impairment and peptic ulcerations. For this reason, it is no longer available in Canada and some European markets.

Preparations, Therapeutic Indications, and Contraindications

Ketorolac is available as 10-mg tablets. It is also available in injectable form in 15-mg/mL, 30-mg/mL, and 60-mg/2 mL preparations. It can be administered orally, intravenously, or more commonly, intramuscularly. It is indicated for the management of acute postoperative pain for a period not exceeding 5 days. It is not recommended in obstetrics or for preoperative analgesia or for long-term treatment.

Dosages

For the acute management of pain, ketorolac is given orally four to six times per day for no longer than 5 days. If given intramuscularly, a loading dose of 30–60 mg of ketorolac followed by a maintenance dose of 15–30 mg every 6 h is recommended. The maximum daily dose is 150 mg the first day and 120 mg thereafter.

Propionic Acids

Ibuprofen

Ibuprofen is a phenylpropionic acid derivative. It possesses anti-inflammatory, analgesic, and antipyretic properties. It is extensively metabolized in the liver into inactive metabolites. Ibuprofen has had an excellent safety record and is available under several trade names for analgesia as OTC medications. It replaced aspirin as the gold standard against which other NSAIDs are compared. It has a relatively short half-life (Table 11.3) and, like diclofenac, it accumulates in the synovial fluid for prolonged periods of time.

Its GI adverse effects are similar to aspirin, but they occur less frequently. Other adverse effects include rash, pruritus, headache, tinnitis, and fluid retention nephritis. Acute renal failure has also been reported.

Preparations, Therapeutic Indications, and Contraindications

Ibuprofen is available as 400-, 600-, and 800-mg tablets. It is indicated for the treatment of osteoarthritis, rheumatoid arthritis, and dysmenorrhea. OTC preparations are used for the treatment of headaches, dysmenorrhea, and musculoskeletal pain. It is contraindicated in patients with angioedema, bronchospasm, nasal polyps, asthma attacks, rhinitis, NSAID-induced urticaria, or in patients allergic to ibuprofen or other NSAIDs.

Dosage

For the relief of pain associated with rheumatoid arthritis and osteoarthritis, ibuprofen is given as 300, 400, 600, or 800 mg three to four times daily. The maximum range per day is 1.2–3.2 g. To relieve pain associated with primary dysmenorrhea, the normal dose is 400 mg every 4 h as needed. To relieve minor aches and pains, and to reduce fever, a dose of 200–400 mg every 4–6 h is the standard, up to a maximum dose of 1.2 g/day. For the relief of pain associated with juvenile arthritis, children are given 30–70 mg/kg/day in divided doses either three or four times daily. A dose of 20 mg/kg/day is given for a mild form of the disease. To reduce fever in children between 6 months and 12 years old, they are given 5–10 mg/kg every 4–6 h, up to a maximum dose of 40 mg/kg/day.

Drug Interactions

Ibuprofen interacts with other therapeutic agents such as:

- *Acetaminophen*: Long-term use of both ibuprofen and acetaminophen may lead to increased risk of nephrotoxicity.
- *Antihypertensives*: The co-administration of antihypertensive agent with ibuprofen may lead to decreased efficacy of the former.
- *Alcohol and other NSAIDs*: The administration of ibuprofen with any other NSAID has been shown to increase the risk of bleeding and GI adverse effects.
- *Bone marrow depressants*: The concomitant administration of ibuprofen and bone marrow depressants may cause increased leukopenic and thrombocytopenic effects of the latter.
- *Cefamandole, cefoperazone, cefotetan, plicamycin, and valproic acid*: Administration of any of these agents with ibuprofen may increase the risk of hypoprothrombinemia, ulceration, and bleeding.
- *Colchicine, platelet aggregation inhibitors, corticosteroids, potassium supplements*: The co-administration of any of these agents with ibuprofen may increase the risk of GI adverse effects and in some cases GI bleeding.
- *Cyclosporine*: The concomitant administration of ibuprofen and cyclosporine may increase the risk of nephrotoxicity as a result of increased plasma levels of cyclosporine.
- *Digoxin*: The administration of ibuprofen and digoxin may lead to increased blood levels of digoxin and thus increased risk of digitalis toxicity.
- *Diuretics (including loop-potassium-sparing, and thiazide)*: The administration of any of these agents with ibuprofen may result in decreased efficacies of these agents.
- *Gold compounds and nephrotoxic drugs*: Co-administration of ibuprofen and any of the gold preparations may result in increased risk of adverse renal effects.
- *Heparin, oral anticoagulants, and thrombolytics*: Increased anticoagulant effects and thus increased risk of hemorrhage.
- *Insulin, and oral antidiabetic drugs*: The combination of ibuprofen and any of these agents may result in increased hypoglycemic effects of these agents.
- *Lithium*: The combination of ibuprofen and lithium may lead to increased blood levels of lithium.
- *Methotrexate*: Ibuprofen and other NSAIDs are contraindicated in patients taking methotrexate because such a combination may result in decreased methotrexate clearance, and thus increased risk of methotrexate toxicity.
- *Probenecid*: The co-administration of probenecid and ibuprofen may result in increased blood levels and toxicity of the latter.

Naproxen

Naproxen is phenylpropionic acid derivative that possesses anti-inflammatory, analgesic, and antipyretic properties. It is the only NSAID that is marketed in the U.S.

as a single enantiomer (other single enantiomer NSAID preparations are available abroad). It has a relatively long half-life rendering it suitable for once- or twice-a-day dosing regimen. Naproxen undergoes phase I and phase II biotransformation reactions and is excreted in the form of inactive conjugates or free acid. Upper GI adverse effects associated with naproxen are significantly less than those with aspirin but double those of ibuprofen [22]. The adverse effects associated with NSAIDs have been observed with naproxen. However, naproxen has had a very good safety record and has been available as an OTC medication for several years.

Preparations, Therapeutic Indications, and Contraindications

Naproxen is available as a free acid in 250-, 375-, and 500-mg tablets, 375- and 500-mg delayed-release tablets, 375- and 500-mg controlled-release tablets, or as an oral suspension (125 mg/5 mL). In the form of naproxen sodium, it is available as 250- and 500-mg tablets by prescription or OTC in 200-mg tablets. Naproxen is indicated for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, juvenile arthritis, acute tendinitis, and bursitis. It is also indicated as an analgesic for musculoskeletal back pain and dysmenorrhea. Because naproxen has the ability to inhibit the migration of polymorphonuclear leukocytes, it is also indicated for the treatment of acute gouty arthritis. Its contraindications are similar to other NSAIDs detailed earlier in the chapter.

Dosage

For the relief of mild to moderate musculoskeletal inflammation, including ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, naproxen in the form of tablets, delayed-release tablets, or oral suspension is given in the amount of 250–500 mg twice a day, up to a maximum of 1,500 mg/day. Naproxen sodium, in the form of extended-release tablets, is given in a dose of 750–1,000 mg/day, up to a maximum of 1,500 mg/day. If regular naproxen tablets are used, the normal dose is 275–550 mg twice daily, up to a maximum of 1,650 mg/day. The combination of naproxen tablets and suppositories is acceptable, however, the combined dose (oral plus suppository) should not exceed 1,500 mg/day.

To relieve symptoms of juvenile rheumatoid arthritis and other inflammatory conditions in children, they are given naproxen at 10 mg/kg/day in divided doses twice daily as either oral suspension or tablets.

To relieve symptoms of acute gouty arthritis, adults receiving delayed-release tablets, oral suspension, or regular tablets of naproxen are given an initial dose of 750 mg followed by 250 mg every 8 h until symptoms subside. Adults receiving extended-release tablets of naproxen sodium are given an initial dose of 1,000–1,500 on the first day, then 1,000 mg daily until symptoms subside. The dose should not exceed more than 1,500 mg/day. Adults given naproxen sodium tablets receive an initial dose of 825 mg followed by 275 mg every 8 h until symptoms subside.

For the relief of mild to moderate pain, including acute tendinitis and bursitis, and dysmenorrhea, adults receiving delayed-release tablets of naproxen are normally

given an initial dose of 1,000 mg every day, to be increased as prescribed, up to a maximum of 1,500 mg/day. Adults receiving extended-release tablets of naproxen sodium are given an initial dose of 1,100 mg every day, to be increased as prescribed, up to a maximum of 1,500 mg/day. Adults receiving oral suspension or regular tablets of naproxen are given an initial dose of 500 mg followed by 250 mg every 6–8 h, up to a maximum of 1,250 mg/day. Adults receiving tablets of naproxen sodium are given an initial dose of 550 mg followed by 275 mg every 6–8 h, up to a maximum of 1,375 mg/day.

To relieve fever, mild to moderate musculoskeletal inflammation, and mild to moderate pain, adults receiving OTC tablets of naproxen sodium are usually given 220 mg every 8–12 h or 440 mg followed by 220 mg 12 h later. The maximum dose is 660 mg/day for 10 d unless directed otherwise by a physician. The dose for patients over the age of 65 is reduced to 220 mg every 12 h, up to a maximum of 440 mg for 10 days.

Drug Interactions

Drug interactions involving naproxen are similar to other NSAIDs.

Fenoprofen

Fenoprofen is a propionic acid derivative. It has analgesic and anti-inflammatory properties. It has a relatively short half-life (Table 11.3). The adverse effects associated with fenoprofen are similar to those with other NSAIDs but to a lesser extent. Among all NSAIDs, fenoprofen is most closely associated with toxic effects of interstitial nephritis.

Preparations, Therapeutic Indications, Contraindications, and Drug Interactions

Fenoprofen, as fenoprofen calcium, is available in 200- and 300-mg capsules and 600-mg tablets. It is indicated for the relief of pain, stiffness, and inflammation from rheumatoid arthritis, and osteoarthritis. It is also used as an analgesic in dysmenorrhea and musculoskeletal pain. Contraindications and drug interactions are the same of those described for other NSAIDs.

Dosage

To manage mild to moderate pain, adults receiving capsules or tablets of fenoprofen calcium are given 200 mg every 4–6 h as needed. To relieve pain, stiffness, and inflammation from rheumatoid arthritis or osteoarthritis, adults receiving capsules or tablets of fenoprofen calcium are given 300–600 mg three or four times daily, up to a maximum dose of 3,200 mg/day.

Flurbiprofen

Flurbiprofen is a propionic acid derivative. It undergoes enterohepatic circulation and its R (+) and S (−) enantiomers are extensively metabolized by phase I and phase II biotransformation reactions. Its adverse effects are typical of other NSAIDs.

Preparations, Therapeutic Indications, Contraindications, and Drug Interactions

Flurbiprofen is available in 50- and 100-mg tablets. It is indicated for the treatment of acute or chronic osteoarthritis, and rheumatoid arthritis. As with most other NSAIDs, it is contraindicated in patients with angioedema, bronchospasm, nasal polyps, asthma attacks, rhinitis, NSAID-induced urticaria, or in patients allergic to flurbiprofen or other NSAIDs.

Dosage

To treat acute or chronic rheumatoid arthritis and osteoarthritis, adults receiving extended-release capsules are given 200 mg daily in the evening. If, on the other hand, tablets are to be used, patients are given an initial dose of 200–300 mg/day in divided doses twice to four times a day, up to a maximum dose of 300 mg/day.

Ketoprofen

Ketoprofen is a propionic acid derivative. Its anti-inflammatory and analgesic activities are attributed to its ability to inhibit COX as well as 5-lipoxygenase. Additionally, it has been shown to stabilize lysosomal membranes. As with most other NSAIDs, it is rapidly absorbed. It is metabolized in the liver and undergoes enterohepatic circulation. The GI and CNS adverse effects of ketoprofen are typical of other NSAIDs.

Preparations, Therapeutic Indications, Contraindications, and Drug Interactions

Ketoprofen is available in 25-, 50-, and 75-mg capsules. It is indicated for the management of osteoarthritis and rheumatoid arthritis. It is also used in gout and for primary dysmenorrhea. Its contraindications and drug interactions are typical of other propionic acid derivatives such as ibuprofen and flurbiprofen.

Dosage

For the management of osteoarthritis and rheumatoid arthritis, the usual dose is 75 mg three times a day or 50 mg four times a day. If extended-release caplets are used, the dose is 200 mg once a day. For primary dysmenorrhea, the usual dose is 25–50 mg every 6–8 h as necessary.

Oxaprozin

Oxaprozin is a propionic acid derivative. It possesses anti-inflammatory as well as uricosuric properties rendering it more useful in the treatment of gout than any other NSAID. It has a very long half-life (Table 11.3), which makes it suitable for once-daily dosing regimen.

Preparations, Therapeutic Indications, Contraindications, and Drug Interactions

Oxaprozin is available in 600-mg caplets and 600-mg tablets. It is indicated for the treatment of rheumatoid arthritis and osteoarthritis. Its contraindications and drug interactions are typical of other propionic acid derivatives.

Dosage

To treat rheumatoid arthritis, patients are given 1,200 mg every day with the dosage adjusted based on the patient's response, up to a maximum of 1,800 mg/day in divided doses.

To treat osteoarthritis, patients are given 600–1,200 mg every day, up to a maximum of 1,800 mg/day in divided doses twice or three times a day. An initial loading dose of 1,200–1,800 mg can be given to speed up the onset of action. In patients with renal impairment, the initial dose should be limited to 600 mg every day.

Suprofen

Suprofen is another member of the propionic acid family of NSAIDs. In the past it used be given orally for minor and moderate pain and in osteoarthritis and rheumatic arthritis. However, due to its adverse renal reactions, it was withdrawn from the markets worldwide. Today, it is available as 1% ophthalmic solution and is used to inhibit miosis that may occur during ocular surgery.

Ocular administration of suprofen may cause iritis, chemosis, and photophobia. It should not be used in patients with active herpes simplex keratitis.

Fenamic Acids

Meclofenamate and Mefenamic Acid

These agents are derivatives of fenamic acid. The anti-inflammatory effect of meclofenamate and mefenamic acid is attributed to their ability to inhibit COX and phospholipase A_2. These agents undergo phase I and phase II biotransformation reactions. Conjugated metabolites are excreted in urine and unconjugated metabolites are excreted in the feces. They are not superior to other NSAIDs in their anti-inflammatory effects. The adverse effects associated with these agents are similar to

other NSAIDs. The use of mefenamic acid, in particular, is associated with high incidence of skin reactions. Their GI adverse effects (particularly diarrhea) associated with these agents are more severe and frequent than with other NSAIDs. For this reason they have not received widespread clinical use for the treatment of inflammatory disorders.

Preparations, Therapeutic Indications, Contraindications, and Drug Interactions

Meclofenamate is available in 50- and 100-mg capsules. Mefenamic acid is available as 250-mg capsules. Although both agents can be used for the treatment of rheumatoid arthritis and osteoarthritis, because of the high incidence of toxicity associated with these drugs they fell into disfavor. Most commonly, they are indicated as analgesics to relieve the pain associated with dysmenorrhea. They are contraindicated in pregnancy and should not be used for more than a week.

Dosage

The loading dose of mefenamic acid is 500 mg for the first day, then 250 mg every 6 h thereafter for no more than a week. To relieve pain and inflammation of rheumatoid arthritis and osteoarthritis, meclofenamate is given as 50–100 mg every 6–8 h as needed, up to a maximum of 400 mg/day. To treat primary dysmenorrhea, meclofenamate is given as 100 mg three times a day for up to 6 days.

Enolic Acids (Oxicams)

Piroxicam

Piroxicam is an oxicam. Like most of the NSAIDs discussed thus far, the anti-inflammatory, analgesic, and antipyretic activities associated with piroxicam are attributed to its ability to non-selectively inhibit COX-1 and -2.

Preparations, Therapeutic Indications, Contraindications, and Drug Interactions

At high concentrations, piroxicam has been shown to inhibit the migration of polymorphonuclear leukocytes. Unlike meloxicam (described under COX-2 preferential inhibitors), piroxicam is rapidly absorbed. Due to its enterohepatic circulation, it has a very long half-life (ranges from 30 to 85 h) (Table 11.3), which permits a once-a-day dosing regimen. It is extensively metabolized in the liver and metabolites are excreted in urine and feces. The adverse effects associated with piroxicam are typical of other NSAIDs.

Dosage

Piroxicam is available in 10- and 20-mg capsules. It is indicated for the treatment of rheumatoid arthritis and osteoarthritis. Drug interactions and contraindications are similar to other NSAIDs.

Pyrazolone Derivatives

The pyrazolone derivatives include phenylbutazone and oxyphenbutazone. They are banned in many countries and are rarely used today due to their propensity to cause blood dyscrasias. Metamizol and propiphenazone are available in some countries but not in the U.S. They are primarily used for their analgesic and antipyretic properties.

Other Non-selective COX Inhibitors

There are many other non-selective COX inhibitors including, but not limited to, acemethacin, azapropazone, carprofen, fenbufen, tiaprofen, dexibuprofen, dexketoprofen, flufenamic acid, aceclofenac, and tenoxicam. These agents are not, or no longer, available in the United States and will not be discussed further in this chapter.

COX-2 Preferential Inhibitors

These agents inhibit both COX-1 and COX-2, however, they are more potent COX-2 inhibitors than COX-1. They exhibit approximately 10-fold greater selectivity for COX-2 compared to COX-1.

Nabumetone

Nabumetone, a naphthylalkanone derivative, and is a relatively more potent COX-2 than COX-1 inhibitor [23]. It is a ketone prodrug that is metabolized to the active acetic acid form. It has a relatively long half-life (Table 11.3) permitting a once- or twice-a-day dosing regimen. Unlike many other NSAIDs, it does not undergo enterohepatic circulation.

Adverse Effects

Nabumetone has been reported to cause muscle spasms, myalgia, alopecia, jaundice, photosensitivity, pruritus, and rash. Blood urea nitrogen (BUN), serum creatinine, and electrolyte levels must be monitored in patients taking nabumetone for early signs of impaired renal functions, especially in elderly patients or those who have compromised hepatic or renal functions.

Preparations, Therapeutic Indications, and Contraindications

Nabumetone is available in 500- and 750-mg tablets. It is primarily indicated in the treatment of rheumatoid arthritis. Its contraindications are similar to those of other NSAIDs.

Dosage

For the relief of symptoms of acute and chronic osteoarthritis and rheumatoid arthritis, nabumetone is initially given in a 1-g dose per day or in divided doses twice daily. This is increased to 1.5–2 g/day in divided doses preferably twice daily. The maintenance dose is adjusted according to the clinical response. The maximum dose should not exceed 2 g/day.

Meloxicam

Meloxicam is an enol carboxamide, an oxicam derivative. Although meloxicam inhibits both COX-1 and COX-2, it has a selectivity COX-2/COX-1 ratio of 10 [24]. Unlike most other NSAIDs, meloxicam is slowly absorbed. It has a relatively long half-life (Table 11.3). Although it has been used in Europe and the Middle East for some time, it has been recently been approved for use in the United States.

Preparations, Therapeutic Indications, Adverse Effects, Contraindications, and Drug Interactions

It is available in 3.5-, 7.5-, and 15-mg tablets. It is indicated for the treatment of osteoarthritis. Its adverse effects and contraindications are similar to those described for other NSAIDs. It has been shown to decrease the diuretic effect of furosemide. Other drug interactions are similar to those associated with other NSAIDs.

Dosage

To relieve pain due to osteoarthritis, the dose is 7.5 mg a day, up to a maximum of 15 mg a day.

Etodolac

Etodolac is a pyranoindoleacetic acid derivative. It possesses anti-inflammatory, analgesic, and antipyretic properties. Generally, it is less effective than other NSAIDs in the treatment of rheumatoid arthritis. It is well and rapidly absorbed.

Preparations, Therapeutic Indications, and Contraindications

Etodolac is available in 200- and 300-mg capsules. It is indicated mainly for analgesia and for the treatment of osteoarthritis. The adverse effects and drug interactions associated with etodolac are similar to other NSAIDs. It is contraindicated in patients

who are allergic to etodolac or its components or in patients with angioedema, bronchospasm, rhinitis, nasal polyps, and/or NSAID-induced urticaria.

Dosage

For the treatment of osteoarthritis, 800–1,200 mg etodolac is administered per day in divided doses. Maintenance dose ranges from 600 to 1,200 mg/day in divided doses. The maximum daily dose is 1,200 mg. For patients weighing less than 132 pounds (60 kg), the maximum dose is 20 mg/kg/day. If extended-release tablets are given, the adult dose normally ranges from 400 to 1,000 mg/day.

As an analgesic, a loading dose of 400 mg is used, then 200–400 mg every 6–8 h. For patients weighing 132 pounds (60 kg) or more, the maximum dose is 1,200 mg/day. For patients weighing less than 132 pounds, the maximum dose is 20 mg/kg/day.

Nimesulide

Nimesulide is a sulfonanilide derivative. It is a preferential COX-2 inhibitor and possesses analgesic and antipyretic properties [22]. It is associated with increased risk of hepatotoxicity. This agent is not available in the United States and will not be discussed further in this chapter.

COX-2 Selective Inhibitors

As stated earlier, the large molecular size of COX-2 selective inhibitors does not allow them to gain access to the hydrophobic channel of COX-1. On the other hand, these drugs selectively inhibit COX-2 because the hydrophobic channel of COX-2 is larger than that of COX-1 and thus can be blocked by these agents. The COX-2 selective inhibitors exhibit approximately 100-fold greater selectivity for COX-2 compared to COX-1.

Celecoxib

Celecoxib is a pyrazole derivative. It is a highly selective COX-2 inhibitor. Its potency as an inhibitor of COX-2 is at least 300 times more than that of COX-1 [25]. There is no evidence that celecoxib has any effect on platelet aggregation because platelets contain the COX-1 isoform of the enzyme and not COX-2. Therefore, celecoxib inhibits the formation of PGI_2 rather than TXA_2. It is well absorbed and highly protein-bound. Its half-life is 11 h (Table 11.3). Because it has virtually no effect on COX-1, GI adverse effects (such as peptic ulceration) associated with this agent are

significantly less than non-selective COX inhibitors [26]. It is primarily metabolized by CYP2C9 in the liver.

After the withdrawal of rofecoxib and valdecoxib from the U.S. market, celecoxib is currently the only available FDA-approved COX-2 selective inhibitor in the United States.

Preparations, Therapeutic Indications, and Contraindications

Celecoxib is available in 100- and 200-mg capsules. It is indicated for the relief of pain associated with osteoarthritis and rheumatoid arthritis [27]. As an adjunct medication, it is used to reduce adenomatous colorectal polyps in patients with familial adenomatous polyposis. It is contraindicated in patients allergic to aspirin, celecoxib or its components, or to other NSAIDs, sensitive to sulfonamide derivatives or those who have a history of NSAID-induced nasal polyps with bronchospasms, at risk of developing cardiovascular disease. It is also contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. A warning has been added to Celebrex label indicating that the drug may cause serious cardiovascular thrombotic events, myocardial infarction, and stroke, as well as serious GI adverse events.

Dosage

To relieve pain associated with osteoarthritis, the dose is 200 mg every day or 100 mg twice a day. To relieve pain from rheumatoid arthritis, the dose is 100–200 mg twice a day up to 400 mg/day. As an adjunct medication to reduce adenomatous colorectal polyps in patients with familial adenomatous polyposis, adults are given 400 mg twice a day. For patients with hepatic impairment, the daily dosage should be reduced. For patients weighing less than 50 kg, the therapy should be started with the lowest recommended dose.

Drug Interactions

Celecoxib interacts with the following drugs/drug classes:

- *ACE inhibitors*: Celecoxib has been shown to decrease the antihypertensive effects of ACE inhibitors, which may result in increased risk of renal failure.
- *Aspirin*: Concomitant administration of celecoxib and aspirin results in increased risk of GI complications and bleeding.
- *Lithium*: Celecoxib may cause increased plasma lithium levels.
- *Oral anticoagulants*: Celecoxib potentiates warfarin effect by increasing prothrombin time and thus the risk of bleeding.
- *Fluconazole*: The co-administration of fluconazole and celecoxib results in increased plasma levels of the latter.

- *Furosemide and thiazide diuretics*: Celecoxib has been shown to decrease the diuretic effects of these drugs, which may result in increased risk of renal failure.

Other COX-2 Selective Inhibitors

Due to their increased risk of cardiovascular disease, rofecoxib and valdecoxib were withdrawn from the U.S. market. Etoricoxib never received FDA approval. Some of these agents and lumiracoxib are still in use in some countries abroad.

Selecting the Right NSAID

Prescription and OTC NSAIDs are available from many different sources and in a variety of strengths. Patients should take the minimum dosage to which they achieve a satisfactory clinical response. Although most NSAIDs are equally efficacious, as with other medications, individual variation in clinical response to NSAIDs does exist. For this reason, patients should be aware that what works for others may not work for them and vice versa. Additionally, patients who are on other medications e.g. warfarin should consider NSAIDs that do not interact with oral anticoagulants e.g. ibuprofen. Also, if compliance is a problem, NSAIDs that do not require frequent dosing may increase compliance. Furthermore, there is no relationship between the price of the NSAID and its clinical effectiveness [28]. Likewise, there is no relationship between the price of the NSAID and the incidence of adverse effects. The adverse GI effects of long-term use of non-selective COX inhibitors can be reduced by co-administration of a proton pump inhibitor or H2 receptor antagonist.

In light of the withdrawal of the selective COX-2 inhibitors rofecoxib and valdecoxib from the U.S. market a few years ago due to their association of increased cardiovascular thrombotic events, it is advised that COX-2 inhibitors not be used in preference to non-selective COX inhibitors. When specifically indicated for patients who are at a particularly high risk of developing GI ulcerations, perforations, or bleeding and after an assessment of cardiovascular risk, the lowest effective dose of COX-2 inhibitors should be prescribed and for the shortest period of time. The need for a long-term treatment should be reviewed periodically. In general, as with other medications, NSAID therapy should be directed at achieving the desired effects while minimizing the adverse effects.

Other Non-opioid Analgesics

Acetaminophen

Acetaminophen is a para-aminophenol derivative. It possesses analgesic and antipyretic properties. Although it is a weak COX inhibitor, it is not an NSAID per se.

It has virtually no anti-inflammatory effects and lacks platelet inhibitory effects. Acetaminophen is available as OTC medication under several trade names. The mechanism behind its analgesic and antipyretic effects is not well understood, but believed to be the result of its inhibitory effects on COX in the CNS rather than the periphery. Orally administered acetaminophen is rapidly and completely absorbed. Its half-life is relatively short (2 h). Acetaminophen is extensively metabolized by hepatic conjugation enzymes and is converted to glucuronide and sulfate conjugates. These metabolites are pharmacologically inactive and are readily excreted in urine.

In therapeutic doses, acetaminophen is virtually void of any significant adverse effects. It is significantly safer than aspirin. With larger doses, however, abdominal pain, dizziness, nausea, vomiting, and disorientation have been reported. With massive doses (overdose), hepatic toxicity and liver failure may occur [29, 30].

Mechanism of Acetaminophen Toxicity

Less than 5% of ingested acetaminophen undergoes phase I biotransformation reactions. These reactions, catalyzed by the microsomal CYP450 enzyme system, yield N-acetyl-para-benzoquinone (NABQ). NABQ is a very reactive electrophile that is neutralized by intracellular glutathione. As long as intracellular glutathione is available, virtually no hepatic damage occurs. However, if acetaminophen is taken in massive doses (10–15 g or higher), conjugation pathways become saturated, which leads to the accumulation of NABQ [31]. When the intracellular glutathione pool is depleted, this very reactive compound will bind to nucleophilic groups on the cellular proteins and causes lipid peroxidation, resulting in hepatotoxicity and sometimes death. Agents such as N-acetylcysteine and cysteamine can be used within hours of acetaminophen overdose to protect victims from hepatotoxicity.

Preparations, Therapeutic Indications, and Contraindications

Acetaminophen is available in 160-, 325-, 500-, and 650-mg capsules or tablets. It is also available as extended-release tablets, elixirs, solutions, suspensions, suppositories, chewable tablets, and sprinkles. Additionally, acetaminophen is available in combination with other agents such as caffeine, phenyltoloxamine, antihistamines, and codeine. Generally, it is indicated for the relief of minor to moderate pain associated with headache, musculoskeletal ache, toothache, menstrual cramps, minor arthritis, and common cold. Because it possesses antipyretic properties, acetaminophen is also indicated to reduce fever.

Acetaminophen is considered the analgesic and antipyretic of choice for children with viral infections because acetaminophen, unlike aspirin, does not increase the risk of Reye's syndrome. It is contraindicated in patients allergic to acetaminophen or its components and in patients with hepatic disease.

Table 11.5 Acetaminophen dosages for children of various ages

Age (years)	Dosage every 4 h (mg)	Maximum no. of doses per 24 h
0–3 months	40	5
4–11 months	80	5
1	120	5
2–3	160	5
4–5	240	5
6–80	320	5
9–10	400	5
11	480	5
12–14	640	5
>14	650	5

Dosage

For the relief of mild to moderate pain associated with headache, muscle ache, backache, minor arthritis, common cold, toothache, menstrual cramps, or to reduce fever, the usual dose ranges from 325 to 650 mg every 4–6 h. Also, it can be given in a dose of 1,000 mg three or four times a day, or two extended-release caplets every 8 h, up to a maximum of 4,000 mg/day. Dosages for children of various ages are shown in Table 11.5.

Drug Interactions

Acetaminophen interacts with a number of drugs/drug classes. These include:

- *Oral contraceptives*: Oral contraceptives have been known to decrease the efficacy of acetaminophen.
- *Propranolol*: The concomitant administration of propranolol and acetaminophen results in increased effectiveness of the latter.
- *Anticholinergics*: Anticholinergics interfere with (slow down) the absorption of acetaminophen and thus retard its onset of action.
- *Barbiturates, hydantoins, rifampin, sulfinpyrazone, isoniazid, and carbamazepine*: The co-administration of any of these agents with acetaminophen may result in decreased therapeutic effects and increased hepatotoxic effects of acetaminophen.
- *Probenecid*: Concomitant administration of acetaminophen and probenecid may result in increased therapeutic efficacy of the former.
- *Loop diuretics and lamotrigine*: Acetaminophen may decrease the therapeutic effects of these agents.
- *Zidovudine*: The co-administration of acetaminophen and zidovudine may result in decreased efficacy of the latter.
- *Alcohol*: Chronic alcohol consumption depletes liver mitochondrial GSH (reduced glutathione) and induces cytochrome P450 enzymes. Both actions increase the hepatotoxic effects of NABQ.

Phenacetin

Although phenacetin is still commonly used abroad, this agent is no longer prescribed in the United States. It will not be discussed further in this chapter.

Disease-Modifying Antirheumatic Drugs (DMARDS)

These drugs are usually indicated and used in patients suffering from chronic inflammatory diseases.

Unlike NSAIDs, which only provide symptomatic relief and do not influence the progression of the underlying disease, most DMARDs have been shown to slow the progression of bone and cartilage damage in osteoarthritis and rheumatoid arthritis [32, 33]. These agents may induce remission but cannot repair existing damage. The effects of some of these medications may take up to 6 months before they become evident [34, 35]. This is why these medications are sometimes referred to as "slow-acting drugs." They are chemically and pharmacologically very heterogeneous. The various DMARD subclasses are shown in Table 11.6. These therapeutic agents are used for the treatment of patients with severe rheumatic disorders that have not responded adequately to NSAIDs [36].

Table 11.6 Disease-modifying antirheumatic drugs

Synthetic	Biologic
Methotrxate	Anakinra
Cyclosporine	Abatacept
Azathioprine	Rituximab
Sulfasalazine[a]	Anti-TNF-α agents
Leflunomide	Infliximab
Mycophenolate mofetil[a]	Etanercept
D-Penicillamine	Adalimumab
Minocycline	
Antimalarial	
Chloroquine	
Hydroxychloroquine	
Alkylating agents	
Chlorambucil	
Cyclophosphamide	
Gold preparations	
Aurothiomalate	
Aurothioglucose	
Auranofin	

[a]Prodrug

Synthetic DMARDs

Methotrexate

Methotrexate is an antineoplastic and immunomodulating agent that has several mechanisms of action [37]. As a folic acid analog, it inhibits dihydrofolate reductase, thereby limiting the availability of tetrahydrofolate for DNA synthesis. Thus, the replication of T lymphocytes and other rapidly dividing cells that play a role in the inflammatory process is inhibited. Additionally, it interferes with the migration of polymorphonuclear leukocytes to the site of inflammation. Methotrexate also reduces the production of free radicals and inhibits the production of some cytokines [38]. It is considered the DMARD of first choice for the treatment of rheumatoid arthritis. It is as efficacious as other DMARDs with relatively few adverse effects especially when indicated in low doses on weekly basis. At low doses it appears to act as an anti-inflammatory rather than an immunosuppressant.

Preparations, Therapeutic Indications, Dosage, and Contraindications

Methotrexate is available in 2.5-mg tablets. It is indicated for the treatment of rheumatoid arthritis and psoriasis; it is also used for systemic lupus erythematosus and psoriatic arthritis. The dose ranges between 7.5 and 20 mg once per week. The most common dosage, though, is 15 mg per week. It is contraindicated in pregnancy, breastfeeding mothers, and patients hypersensitive to methotrexate or its component.

Adverse Effects

At low doses, most of methotrexate's adverse effects are mild which include nausea, stomatitis, headache, rash, GI disturbances, and diarrhea. Elevation of hepatic aminotransferases occurs frequently. Mild and in some cases moderate immunosuppression have been reported in rheumatoid arthritis patients taking methotrexate. Severe toxicity such as cirrhosis, pulmonary fibrosis, and bone marrow depression are rare.

Drug Interactions

Methotrexate interacts with a number of drugs/drug classes including:

- Bone marrow depressants: The combination of bone marrow depressants and methotrexate may result in the potentiation of the effects of these agents.
- Folic acid: The administration of folic acid and methotrexate may decrease the effect of the latter.

- Hepatotoxic agents: Concomitant administration of hepatotoxic agents and methotrexate increases the risk of hepatotoxicity.
- Neomycin: It has been shown to decrease the absorption of many drugs including methotrexate.
- Conventional NSAIDs: The combination of methotrexate and any of the COX inhibitors may increase the risk of methotrexate toxicity.
- Sulfonamides: The concomitant administration of sulfonamides and methotrexate increases the risk of hepatotoxicity.
- Vaccines: The combination of killed-virus or live-virus vaccine with methotrexate may increase the risk of infection.

Cyclosporine

Cyclosporine is an immunosuppressant [39]. It exerts its effect by inhibiting the production of IL-1 and IL-2 receptors. It also inhibits the interaction between T cells and macrophages. The cyclosporine-binding protein, cyclophilin, may play a role in cyclosporine's actions. It is indicated for the treatment of rheumatoid arthritis. It is also indicated for the prevention of graft rejection.

Preparations, Therapeutic Indications, and Dosage

Cyclosporine is available in 25-mg and 100-mg capsules and 100-mg/mL oral solution. It is indicated for the treatment of severe and active rheumatoid arthritis. Adults receive 25 mg/kg/day in divided doses every 12 h. After 8 weeks, this dose should be increased by 0.5–0.75 mg/kg/day, and again after 12 weeks. The maximum dosage is 4 mg/kg/day. Cyclosporine is contraindicated in patients with compromised renal function, neoplastic diseases, and uncontrolled hypertension. It is also contraindicated in patients who are hypersensitive to cyclosporine or any of its components.

Adverse Effects

The main adverse effects associated with cyclosporine are nephrotoxicity. Liver dysfunction, hypertension, hyperkalemia, and in some cases lymphoma have been reported.

Drug Interactions

Cyclosporine interacts with a wide array of therapeutic agents including aminoglycosides, amphotericin B, calcium channel blockers, erythromycin and other antibiotics,

oral contraceptives, colchicines, sulfonamides, digoxin, foscarnet, HMG-CoA reductase inhibitors (statins), various NSAIDs, probucol, terbinafine, and metoclopramide. Most of the drug interactions involving cyclosporine result in increased toxicity, especially nephrotoxicity.

Azathioprine

Azathioprine is an immunosuppressive agent. It is a purine analog whose primary metabolite, 6-thioinosinic acid, inhibits the synthesis of inosinic acid and suppresses T- and B-cell functions. Like other DMARDs, it has a slow onset of action. As with other immunosuppressive agents, the main adverse effects associated with azathioprine are bone marrow suppression, increased risk of infections, and less frequently malignancies.

Preparations, Therapeutic Indications, and Dosage

Azathioprine is available as azathioprine sodium in 50-mg tablets. It is primarily indicated to prevent graft rejection. It is also used for the treatment of rheumatoid arthritis. Data from controlled clinical trials has shown its efficacy in other inflammatory diseases such as systemic lupus erythematosus, psoriatic arthritis, and polymyositis. For rheumatoid arthritis, adults are given an initial dose of 1 mg/kg/day (50–100 mg/kg/day) either as a single dose or divided into two doses per day, for 6–8 weeks. If there are no therapeutic effects and/or adverse effects from the initial dose, the dosage should be increased 0.5 mg/kg every 4–6 weeks up to 2.5 mg/kg. The optimal dose is 2–2.5 mg/kg/day. If the patient also takes allopurinol, the dosage must be reduced to 25–33% of the usual dosage.

Adverse Effects

The most notable adverse reaction is bone marrow suppression and GI disturbances. Increased infection risk and lymphomas in patients taking azathioprine have been reported. Azathioprine is contraindicated in patients who are hypersensitive to the drug.

Drug Interactions

Azathioprine interacts with several therapeutic agents, including ACE inhibitors, and agents that affect bone marrow development. It also interacts with allopurinol, anticoagulants, methotrexate, cyclosporine, and nondepolarizing neuromuscular blockers.

Sulfasalazine

Sulfasalazine is a sulfonamide. It is a prodrug that is metabolized into 5-aminosalisylic acid and sulfapyridine. Its mechanism of action is not well understood. It is believed, however, that sulfapyridine and/or the parent compound is/are responsible for the drug's antirheumatic effect.

Adverse Effects

Adverse effects associated with sulfasalazine include rash, nausea, vomiting, chills, depression, fatigue, and headaches. Agranulocytosis and neutropenia have been reported. Reversible infertility in men using sulfasalazine has been documented. The drug, however, does not affect fertility in women.

Preparations, Therapeutic Indications, Dosage, and Contraindications

Sulfasalazine is available as 500-mg enteric-coated tablets. It is used for rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel diseases, and juvenile arthritis. For rheumatoid arthritis, adults initially are given 500–1,000 mg every day for 1 week. Then, the dose can be increased by 500 mg/day every week, up to a maximum of 2,000 mg/day in divided doses. If clinical response is not achieved after 12 weeks of therapy, the dose can be increased to 3,000 mg/day. The maintenance dose is 1,000 mg every 12 h, up to a maximum of 3,000 mg/day.

Drug Interactions

Sulfazalazine is known to interact with the following drugs/drug classes:

- *Bone marrow depressants*: Concomitant administration of sulfasalazine and any bone marrow depressant may result in increased leukopenic and thrombocytopenic effects of both agents.
- *Hepatotoxic drugs*: Co-administration of sulfasalazine and any hepatotoxic agent may result in increased hepatotoxicity.
- *Methotrexate*: Co-administration of methotrexate with sulfasalazine results in the potentiation of the effects of the former.
- *Folic acid*: Sulfasalazine has been known to increase folic acid absorption.
- *Digoxin*: Sulfasalazine may inhibit digoxin absorption and thus limit its bioavailability.
- *Hydantoin*, oral anticoagulants, and oral antidiabetic drugs: Sulfasalazine is known to potentiate the therapeutic and toxic effects of these agents.

Gold

Like methotrexate, gold preparations have been shown to reduce pain and slow the progression of bone and articular destruction [40]. Although the exact mechanisms of action of gold are not fully understood, it is believed to inhibit the lysosomal enzymes, reduce histamine release from mast cells, and suppress the phagocytic activity of polymorphonuclear leukocytes. Gold also interferes with the functions of macrophages resulting in inhibiting chemotactic factors. Additionally, it inhibits the release of leukotreine B_4 and PG E_2. Typical of most DMARDs, it has a slow onset of action with a latency period of 3–4 months. Its total-body half-life is approximately 1 year. It accumulates in the synovial membranes, liver, kidney, adrenal glands, spleen, bone marrow, and lymph nodes. It persists in the renal tubules for many years. There is no correlation between gold salt concentration and therapeutic or adverse effects.

Preparations and Contraindications

Aurothiomalate is available in 25- and 50-mg ampules. Aurothioglucose is available as a 500-mg/10 mL multidose vial. Both aurothiomalate and aurothioglucose are parenteral gold preparations and are usually given by deep muscular injection. Auranofin is an oral preparation that is available in 3-mg capsules. Gold therapy is indicated for patients with active rheumatoid arthritis and in patients who have not responded to conventional NSAIDs. Adults are given auranofin at an initial dose of 6 mg every day or 3 mg twice daily. If necessary, the maintenance dose can be raised to 9 mg/day after 3 months of treatment. In children age 6 and older, the initial dose is 0.1 mg/kg/day and the maintenance dose is 0.15 mg/kg/day, up to a maximum of 0.2 mg/kg/day. Drug must be discontinued if clinical response is not achieved after 3 months at 9 mg/day.

Parenteral gold is given intramuscularly in doses of 50 mg/week for 20 weeks. If clinical response is achieved without serious adverse effects, the drug can be continued indefinitely by lengthening the dosing intervals from weekly to biweekly, and then to a monthly dosing regimen.

Gold therapy is contraindicated in pregnancy, and in patients with colitis, bone marrow aplasia, serious liver and kidney disease, and blood dyscrasias.

Adverse Effects

Due to gold's adverse effects, it has a high rate of discontinuance. However, if clinical response is achieved without serious toxicity, it can be continued indefinitely. The main adverse effects associated with gold therapy include pruritic dermatitis, eosinophilia, thrombocytopenia, leukopenia, diarrhea, metallic taste in the mouth, skin pigmentation, blood dyscriasis, and rarely proteinuria.

Drug Interactions

The concomitant administration of gold salts and phenytoin may result in increased plasma phenytoin levels.

Alkylating Agents

Chlorambucil

The active metabolite of chlorambucil (phenylacetic acid mustard) interferes with cell replication by crosslinking to the DNA. It is used in patients with rheumatoid arthritis, and in patients with systemic lupus erythematosus and/or vasculitis.

Preparations and Dosage

Chlorambucil is available in 2-mg tablets. The usual oral dosage is 0.1–0.2 mg/kg/day for 3–6 weeks. This usually amounts to 4–10 mg/day for the average patient. The entire daily dose may be given at one time. The dosage must be carefully adjusted according to the response of the patient and must be reduced as soon as there is an abrupt fall in white blood cell count.

Adverse Effects

The main adverse effects associated with the use of chlorambucil are dose-dependent infertility, bone marrow suppression, and increased risk of leukemia.

Drug Interactions

Chlorambucil interacts with a number of therapeutic agents including anticoagulants, barbiturates, digoxin, filgrastim (G-CSF), immunosuppressive agents, NSAIDs, platelet inhibitors, salicylates, sargramostim (GM-CSF), strontium-89 chloride, thrombolytic agents, and live-virus vaccines.

Cyclophosphamide

As with chlorambucil, Cyclophosphamide's active metabolite, phosphoramide mustard, interferes with cell replication by crosslinking to their DNA resulting in T-cell suppression. Its uses are similar to those described for chlorambucil.

Preparations and Dosage

Cyclophosphamide is available in 25- or 50-mg tablets. For rheumatoid arthritis, cyclophosphamide is given as 50–150 mg daily in a single dose. It should be taken with breakfast. Fluid should be taken throughout the day.

Adverse Effects

The main adverse effects associated with cyclophosphamide use are dose-dependent infertility, bone marrow suppression, alopecia, and hemorrhagic cystitis.

Drug Interactions

Cyclophosphamide interacts with anthracyclines, anticoagulants, antithymocyte globulin, barbiturates, bupropion, carbamazepine, cocaine, desmopressin, digoxin, etanercept, filgrastim (G-CSF), fosphenytoin, immunosuppressive agents, infliximab, mibefradil, mitotane, mivacurium, NSAIDs, phenytoin, platelet inhibitors, rifabutin, rifampin, rifapentine, salicylates, sargramostim (GM-CSF), St. John's wart, strontium-89 chloride, succinylcholine, tamoxifen, thrombolytic agents, trastuzumab, and live-virus vaccines.

Antimalarial Agents

Chloroquine and its major metabolite hydroxychloroquine are the main antimalarial drugs used in rheumatoid arthritis. They have been shown to cause remission of rheumatoid arthritis but are incapable of retarding the progression of the bone and articular damage. In addition to rheumatoid arthritis, they are also used in systemic lupus erythematosus. The mechanisms of their anti-inflammatory actions are not well understood. However, they are believed to decrease leukocyte migration, interfere with the action of acid hydrolases and the functions of T lymphocytes, and inhibit DNA synthesis.

Preparations and Dosage

Chloroquine phosphate is available in 250- and 500-mg tablets. Hydroxychloroquine sulfate is available in 200-mg tablets. For treatment of rheumatoid arthritis, adults receive a daily dose of 400–600 mg either as one dose or divided into two. If side effects occur, a temporary reduction in the dose can be made and a few days later the dose can gradually be increased. If a good response is obtained after 4–12 weeks, then the dosage is reduced by 50% and continued at a maintenance dose of 200–400 mg/day. Doses must be taken with food, milk, or water.

Adverse Effects

The main adverse effect associated with chloroquine and hydroxychloroquine is ocular toxicity. At least once-a-year ophthalmologic monitoring of patients on chloroquine or hydroxychloroquine is recommended. Other adverse effects include GI disturbances in the form of dyspepsia, nausea, vomiting, and abdominal pain. Rashes have been reported in patients taking these agents.

Drug Interactions

Chloroquine and hydroxychloroquine interact with botulinum toxin Types A and B, digoxin, kaolin (pectin), and penicillamine. Chloroquine also interacts with cimetidine, mefloquine, praziquantel, prilocaine, and rabies vaccine. Hydroxychloroquine also interacts with metoprolol.

D-Penicillamine

D-Penicillamine is a metabolite of the antibiotic agent penicillin and an analog of the sulfhydryl-containing amino acid cysteine. Its mechanism of action is not well understood. It is believed, however, to interfere with the synthesis of collagen, DNA, and mucopolysaccharides. As with other DMARDs, it is slow acting with a latency period of 3–4 months. It has been used in patients with active and severe rheumatoid arthritis who have not had adequate response to conventional NSAIDs or gold therapies. Because of its toxicity and interference with the absorption of many therapeutic agents, it is rarely used today.

Adverse Effects

Its adverse effects include dermatitis, anorexia, vomiting, proteinuria, leukopenia, thrombocytopenia, aplastic anemia, autoimmune disease, and metallic taste.

Patients on penicillamine should be closely monitored. Blood and platelet count should be performed every 2 weeks. It is contraindicated in pregnancy and in patients with renal insufficiency. Because penicillamine is a metal-chelating agent, it should not be given in combination with gold. Also, it should not be combined with phenylbutazone or other cytotoxic agent.

Drug Interactions

Penicillamine interacts with aluminum hydroxide, antimalarial agents, antineoplastic agents, gold compounds, immunosuppressive agents, iron salts, polysaccharide–iron complex, and pyridoxine (vitamin B6).

Minocycline

Minocycline is a tetracycline antibiotic. It is modestly effective in the treatment of rheumatoid arthritis and is generally well tolerated. It can be useful in the treatment of early, mild disease [41].

Leflunomide

Leflunomide is an immunosuppressive agent that has proven effective in the treatment of rheumatoid arthritis. Its efficacy is comparable to that of methotrexate. Its active metabolite (A77-1726) inhibits the de novo synthesis of ribonucleotides resulting in arresting the cell cycle at the G1 phase. This prevents the proliferation of activated T lymphocytes and interferes with the functions of B cells.

Preparations, Indications, Dosage, and Contraindications

Leflunomide is available in 10-, 20-, and 100-mg tablets. It is indicated for the treatment of rheumatoid arthritis [42]. In this regard, it is as effective as methotrexate. It can be taken concomitantly with methotrexate in patients who did not respond to the latter agent alone.

The loading dose is 100 mg/day followed by a maintenance dose of 20 mg/day. The 10-mg tablet is used for dose adjustment, if necessary. Leflunomide is contraindicated in pregnancy and in patients hypersensitive to leflunomides or its components.

Adverse Effects

The main adverse effects associated with leflunomide are diarrhea and elevated plasma levels of liver enzymes. Other adverse effects reported in patients using leflunomide are weight gain, mild alopecia, and increased blood pressure.

Drug Interactions

Leflunomide interacts with a number of drug/drug classes including azathioprine, charcoal, cholestyramine, cyclosporine, ethanol, fosphenytoin, isoniazid, ketoconazole, methotrexate, NSAIDs, phenytoin, rifampin, sulfasalazine, tacrine, tolbutamide, troglitazone, live-virus vaccines, and warfarin.

Mycophenolate Mofetil

Mycophenolate mofetil is an immunosuppressant derived from *Pennicillium stoloniferum*. It is a prodrug that is converted to the active immunosuppressive mycophenolic acid. It is a reversible inhibitor of cytosine monophosphate dehydrogenase which results in inhibiting purine synthesis. The net result of its mechanism of action is inhibition of T-cell lymphocyte proliferation and interfering with leukocyte adhesion to endothelial cells.

Preparations, Therapeutic Indications, and Adverse Effects

The drug is available in oral and intravenous forms; as 500 mg tablet, 250 mg capsule, 200 mg/mL suspension, and as an IV solution of 500 mg. It is used to treat steroid refractory graft versus host disease in hematopoietic stem cell transplant patients and in solid organ transplant patients for refractory rejection. It has also been used for the treatment of renal disease secondary to systemic lupus erythematosus (lupus nephritis) and some dermatologic disorders, and occasionally in rheumatoid arthritis [43]. However, its efficacy in rheumatoid arthritis remains to be determined.

Adverse Effects

The adverse effects associated with mycophenolate mofetil are similar to those of azathioprine. They include headache, GI disturbances in the form of nausea, vomiting, diarrhea, and abdominal pain. Hypertension and reversible myelosuppression (primarily neutropenia) have been reported.

Drug Interactions

Mycofenolate mofetil interacts with the following drugs/drug classes:

- Acyclovir and ganciclovir: Mycophenolate or its parent prodrug appears to compete with acyclovir and ganciclovir for tubular secretion resulting in increased plasma levels of both drugs.
- Cholestyramine: It decreases the absorption of mycophenolic acid. Consequently, mycofenolate mofetil is not recommended to be administered with cholestyramine or other agents that may interfere with enterohepatic recirculation.
- Cyclosporine: It prevents the excretion of mycophenolic acid into the bile that would lead to its enterohepatic recirculation.
- Sevelemar: It interferes with the absorption of mycophenolic acid.
- Norfloxacin and metronidazole: Neither of these two drugs effect the pharmacokinetics of mycophenolic acid, however, the two drugs combined significantly reduces the absorption of mycophenolic acid.
- Drugs that alter the GI flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference with its hydrolysis may decrease the amount of mycophenolic acid available for absorption.
- Live Vaccines: The use of live attenuated vaccines during treatment with mycophenolate mofetil should be avoided as vaccinations may be less effective.

Biologic DMARDs

Anakinra

Anakinra represents the first of a new class of DMARDs. This recombinant IL-1 receptor antagonist is approved for the treatment of rheumatoid arthritis. Anakinra acts by competitively inhibiting the binding of IL-1 to the IL-1 receptor. This results in a significant reduction of macrophages and lymphocytes in the synovial tissue. Anakinra has been shown to be effective in reducing joint pain and swelling either as a monotherapy or in combination with methotrexate [44].

Therapeutic Indications

Anakinra is available as 100 mg pre-filled syringes. It is indicated for the reduction of signs and symptoms of rheumatoid arthritis in patients who have not responded to other DMARDs. The dosing regimen for adults is 100 mg/day given subcutaneously. Anakinra can be used as a monotherapy or in combination with methotrexate.

Adverse Reactions and Contraindications

Generally, adverse reactions associated with anakinra are rare. Neutropenia and increased risk of serious infections especially in asthmatic patients have been documented. Some patients experienced headache, GI disturbances, sinusitis, infection, itching due to reaction at the injection site, diarrhea, and erythema. It is contraindicated in patients who are hypersensitive to *E. coli*-derived proteins and/or latex. Also, anakinra should not be given to patients with renal impairment or with neutropenia. Before initiation of therapy with the drug, patients should be evaluated for tuberculosis risk factors and should be screened for latent or active tuberculosis.

Drug Interactions

Because anakinra interferes with the immune response mechanisms, live-virus vaccines should not be given to patients receiving anakinra. In addition, the drug should not be used with TNF-α blocking agents as the risk of serious infections increases with these agents.

Abatacept

Abatacept is a recombinant soluble fusion protein comprising the extracellular domain of human CTLA4 (cytotoxic T-lymphocyte antigen 4) and a fragment of the Fc domain of human IgG_1. It is a selective co-stimulation modulator with inhibitory activity on T lymphocytes. When a T cell engages with an antigen-presenting cell (APC), CD28 on the T cell produces a signal that allows for the binding of T cell with CD80 or CD86 on the APC leading to the activation of T cell. Abatacept, like the naturally occurring CTLA4, competes with CD28 for CD80 and CD86 binding and thereby selectively modulating T-cell activation.

Preparations, Indications, and Dosage

Abatacept is approved for the treatment of moderate to severe rheumatoid arthritis in adults and the treatment of moderate to severe polyarticular juvenile idiopathic arthritis in pediatric patients who are 6 years of age or older. It is available in 250 mg per vial, lyophilized for reconstitution. It is administered as an intravenous infusion every 2 weeks for the first 4 weeks followed by once a month infusion. Dosing is dependent on body weight ranging from 500 to 1,000 mg. For patients weighing less than 60 kg, the given dose is 250 mg, for patients weighing between 60 and 100 kg, the dose is 750 mg, and 1,000 mg is given to patients weighing more than 100 kg. It can be used as a monotherapy or in combination with other DMARDs [45, 46].

Adverse Effects and Contraindications

As with all biologic agents used in rheumatoid arthritis, there is an increased risk of infection, particularly in the upper respiratory tract. Dyspepsia, rash, cough, dizziness, headache, and nasopharingitis have been reported. Increased risk of lymphoma has also been documented.

Drug Interactions

Abatacept interacts with the following drugs/drug classes:

- Abatacept is not recommended for use with live vaccines or concomitantly with any TNF antagonists or any other biologic rheumatoid therapy such as anakinra as the risk of serious infection may increase.
- Blood glucose testing: Parenteral drug preparations that contain maltose (such as abatacept) may give falsely elevated blood glucose readings on the day of infusion when dehydrogenase pyrroloquinolinequinone (GDH-PQQ)-based glucose monitoring system is used.

Rituximab

Rituximab is a chimeric monoclonal antibody against the protein CD20. It is used in the treatment of B-cell non-Hodgkin's lymphoma and B-cell-related leukemias.

Rituximab has been shown to be effective in rheumatoid arthritis. It is approved for use concomitantly with methotrexate for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to anti-TNF-α therapy [47]. There is evidence for its efficacy in a range of other autoimmune diseases such as systemic lupus erythematosus.

Preparations and Dosage

Rituximab is available as a parenteral preparation (10 mg/mL) and is given as two IV infusions of 1,000 mg each separated by 2 weeks.

Adverse Effects

The most common adverse reactions of rituximab observed in rheumatoid arthritis patients are upper respiratory tract infection, hypertension, transient hypotension, nausea, arthralgia, pruritus, and pyrexia.

Other serious adverse reactions associated with rituximab include infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, progressive multifocal leukoencephalopathy, viral infections, cardiovascular events, and renal toxicity.

Anti-TNF-α Agents

Cytokines play a key role in the inflammatory process. TNF-α, however, has been implicated as playing a pivotal role in the pathology of several systemic inflammatory diseases. Consequently, TNF-α has emerged as an important therapeutic strategy in alleviating the symptoms of immune-mediated inflammatory diseases. Currently three drugs that interfere with TNF-α are available in the United States. They are approved for the treatment of rheumatoid arthritis and other rheumatic diseases.

Infliximab

It is a chimeric mouse–human monoclonal antibody that is specific to human TNF-α. It binds TNF-α, thus blocking it from binding to its receptor. This prevents the induction of the release of proinflammatory cytokines. As a result, a significant reduction in the migration of proinflammatory cells to the inflammation site is achieved.

Preparations, Therapeutic Indications, and Dosage

Infliximab is available in 100-mg vials that must be diluted with 10 mL sterile water. This preparation should be further diluted in a total volume of 250 mL normal saline.

Infliximab is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and psoriatic arthritis [48, 49]. However, it is being used in other diseases such as juvenile chronic arthritis, psoriasis, and ulcerative colitis. It has been shown that the conjunction therapy of infliximab with methotrexate, is significantly more effective in retarding the progression of the articular damage than methotrexate alone. In addition to methotrexate, other DMARDs such as cyclosporine, antimalarials, and azathioprine can be used as a background therapy for infliximab.

For rheumatoid arthritis, the dose is 5 mg/kg given as a single intravenous infusion followed by additional 5 mg/kg at 2 and 6 weeks after the first infusion. Maintenance dose is every 8 weeks. Infliximab should not be infused with any other medication or through plasticized polyvinyl chloride infusion devices.

Adverse Effects and Contraindications

The main adverse effects associated with infliximab are upper respiratory tract infection, headaches, nausea, cough, sinusitis, and rash. It is also associated with the activation of latent tuberculosis and other opportunistic infections. Rare cases of hepatitis, activation of hepatitis B, vasculitis, and leukopenia have been reported. Although the incidence of solid malignancies is not increased with infliximab, however, as with other anti-TNF-α, lymphomas might be a concern. It is contraindicated in patients with multiple sclerosis, and in patients who are allergic to infliximab, its components, and/or murine proteins. Before initiation of therapy with the drug, patients should be evaluated for tuberculosis risk factors and should be screened for latent or active tuberculosis.

Drug Interactions

Infliximab interacts with anakinra, immunosuppressive agents, toxoids, and live-virus vaccines.

Etanercept

Etanercept is a chimeric recombinant fusion protein combining the p75 region of TNF receptor and the Fc region of IgG_1. It binds specifically to TNF-α and blocks it from binding to its receptor. As with infliximab, this results in a significant reduction in the release of proinflammatory cytokines and decreased number of migrating proinflammatory cells to the inflammation site [50–52]. Etanercept is as effective as methotrexate. However, it has the advantage of an earlier onset of action.

Preparations, Therapeutic Indications, and Dosage

Etanercept is approved for the treatment of rheumatoid arthritis, juvenile chronic arthritis, ankalosing spondilitis, psoriatic arthritis, and psoriasis. It can be used as monotherapy or in conjunction with methotrexate. Etanercept is available in 25-mg single-use vials and is typically administered subcutaneously, 25 mg twice weekly for the treatment of active rheumatoid arthritis alone or in combination with methotrexate.

Adverse Effects and Contraindications

Its adverse effects are similar to those of infliximab. It is contraindicated in patients who are sensitive to etanercept, its components, and/or hamster proteins. Before initiation of therapy with the drug, patients should be evaluated for tuberculosis risk factors and should be screened for latent or active tuberculosis.

Drug Interactions

Etanercept interacts with anakinra, azathioprine, cyclophosphamide, leflunomide, methotrexate, toxoids, and live-virus vaccines.

Adalimumab

Adalimumab is a recombinant human IgG_1 anti-TNF monoclonal antibody. It complexes with souble TNF-α and prevents its interaction with p55 and p75 cell surface receptors resulting in the down-regulation of macrophage and T-cell function [53].

Preparations, Indications, and Dosage

It is available as pre-loaded 40 mg/0.8 mL syringes and pre-loaded pen devices, both for subcutaneous injection. It is approved for the treatment of rheumatoid arthritis, ankylosing spondilitis and psoriatic arthritis, Crohn's disease and juvenile chronic arthritis, moderate to severe chronic psoriasis, and juvenile idiopathic arthritis. It can be used concomitantly with methotraxate or other DMARDs. The standard dose is 40 mg every 2 weeks.

Adverse Effects and Contraindications

As with other anti TNF-α agents, the risk of infection including sepsis, tuberculosis, and other opportunistic infections is increased especially with patients on concomitant immunosuppressive therapy. Vasculitis and leucopenia, though rare, has been reported.

Before initiation of therapy with adalimumab, patients should be evaluated for tuberculosis risk factors and should be tested for latent and active tuberculosis infection.

Drug Interactions

Adalimumab interacts with the following drugs/drug classes:

- Methotrexate: Methotrexate significantly reduces the absorption of adalimumab.
- Other TNF-α blockers, anakinra, rilonacept, abatacept: Combination of adalimumab with these agents may result in increase in the adverse effects of adalimumab, especially the risk of serious infections.
- Echinacea: It may diminish the therapeutic effect of adalimumab.
- Abciximab: It may enhance the potential for hypersensitivity or allergic reactions to adalimumab.
- Vaccines: Adalimumab may diminish the therapeutic effect of vaccines.

Rilonacept – Potential Use in Systemic Juvenile Idiopathic Arthritis

Rilonacept is a dimeric fusion protein that consists of the extracellular domains of the IL-1RAcP (IL-1 receptor access protein) and the human IL-1RI fused to the Fc portion of human IgG_1. It acts as a decoy receptor (IL-1 specific cytokine trap) that binds IL-1, thereby preventing it from binding to its endogenous cell-surface receptor. It has been recently approved for the long-term treatment of cryopyrin-associated periodic syndrome (CAPS) disorders: familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome (MWS) for adults and children 12 years and older [54].

Currently a phase II trial sponsored by the National Institute of Arthritis and Skin Diseases to determine the efficacy of early intervention with rilonacept in the treatment of systemic juvenile idiopathic arthritis in children and young adults is currently recruiting subjects.

DMARDs in the Pipeline

A number of prospective biologic DMARDs are currently in various stages of development. These agents include new or modified TNF-α inhibitors (golimumab, certolizumab pegol), new monoclonal antibodies against various ILs (IL-1, IL-6, IL-12, IL-15, IL-17, IL-23), and B-cell depleting agents (ocrelizumab, ofatumumab). In addition, a number of prospective small molecule DMARDs with possible oral administration which appear to be promising for the treatment of rheumatoid arthritis are also in various stages of development. These include p38, JAK, and Syk kinase inhibitors. They block the signal transduction mechanisms that lead to the transcription of proinflammatory genes.

Treatment Paradigms in Inflammatory Diseases

Not very long ago DMARDs were indicated to patients with inflammatory disease one at a time for few months before physicians could determine the drug's efficacy and switch to a new DMARD if necessary. A few years ago, however, the treatment paradigm has shifted to the more aggressive combination therapy in patients not responding adequately to monotherapy.

Nowadays, with the advent of biologic DMARDs such as anti-TNF-α and IL antagonists, combination therapy can be designed in a more rational way taking into consideration different/complementary mechanisms of action and with non-overlapping toxicity and pharmacokinetics. Combination therapy of methotrexate (as a background therapy) and another DMARD has become the norm in treating moderately aggressive rheumatoid arthritis and other chronic inflammatory diseases in patients not responsive to individual DMARDs. Current data suggest that some DMARDs such as etanercept, rituximab, adalimumab, infliximab, leflunomide, cyclosporinee, or chloroquine when combined with methotrexate as a background therapy results in improved efficacy [55].

Drugs Used in Gout

Gout is a metabolic disorder characterized by elevated plasma levels of uric acid (hyperuricemia). Because uric acid (a product of purine metabolism) is poorly soluble in the blood, monosodium urate crystals accumulate in tissues particularly in the joints and kidneys. This deposition of urate crystals triggers an inflammatory process characterized by the phagocytosis of these urate crystals by synoviocytes, the release of chemotactic mediators, and the migration of polymorphonuclear leukocytes and mononuclear phagocytes into the affected joint, which release more cytokines such as IL-1, PGs, and LKB_4. Acute gouty attacks can involve any joint especially the first metatarso-phalangeal joint.

Treatment of Acute Gouty Attacks

The main strategy behind the treatment of acute gouty attacks is to reduce the inflammation as early as possible. This is usually accomplished by the utilization of NSAIDs or colchicine (Table 11.7).

Table 11.7 Agents used in gout

	Management of chronic gout	
Treatment of acute gouty attack	Unicosuric agents	Inhibitors of uric acid synthesis
Indomethacin[a]	Probenecid	Allopurinol
Colchicine	Sulfinpyrazone	Febuxostat
	Oxaprozin[b]	

[a]Other NSAIDS are effective, however, aspirin, other salicylates and tolmetin are not recommended
[b]An NSAID

Indomethacin

Although most NSAIDs are effective in treating acute gouty episodes, indomethacin is the drug of choice for treatment of acute gout. In this context, indomethacin not only inhibits the production of PGs, but also inhibits the phagocytosis of the monosodium urate crystals by the mononuclear phagocytes. The dosing schedule is 50 mg every 6 h until an adequate response is achieved, the dose is then reduced to 25 mg three times a day for 5 days. The pharmacology of indomethacin is discussed in detail elsewhere in this chapter.

Colchicine

Colchicine has proven effective in alleviating pain and inflammation associated with acute gouty attacks. The mechanism of action behind its anti-inflammatory effect is its ability to bind tubulin protein of cells in the immune system (such as polymorphonuclear leukocytes), thus interfering with their migration, phagocytosis, and the release of proinflammatory mediators such as LKB_4. Adverse reactions associated with colchicine include diarrhea, nausea, hair loss, and rarely dose-dependent bone marrow suppression.

Preparations and Dosage

Colchicine is available in 0.5-, 0.6-, and 6-mg tablets and in injectable form (1 mg per vial). For the prevention of acute gouty attacks, oral colchicine is given as 0.5–0.6 mg every day. The same dose can be given two or three times a day. It can also be given as 0.5–1 mg on the first day, followed by 0.5 mg every 2 h until pain is alleviated. Parenteral colchicine can be given in an intravenous infusion as 0.5–1 mg every day or twice a day. The maximum amount should not exceed 4 mg/day.

Drug Interactions

Colchicine interacts with a number of therapeutic agents including anticoagulants, antineoplastics, cyclosporine, NSAIDs, and vitamin B_{12}.

Management of Chronic Gouty Arthritis

The strategy behind the treatment of chronic gouty arthritis is to keep uric acid levels in the blood below saturation (6 mg/dL or less) to prevent its accumulation in tissues [56, 57]. This can be accomplished by either reducing the rate of production of uric acid by inhibiting xanthine oxidase or by increasing the rate of uric acid excretion by uricosuric agents (Table 11.7).

Xanthine Oxidase Inhibitors

Allopurinol

Allopurinol is a purine analog and as a hypoxanthine isomer, it reduces uric acid synthesis by competitively inhibiting xanthine oxidase. Competitive inhibition results in decreased plasma uric acid levels and increased xanthine and hypoxanthine levels that are more soluble in plasma and are readily excreted (Fig. 11.2). The main adverse effects associated with allopurinol are GI intolerance, diarrhea, vomiting, and nausea [58].

Preparations, Therapeutic Indications, Dosage, and Contraindications

Allopurinol is available in 100- and 300-mg tablets and in parenteral form. It is indicated for the treatment of gout. It is given as 100 mg/day until plasma uric acid levels subside to 6 mg/dL or less. Parenterally, it is administered as 200–400 mg/day as a single infusion or in divided infusions two, three, or four times a day.

Drug Interactions

It potentiates the effects of 6-mercaptopurine, azathioprine, dicumarol, and warfarin. It also interacts with ACE inhibitors, amoxicillin, ampicillin, chlorpropamide, cyclophosphamide, thiazide diuretics, and with vitamin C when taken in large doses.

Febuxostat

Febuxostat is a highly potent selective nonpurine inhibitor of xanthine oxidase (Fig. 11.2). It has been recently approved for the chronic management of hyperuricemia in patients with gout. It is extensively metabolized into inactive metabolites in the liver. In a controlled clinical trial, febuxostat was more effective in lowering serum urate levels at 80 mg once daily dose than allopurinol at 300 mg daily dose. In addition, febuxostat does not appear to require dose adjustment for patients with mild-to-moderate renal or hepatic impairment [59, 60].

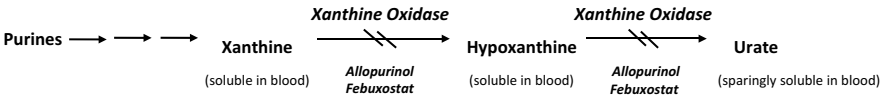

Fig. 11.2 Inhibition of purine metabolism by allopurinol and febuxostat

Available Preparations and Dosage

Febuxostat is available in 40- and 80-mg tablets. The recommended starting dose is 40 mg once daily. A dose of 80 mg per day is recommended for patients who do not achieve a serum uric acid level of less than 6 mg/dL after 2 weeks of treatment.

Adverse Events and Contraindications

The most frequent adverse effects associated with febuxostat are headaches, nausea, rash, diarrhea, liver function abnormalities, and joint pain. Increased risk of cardiovascular events might be a concern at higher doses. Febuxostat is not recommended for the treatment of asymptomatic hyperuricemia.

Drug Interactions

The co-administration of febuxostat and azathioprine, mercaptopurine, or theophylline is contraindicated as it may cause increased plasma concentration of these drugs resulting in severe toxicity.

Uricosuric Agents

Uricosuric agents are those agents that – at large concentrations – increase the rate of excretion of uric acid by inhibiting its reabsorption at the active anionic transport sites in the proximal renal tubules [61]. This results in decreased urate levels in the plasma. These agents should not be used in patients who already secrete large quantities of uric acid in order to prevent the formation of uric acid calculi in the kidney. Uricosuric therapy is indicated only after several gouty attacks have occurred, evidence of tophaceous gout becomes clear, or when uric acid concentration is at a level that causes tissue damage. It is important to note that aspirin and other salicylates are contraindicated in patients with gout because at low doses (analgesic doses) salicylates inhibit the secretory transporters of uric acid resulting in its retention [62]. In case other NSAIDs cannot be tolerated, aspirin can be given to patients with gout. However, it must be administered in high doses (anti-inflammatory doses) because at high doses salicylates have been shown to reduce the rate of reabsorption of uric acid by active transport sites in the renal proximal tubule.

Probenecid

Probenecid is a sulfonamide derivative. It is available in 500-mg tablets. It is indicated for the treatment of chronic gouty arthritis and hyperuricemia due to chronic gout. It is given in 250-mg dose twice a day for 1 week, then increased to a maintenance dose of 500 mg twice a day. The dose can be increased until uric acid excretion surpasses 700 mg/day. Maximum dose should not exceed 3 g/day.

Adverse Effects

The adverse effects associated with probenecid include dizziness, headache, anorexia, vomiting, nausea, facial flushing, and rash. It is contraindicated in patients who are less than 2 years old, are with blood dyscrasias, have renal calculi, or are hypersensitive to probenecid or its components.

Drug Interactions

Probenecid may increase the effects of a wide array of therapeutic agents, including acyclovir, allopurinol, antineoplastics, zidovudine, thiopental, sulfonylureas, rifampin, sulfonamides, riboflavin, aminosalicylate sodium, cephalosporins, ciprofloxacin, clofibrate, dapsone, ganciclovir, imipenem, methotrexate, nitrofurantoin, norfloxacin, penicillins, diazoxide, mecamylamine, pyrazinamide, furosemide, dyphilline, lorazepam, and NSAIDs, by slowing their normal removal via the kidney.

Sulfinpyrazone

Sulfinpyrazone is a pyrazolone derivative. It is available in 100-mg tablets and 200-mg capsules. It is indicated for the treatment of chronic gouty arthritis. It is given as 100–200 mg/day progressing to 400 mg twice a day until plasma urate level is under control. Its adverse effects include dizziness and rash. It is contraindicated in patients with peptic ulcer disease, blood dyscrasias, or hypersensitivity to sulfinpyrazone or its components.

Drug Interactions

Sulfinpyrazone interacts with several therapeutic agents including acetaminophen, salicylates, antineoplastics, cefamandole, cefoperazone, cefotetan, moxalactam, plicamycin, valproic acid, diazoxide, mecamylamine, pyrazinamide, hydantoin, niacin, nitrofurantoin, NSAIDs, oral anticoagulants, anti-platelet drugs, oral antidiabetic drugs, probenecid, theophylline, and verapamil.

Oxaprozin

Oxaprozin is a non-selective COX inhibitor that possesses mild uricosuric effects. This agent was discussed in detail under NSAIDs.

Rilonacept – Potential Use for the Prophylaxis of Gout Flares

As mentioned earlier, Rilonacept is a dimeric fusion protein that acts as a decoy receptor (IL-1 specific cytokine trap) that binds IL-1, thereby preventing it from binding to its endogenous cell-surface receptor. It has been recently approved for the long-term treatment ofCAPS.

Currently a phase III multi-center, randomized, double-blind, placebo-controlled trial of the safety of rilonacept for the prophylaxis of gout flares in patients on urate-lowering therapy is under way.

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References

1. Golan DE, Tashjian, AH, Jr, Armstrong EJ, Armstrong, AW. Principles of Pharmacology, the pathophysiologic basis of drug therapy. 2nd ed. Philadelphia, Wippincott Williams and Wilkins. pp. 747–768 (2008).
2. Vane JR, Bakhle YS, and Botting RM. Cyclooxygenase 1 and 2. Annu Rev Pharmacol Toxicol 38:97–120 (1998).
3. Meade EA, Smith WL, and DeWitt DL. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other nonsteroidal anti-inflammatory drugs. J Biol Chem 268:6610–6614 (1993).
4. Mitchell JA, Akarasereenont P, Thiememann C, Flower RJ, and Vane JR. Selective of non-steroidial anti-inflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci USA 90:11693–11697 (1993).
5. Vane JR and Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res 44:1–10 (1995).
6. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, and Fitzgerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA 96:272–277 (1999).
7. Bannwarth B, Demotes-Mainard F, Schaeverbeke T, Labat L, and Dehais J. Central analgesic effects of aspirin-like drugs. Fundam Clin Pharmacol 9:1–7 (1995).
8. Velo GP and Milanino R. Nongastrointestinal adverse reactions to NSAID. J Rheumatol 17 (Suppl 20):42–45 (1990).
9. Gabriel SE, Jaakkimainen L, and Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 115:787–796 (1991).
10. Verbeeck RK. Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. Clin Pharmacokinet 19:44–66 (1990).

11. Weissmann G. Aspirin Sci Am 264:84–90 (1991).
12. Vane J. Towards a better aspirin. Nature 367:215–216 (1994).
13. Lecomte M, Lancoville O, Ji C, DeWitt DL, and Smith WL. Acetylation of human prostaglandin endoperoxide synthase-2 (cyclooxygenase-2) by aspirin. J Biochem 269:13207–13215 (1994).
14. Diaz-Gonzalez F and Sanchez-Madrid F. Inhibition of leukocyte adhesion: an alternative mechanism for action for anti-inflammatory drug. Immunol Today 19:169–172 (1998).
15. Willard JE, Lange RA, and Hillis LD. The use of aspirin in ischemic heart disease. N Engl J Med 327:175–181 (1992).
16. Patrono C. Aspirin as an antiplatelet drug. N Engl J Med 330:1287–1294 (1994).
17. Miners JO. Drug interactions involving aspirin (acetylsalicylic acid) and salicylic acid. Clin Pharmacocinet 17:327–344 (1989).
18. Svensson CI and Yaksh TL. The spinal phospholipase-cyclooxygenase-prostanoid cascade in nociceptive processing. Annu Rev Pharmacol Toxicol 42:553–583 (2002).
19. Douidar SM, Richardson J, and Snodgrass WR. Role of indomethacin in ductus closure: an update evaluation. Dev Pharmacol Ther 11:196–212 (1988).
20. Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, Verburg KM, Isakson PC, Hubbard RC, and Geis GS. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison. Lancet 354:2106–2111 (1999).
21. Norton ME, Merrill J, Cooper BA, Kuller JA, and Clyman RI. Neonatal complications after the administration of endomethacin for preterm labor. N Engl J Med 329:1602–1607 (1993).
22. Bjarnason I and Thjodleifsson B. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract. Rheumatology (Oxford) 38(Suppl 1):24–32 (1999).
23. Scott DL and Palmer RH. Safety and efficacy of nabumetone in osteoarthritis: emphasis on gastrointestinal safety. Aliment Pharmacol Ther 14:443–452 (2000).
24. Turck D, Roth W, and Busch U. A review of the clinical pharmacokinetics of meloxicam. Br J Rheumatol 35(Suppl 1):13–16 (1996).
25. Davies NM, McLachlan AJ, Day RO, and Williams KM. Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclooxygenase-2 inhibitor. Clin Pharmacokinet 38:225–242 (2000).
26. Simon LS, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC, Isakson PC, Verberg KM, Yu SS, Zhao WW, and Geis GS. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized, controlled trial. JAMA 282:1921–1928 (1999).
27. Bensen WG, Fiechtner JJ, McMillen JI, Zhao WW, Yu SS, Woods EM, Hubbard RC, Isakson PC, Verburg KM, and Geis GS. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. Mayo Clin Proc 74:1095–1105 (1999).
28. Green JM and Winickoff RN. Cost-conscious prescribing of nonsteroidal anti-inflammatory drugs for adults with arthritis. Arch Intern Med 152:1995–2002 (1992).
29. Rumack BH, Peterson RC, Koch GG, and Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med 141:380–385 (1981).
30. Linden CH and Rumack BH. Acetominophen overdose. Emerg Med Clin North Am 2: 103–119 (1984).
31. Black M. Acetaminophen hepatotoxicity. Annu Rev Med 35:577–593 (1984).
32. Arnold M, Schreiber L, and Brooks P. Immunosuppressive drugs and corticosteroids in the treatment of rheumatoid arthritis. Drugs 36:340–463 (1988).
33. Fries JF, Williams CA, Ramey D, and Bloch DA. The relative toxicity of disease-modifying antirheumatic drugs. Arthritis Rheum 36:297–306 (1993).
34. Furst DE. Rational use of disease-modifying antirheumatic drugs. Drugs 39:19–37 (1990).
35. Wolfe F, Hawley DJ, and Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 17:994–1002 (1990).
36. Stewart CF and Evans WE. Drug–drug interactions with antirheumatic agents: review of selected clinically important interactions. J Rheumatol 17(Suppl 22):16–23 (1990).

37. Kremer JM and Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. Arthritis Metab 35: 138–145 (1992).
38. Arend WP and Dayer JM. Cytokines and cytokine inhibitors or antagonists in rheumatoid arthritis. Arthritis Rheum 33:305–315 (1990).
39. Faulds D, Goa KL, and Benfield P. Cyclosporine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in immunoregulatory disorders. Drugs 45: 953–1040 (1993).
40. Epstein WV, Henke CJ, Yelin EH, and Katz PP. Effect of parenterally administered gold therapy on the course of adult rheumatoid arthritis. Ann Intern Med 114:437–444 (1991).
41. Stone M, Fortin PR, Pacheco-Tena C, and Inman RD. Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. J Rheumatol. 30:2112–2122 (2003).
42. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, Loew-Friedrich I, Oed C, and Rosenburg R. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 353:259–266 (1999).
43. Dooley MA, Cosio FG, Nachman PH, Falkenhain ME, Hogan SL, Falk RJ, and Hebert LA. Mycophenolate mofetil therapy in lupus nephritis. J. Am. Soc. Nephrol. 10:833–839 (1999).
44. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, Kremer J, Bear MB, Rich WJ, McCabe D. Treatment of rheumatoid arthritis with anakinra, a recombinant human IL-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 46:614–624 (2002).
45. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, Li T, Schmidely N, Le Bars M, Dougados M. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 67:547–54 (2008).
46. Westhovens R, Kremer JM, Moreland LW, Emery P, Russell AS, Li T, Aranda R, Becker JC, Qi K, Dougados M. Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. J Rheumatol. 36:736–42 (2009).
47. Keystone E, Emery P, Peterfy CG, Tak PP, Cohen S, Genovese MC, Dougados M, Burmester GR, Greenwald M, Kvien TK, Williams S, Hagerty D, Cravets MW, and Shaw T. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis 68:216–221 (2009).
48. Harriman G, Harper LK, and Schaible TF. Summary of clinical trials in rheumatoid arthritis using infliximab, an anti-TNF-α treatment. Ann Rheum Dis 58:161–164 (1999).
49. Jones RE and Moreland LW. Tumor necrosis factor inhibitors for rheumatoid arthritis. Bull Rheum Dis 48:1–4 (1999).
50. Garrison L and McDonnell ND. Etanercept: therapeutic use in patients with rheumatoid arthritis. Ann Rheum Dis 58(Suppl I):I165–I169 (1999).
51. Jarvis B and Faulds D. Etanercept: a review of its use in rheumatoid arthritis. Drugs 57: 945–966 (1999).
52. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PG, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange ML, McDonnell ND, and Weinblatt ME. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 130:478–486 (1999).
53. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, Sharp JT, Ory PA, Perdok RJ, Weinberg MA. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis, results of double blind, randomized, placebo-controlled trial. Arthritis Rheum 52:3279–3289 (2005).
54. Hoffman HM. Rilonacept for the treatment of cryopyrin-associated periodic syndromes (CAPS). Expert Opin Biol Ther 9:519–531 (2009).

55. Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. Annals Int. Med. 134: 695–706 (2001).
56. Emmerson BT. The management of gout. N Engl J Med 334:445–451 (1996).
57. Star VL and Hochberg MC. Prevention and management of gout. Drugs 45:212–222 (1993).
58. Hande KR, Noone RM, and Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med 76:47–56 (1984).
59. Schumacher HR Jr, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. Rheumatology 48:188–194 (2009).
60. Schumacher HR Jr. Febuxostat: A non-purine, selective inhibitor of xanthine oxidase for the management of hyperuricaemia in patients with gout. Expert Opin Investig Drugs 14: 893–903 (2005).
61. Dan T and Koga H. Uricosurics inhibit urate transporter in rat renal brush border membrane vesicles. Eur J Parmacol 187: 303–312 (1990).
62. Yu TF, Dayton PG, and Gutman AB. Mutual suppression of the uricosuric effects of sulfinpyrazone and salicylate: a study in interactions between drugs. J Clin Invest 42:1330–1339 (1963).

General References

Brenner GM. Pharmacology, 1st ed. Philadelphia: Saunders, 2000:317–328.
Brody TM, Larner J, and Minneman KP. Human pharmacology: molecular to clinical, 3 rd ed. St. Louis: Mosby, 1998:249–258.
Craig CR and Stitzel RE. Modern pharmacology, 4th ed. Boston: Little, Brown, 1990:477–508.
Ellenhorn MJ, Schonwald S, Ordog G, and Wasserberger J. Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning, 2nd ed. Baltimore: Williams & Wilkins, 1997:175–223.
Hardman JG and Limbird LE. Goodman and Gilman's: the pharmacological basis of therapeutics, 10th ed. New York: McGraw-Hill, 2001:687–732.
Kalant H and Roschlau WH. Principles of medical pharmacology, 5th ed. New York: Oxford University Press, 1998:410–427.
Katzung BG. Basic & clinical pharmacology, 10th ed. New York: McGraw-Hill, 2007:573–598.
Klaassen CD. Casarett and Doul's toxicology: the basic science of poisons, 5th ed. New York: McGraw-Hill, 1996:969–986.
Page C, Curtis M, Sutter M, Walker M, and Hoffman B. Integrated pharmacology, 2nd ed. St. Louis: Mosby International, 2002:437–454.
Rang HP, Dale MM, Ritter JM, and Gardner P. Pharmacology, 4th ed. New York: Churchill Livingstone, 2001:229–240.
Smith CM and Reynard AM. Essentials of pharmacology, 1st ed. Philadelphia: Saunders, 1995: 147–163.
Tryniszewski C. Nurses drug loose leaf. San Francisco: Blanchard & Loeb, 2001:1–796.

Part VI
Environmental and Social Pharmacology

Chapter 12
Food and Drug Interactions

Shahla M. Wunderlich and Jacqueline Piemonte

Abstract The relationships and interactions between foods, the nutrients they contain, and drugs have gained tremendous recognition in the healthcare and medical fields. Certain foods and specific nutrients in foods, if ingested concurrently with some drugs, may affect the overall bioavailability, pharmacokinetics, pharmacodynamics, and therapeutic efficacy of the medications. Furthermore, the therapeutic efficacy of many drugs depends on the nutritional status of the individual. In other words, the presence or absence of some nutrients in the gastrointestinal tract and/or in the body's physiological system, such as in the blood, can enhance or impair the rate of drug absorption and metabolism resulting in treatment failure. These types of interactions are considered to be nutrient–drug interactions.

There are also drug–nutrient interactions, which mean that the presence of some drugs can significantly affect the food and nutrient metabolism and bioavailability in humans. Medications can alter appetite and taste, and also change the absorption and metabolism of nutrients. This can lead to impaired nutritional status, such as depletion of some minerals and vitamins from the digestive system and sometimes weight problems. The use of certain drugs may affect the GI tract function and lead to a loss of body electrolytes and fluid. Limiting prescription drugs to essential medications for as brief a period as possible and periodic re-evaluations are essential for minimizing adverse reactions. There are many clinical issues and questions regarding drug–nutrient interactions which require further research. However, there is already enough evidence to conclude that some drugs affect nutritional status, sometimes adversely, and that nutritional factors can alter the therapeutic efficacy of some drugs significantly. This chapter describes some of the more common interactions between food and drugs.

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Pharmacological and Nutritional Aspects

In this chapter, drugs refer to the chemical formulations used to prevent or treat disease conditions, i.e., those which are prescribed or are over-the-counter medications. Nutrients are considered to be the chemicals found in foods that are essential for the normal physiological functions of the human body and optimal health. Therefore, these two groups of chemicals may simply interact with each other when they are present at the same time within the human body.

As an example of how this interaction can occur, the metabolism or biotransformation of many drugs in the liver depends on enzyme systems such as the mixed-function oxidase system (MFOS), a multienzyme system responsible for the metabolism of drugs and other foreign compounds. This system includes cytochrome P450, nicotinamide-adenine-dinucleotide-phosphate (NADPH), cytochrome P450 reductase, and phosphatidylcholine among others. Microsomal cytochrome P450 monooxygenase system metabolizes many drugs by hydroxylation. Both NADH and NADPH donate reducing equivalents.

Example:

$$\text{DRUG-H} + \text{O}_2 + 2\text{Fe}^{2+}(\text{P450}) + 2\ \text{H}^+ \rightarrow \text{DRUG-OH} + \text{H}^2\text{O} + 2\text{Fe}^{3+}(\text{P450})^{\text{Hydroxylase}}$$

Oxygen is also needed as shown in the equation. Drugs such as aminopyrine, aniline, bezphetamine bezypyrene, and morphine are metabolized by this system. Some drugs such as phenobarbital can induce the formation of microsomal enzymes and cytochrome P450.

Phosphatidylcholine, or lecithin, a phospholipid, is indirectly involved in the biotransformation of drugs or detoxification whereby the drugs are transformed from lipid soluble molecules into water-soluble molecules. Phosphatidylcholine is a constituent of natural cell membranes and it participates in complex cellular signaling events for detoxification. Detoxification in the liver is divided into two phases. In phase I, cytochrome P450 enzymes act on toxins to oxidize, reduce, or hydrolyze them, after which some of them can be excreted. Whereas, in phase II, conjugation enzymes covert toxins to water-soluble forms for excretion or elimination.

Many essential nutrients are required for the optimal function of this enzyme system. For example, low levels of protein, essential amino acids, ascorbic acid, retinol, tocopherol, and other nutrients in the diet and in the body's physiological system can decrease the function of this enzyme system in the liver. The presence of some drugs, with certain nutrients in food or in supplements, can lead to biochemical interactions that alter the absorption and metabolism of drugs or nutrients in this vital organ. Awareness of these interactions and provision of the appropriate interventions can optimize the effectiveness and minimize the toxicities of medications.

Nutrient–Drug Interactions

Nutrient–drug interactions can occur in three phases which will be described in this section.

Pharmaceutical Phase: The Initial Phase of Drug Dissolution and Disintegration

Some foods and nutrients that influence the luminal pH may impact drug dissolution and disintegration and therefore, the acidity of these foods may alter the effectiveness and solubility of certain drugs. For example, high levels of ascorbic acid (vitamin C) can change the pH of the gastrointestinal (GI) tract and therefore influence the solubility of certain medications. One drug affected by gastric pH is saquinavir, a protease inhibitor for HIV treatment. Its bioavailability increases by solubilization induced by changes in the gastric pH. Foods that raise gastric pH, on the other hand, can also prevent dissolution of some drugs such as isoniazid.

Pharmacokinetic Phase: Absorption, Transport, Distribution, Metabolism, and Excretion of Drugs

The pharmacokinetic phase, the more studied stage of nutrient–drug interactions, is the study of the absorption, distribution metabolism, and excretion of drugs. The most significant nutrient–drug interactions involve the absorption process. The intestine, a primary absorptive organ, plays an important role in drug absorption at many levels. Intestinal functions, such as motility, or the affinity of drugs to attach to intestinal carrier systems, can influence the rate and degree of drug absorption. Foods and the nutrients within foods can accelerate (Table 12.1) or reduce (Table 12.2) drug absorption and hence alter the bioavailability of drugs [1].

Foods that affect the degree of ionization and solubility or chelating reaction (i.e., form an inactive complex) change the drug absorption significantly. Examples of chelating reactions are:

1. Combination of tetracycline with divalent minerals, such as calcium in milk or antacids. Calcium may affect absorption of quinolones adversely. Therefore, the ingestion of foods rich in calcium should be avoided in the presence of antimicrobial medications.
2. Reactions between iron (ferrous or ferric) and tetracycline, fluoroquinolone antibiotics-ciprofloxacin (Cipro), ofloxacin (Floxin), lomefloxacin (Maxaquin), and enoxacin (Penetrex). Furthermore, the bioavailability of ciprofloxacin and ofloxacin were reduced by 52% and 64% in the presence of iron.

Table 12.1 Examples of food (nutrient) interactions that accelerate the absorption of some drugs

Drug	Mechanism	Remarks
Carbamazepine	Increased bile production: enhanced dissolution and absorption; maintain diet high in folic acid and vitamin D	Take with food Avoid alcohol, limit caffeine
Diazepam	Food enhances enterohepatic recycling of drug: increased dissolution secondary to gastric acid secretion	None
Dicumarol	Increased bile flow; delayed gastric emptying permits dissolution and absorption	Drug taken with meal
Erythromycin	Unknown	Take with food
Griseofulvin	Drug is lipid soluble, enhanced absorption	Take with high-fat foods, or suspend in corn oil unless contraindicated
Hydralazine	Food reduces first-pass extraction and metabolism, blocks enzymatic transformation in GI tract	Take with food
Hydrochlorothiazide	Delayed gastric emptying enhances absorption from small bowel	Take with food
Labetalol	Food may reduce first-pass extraction and metabolism	Take with food
Lithium citrate	Purgative action decreases absorption	Take on full stomach
Metoprolol	Food may reduce first-pass extraction and metabolism	Take with food
Nitrofurantoin	Delayed gastric emptying permits dissolution and increased absorption	Take with food
Phenytoin	Delayed gastric emptying and increased bile production improves dissolution and absorption; Calcium and enteral feeding may reduce absorption, separate by 2 h	Always take at same time in relation to meals
Propoxyphene	Delayed gastric emptying improves dissolution and absorption	Take with food
Propranolol	Food may reduce first-pass extraction and metabolism	Take with food
Spironolactone	Delayed gastric emptying permits dissolution and absorption; bile may solubilize	Take with food Do not take potassium supplements; doing so may result in excessive potassium levels, which can cause arrhythmias

Data from [1]

3. Zinc and fluoroquinolones may result in inactive compounds and therefore decreased absorption of drugs [2]. It was observed that availability of lomefloxacin, a third generation fluoroquinolone, was depressed in the presence of nickel and zinc in simulated gastric juice and in the presence of Fe^{2+} in simulated intestinal juice, while many metals like magnesium, chromium, iron (both Fe^{2+} and Fe^{3+}), cobalt, nickel, copper, and cadmium depressed the availability of lomefloxacin at blood pH [3].

Table 12.2 Examples of food (nutrient) interactions that delay the absorption of some drugs

Drug	Mechanism	Remarks
Acetaminophen	High pectin foods act as absorbent and protectant	Take on empty stomach if not contraindicated
Ampicillin	Reduction in stomach fluid volume	Take with water
Amoxicillin	Reduction in stomach fluid volume	Take with water
Aspirin	Direct interference; change in gastric pH	Taking on empty stomach is not advisable
Atenolol	Mechanism unknown, possibly physical barrier	Take on empty stomach if tolerated
Captopril	Mechanism unknown	Take before meals
Cephalosporins	Mechanism unknown	None
Chlorpromazine	Drug undergoes first-pass metabolism in gut: delayed gastric emptying affects bioavailability	None
Cimetidine	Mechanism unknown	May not be clinically significant
Digoxin	High-fiber, high-pectin foods bind drug	Take drug same time with relation to food. A low-sodium diet and a potassium supplement may be recommended. Avoid taking with high-fiber foods.
Erythromycin stearate	Mechanism unknown; also impaired by water	None
Furosemide	Mechanism unknown	May not be clinically significant
Glipizide	Mechanism unknown	Affects blood glucose; more potent when taken half hour before meals
Isoniazid	Food may reduce first-pass extraction and metabolism	Take on empty stomach if tolerated
Levodopa	Drug competes with amino acids for absorption transport	Avoid taking drug with high-protein foods
Lincomycin	Mechanism unknown	Take on empty stomach; food impairs absorption
Methyldopa	Competitive absorptions	Avoid taking with high-protein foods, limit caffeine intake
Metronidazole	Mechanism unknown	None
Nafcillin	Mechanisms unknown: may be alteration of gastric fluid on pH	Take on empty stomach
Penicillamine	May form chelate with calcium or iron	Avoid taking with dairy products or iron-rich foods or supplements
Penicillin G	Delayed gastric emptying; gastric acid degradation; impaired dissolution	Take on empty stomach
PenicillinV	More rapid dissolution in gastric fluids	Take on empty stomach with full glass of water
Piroxicam	Mechanism unknown	None
Propantheline	Mechanism unknown	Evaluate take with meals directions
Quinidine	Possibly protein binding	May take with food to prevent GI upset

(continued)

Table 12.2 (continued)

Drug	Mechanism	Remarks
Rifampin	Mechanism unknown: conflicting reports	Absorption limited with dose less than 150 mg: unaffected dose greater than 700 mg, avoid antacids
Sulfonamides	Mechanism unknown: may be physical barrier	Taking with meals may prolong gastric emptying
Tetracyclines	Binds with calcium ions or iron salts forming insoluble chelates	Take 1 h before, 2 h after meals; do not take with milk
Valproic acid	Mechanism unknown	Delayed absorption may give uniform blood levels

Data from [1]

Table 12.3 summarizes some important food–drug interactions.

The rate of gastric emptying is significantly influenced by the composition of the food ingested. This rate, consequently, can affect the bioavailability of the drugs. High fiber and high fat foods are known to normally delay the gastric emptying time. Some drugs, such as nitrofurantoin and hydralazine, are better absorbed when gastric emptying is delayed because of longer exposure to the low pH of the stomach. Other drugs, such as L-dopa, penicillin G, and digoxin, degrade and become inactive when they are exposed to the low pH of the stomach for a long time.

The sodium-restricted diet prescribed for individuals with high blood pressure can also enhance renal tubular absorption of certain drugs, such as the antipsychotic lithium, leading to toxic blood levels [4]. On the other hand, sodium restriction indicated for individuals with high blood pressure may interfere with the antihypertensive action of diuretics, beta blockers, and angiotensin-converting enzyme (ACE) inhibitors. This may have the opposite effect in individuals taking calcium antagonists, nifedipine, and verapamil. A low sodium diet has been shown to potentiate the antihypertensive and antiproteinuric effects of losartan in type-2 diabetes giving a blood pressure reduction of a magnitude similar to that from a second antihypertensive drug [5].

The full extent of drug interaction with grapefruit juice is still unclear and more scientific research is needed to clarify the effects of different components in grapefruit juice on specific drugs. Some drugs become more bioavailable when taken with grapefruit juice and therefore should not be taken at the same time. The flavonoid, naringenin, in grapefruit and its mechanism of inhibiting metabolic enzymes is reported to be the key component [6]. A series of flavonoids present in grapefruit juice identified as esterase inhibitors, specifically kaempferol and naringenin, are shown to mediate pharmacokinetic drug interaction with the prodrugs lovastatin and enalapril due to their esterase inhibition [7]. Other components such as quercetin (also found in strawberries) and furocoumarin derivatives have been found to inhibit some drug oxidation in humans. Fruit juices have been found to be potent in vitro inhibitors of a number of organic anion-transporting polypeptides (OATPs), and to decrease the absorption of the nonmetabolized OATP substrate, fexofenadine [8]. Other recent reports indicate that constituents of grapefruit juice not only may influence

Table 12.3 Some important food–drug interactions

Drug	Nutrient type	Effect of interaction	Recommendation
Azithromycin (Zithromax)	Food	Decreased absorption of azithromycin reducing bioavailability by 43% and maximum concentration by 52%	Space drug and nutrient at least 2 h apart
Captopril (Capoten)	Food	May decrease absorption of captopril	Take drug on an empty stomach or consistently at the same time each day
Erythromycin	Food	Decreased absorption of erythromycin base or stearate	Space drug and nutrient at least 2 h apart
Fluoroquinolones	Iron, Mg++	Decreased absorption of fluroquinolones due to complextaion with divalent cations	Space drug and nutrient at least 2 h apart
Ciprofloxacin (Cipro)	Zn++, Ca++, Mg++		
Ofloxacin (Floxin)	Zn++		
Lomefloxacin (Maxaquinn)			
Enoxacin (Penetrex)			
Isoniazid	Food	May delay and decrease absorption of isoniazid	Space drug and nutrient at least 2 h apart
MAOIs[a]	Food	Hypertensive crisis	Avoid foods high in protein and tyramine, including aged, fermented, pickled, or smoked foods
Phenelzine (Nardil)			
Isocarboxazid (Marplan)			
Tranylcypromine (Parnate)			
Oral penicillins	Food	Decreased absorption of penicillins	Space drug and nutrient at least 2 h apart
Zidovudine (Retrovir)	Food	Decreased concentration of zidovudine	Space drug and nutrient at least 2 h apart
Sucralfate (Carafate)	Food	Decreased effect of sucralfate, binding of sucralfate to protein components of food	Administer drug 1–2 h before meals
Tetracycline	Dairy or iron	Decreased absorption of tetracycline as a result of chelation	Space drug and nutrient at least 2 h apart
Theophylline	High-fat diet	Rate of absorption can be affected, causing elevated theophylline concentrations	Avoid concomitant administration of food high in fat content or medicine 1 h before eating
Timed release (Theo- Dur Sprinkle, Theo-24, Uniphyl)			
Warfarin, (Coumadin, Panwarfin)	Food high in Vitamin K	Vitamin K can antagonize the effect of warfarin	Maintain a balanced diet without abrupt intake of large amounts of foods rich in vitamin K

Data from [2]

[a]*MAOIs* monoamine oxidase inhibitors

Table. 12.4 Grapefruit and drug interactions[a]

Drug	Interaction
Calcium channel blockers	
Amlodipine (Norvasc)	Yes
Felodipine (Plendil)	Yes
Nifedipine (Procardia)	Yes
Nimodipine (Nimotap)	Yes
Nisoldipine (Sular)	Yes
Diltiazem (Cardizem)	No
Verapamil (Calan, Isoptin)	No
HMG-CO inhibitors (statin)	
Atorvastatin (Lipitor)	Yes
Cervastatin (Baycol)	Yes
Lovastatin (Mevacor)	Yes
Simvastatin (Zocor)	Yes
Fluvastatin (Lescol)	? No
Pravastatin (Pravacol)	? No
Others	
Sildenafil (Viagra)	Yes
Diazepam (Valium)	Yes
Buspirone (Buspar)	Yes
Quinidine	No
Prednisone	No
Quinine	No
Ethinyl estradiol	No

Data from [13]

[a]This is a partial list; many other medications are being investigated

intestinal drug metabolism, but can also interfere with the secretory transport system in the intestine such as P-glycoprotein [9, 10]. The interactions of the many compounds in grapefruit juice with cyclosporine have been studied more extensively. Drugs such as some calcium channel blockers; most notably felodipine and some antiviral agents such as saquinavir are examples of those that are affected in the presence of grapefruit juice. Table 12.4 provides some examples of drugs that have demonstrated some interaction with grapefruit [11–13].

Drugs are eliminated from the body unchanged or as metabolites primarily by the kidneys, lungs, or gastrointestinal tract via bile. The drug excretion can also be affected by dietary nutrients, such as protein and fiber, or nutrients that influence the urinary pH. Of particular concern in this regard are the elderly, who may be deficient in their ability to clear drugs from the body due to declining lung, kidney/bladder, gastrointestinal, and circulatory efficiency. Accumulation of standard antibiotic doses leads to heightened risk of achieving toxic levels and increases the chance of unfavorable interactions with other medications and nutrients [14].

Pharmacodynamic Phase: The Enhancement and Inhibition of Drugs

The mechanism of a drug action depends on its agonist or antagonist activities, which will enhance or inhibit the normal metabolic and physiologic functions in the human body. Drugs, therefore, can produce desirable or undesirable effects. The magnitudes of these effects are influenced by the drug's absorption, distribution, biotransformation, and excretion and some nutrients can alter all these stages [15]. For example, the anticlotting medication warfarin (Coumadin), structurally similar to vitamin K, opposes clotting by interfering with vitamin K's action. Therefore, the warfarin dose should be high enough to counteract vitamin K. However, in patients with greatly fluctuating INRs (International Normalized Ratios), a measure of warfarin's effectiveness, a lower dietary intake of vitamin K has been observed than in those with stable INRs. This observation has lead to the theory that supplemental oral vitamin K (as opposed to attempting to maintain a consistent dietary intake of vitamin K) at a fixed daily dose may lead to a stabilization of INR. Four studies that evaluated the use of daily oral vitamin K supplementation demonstrated that concomitant supplementation of vitamin K can significantly improve anticoagulation control in patients with unexplained instability of response to warfarin [16–19].

The antineoplastic drugs that heavily rely on oxidizing properties to kill tumor cells, for example, have been reported to have an antagonistic relationship with high doses of vitamin C, an antioxidant which neutralizes free radicals. Limited preclinical data suggest that vitamin C may either stimulate or inhibit tumor growth depending on the form, dose, and timing of supplementation, cancer site, and type of chemotherapy [20]. The American Institute of Cancer Research (AICR) recommends that cancer patients should follow a reasonable diet sufficient in the fruits and vegetables that provide vitamin C at least at the Recommended Daily Allowances (RDA) level but that they should not take more supplemental vitamin C than the amount obtained in a reliable daily multi-vitamin containing vitamin C at the level comparable with RDAs [21].

The effect of the tumor reducing drug tamoxifen is strengthened with the addition of dietary flaxseed. Decreased tumor size was attributable to reduced tumor cell proliferation and increased apoptosis [22]. Lignan-rich sesame seeds, on the other hand, were found to negate the tumor-inhibitory effect of tamoxifen in estrogen-responsive breast tumors [23]. Some evidence from animal studies suggests that high intakes of soy isoflavones, particularly genistein, can interfere with the antitumor effects of tamoxifen [24, 25]. The recommendation of the AICR is for women on estrogen medications such as tamoxifen or aromatase inhibitors to limit or avoid soy until more data is available. Ingestion of soy products simultaneously with thyroid hormones appears to reduce the absorption of the hormones in individuals with suboptimal iodine levels. To be safe, people taking thyroid medication should not consume soy products within 3 h of taking their medication [26–28].

Methotrexate (MTX), similar structurally to the B vitamin folate, can cause severe folate deficiency. However, research has shown a reduction in the efficacy of methotrexate for treatment of rheumatoid arthritis with folic acid supplementation [29]

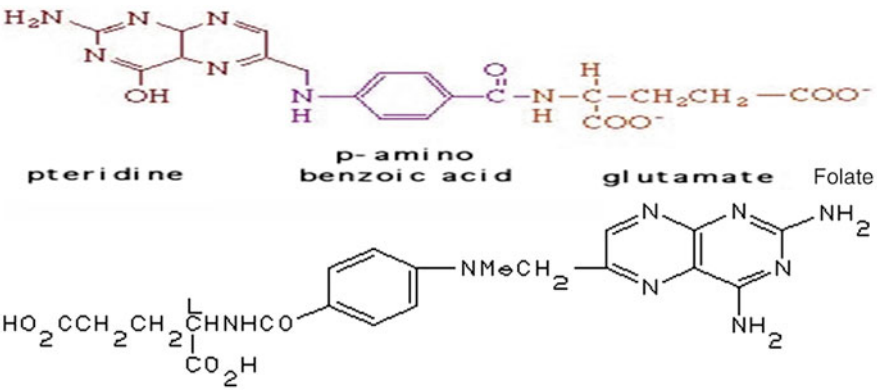

Fig. 12.1 The chemical structures of methotrexate and folate

as well as in the treatment of moderate to severe plaque psoriasis [30]. Figure 12.1 demonstrates the similarities between the chemical structures of these compounds. Aspirin can cause folate deficiency as well, when it is taken for a long period of time, because aspirin competes with folate protein carrier.

Drug–Nutrient Interactions

Drug–food interactions also play an important role in the nutritional status and nutrient requirements of individuals. A drug can enhance or inhibit nutrient bioavailability and therefore, affect the nutritional status of individuals. Individuals, such as the elderly, who are taking multiple medications for a long period of time, are often found to be deficient in one or more nutrients [31, 32].

The presence of multiple diseases, medications, malnutrition, and impaired metabolism in the elderly increases the risk of drug–nutrient interactions [33]. Other age groups, such as young children and adolescents, are also particularly at risk. There is a potential problem with drug nutrient interactions in adolescents because their nutrient needs are higher than those of adults. Rapidly dividing tissues during the adolescent growth spurt increase requirements for folate. Methotrexate, a drug commonly used at low doses for the treatment of psoriasis, rheumatoid arthritis, and certain liver disorders, limits the availability of methyl groups derived from one-carbon metabolism by inhibiting competitively a key enzyme in the intracellular folate metabolism, dihydrofolate reductase. The antiepileptic drug valproic acid (VPA) as well as phenytoin and carbamazepine are associated with two major adverse effects: teratogenicity and folate deficiency [34]. Drugs such as aspirin, barbiturates, primidone, ethinyl estradiol, and cycloserine are also reported to affect vitamin B folate metabolism [35, 36].

Pregnant women and infants are the other groups also at particular risk. L-carnitine plays an important role in lipid metabolism by facilitating the transport

of long-chain fatty acids across the mitochondrial inner membrane followed by fatty acid beta-oxidation. A study which investigated the inhibitory effect of five fluoroquinolones, ciprofloxacin (CPFX), gatifloxacin (GFLX), ofloxacin (OFLX), levofloxacin (LVFX), and grepafloxacin (GPFX), on L-carnitine transport mediated by an organic cation transporter OCTN2 in placental cell line BeWo cells, found that all of the fluoroquinolones inhibited L-carnitine transport, GPFX being the strongest inhibitor [37]. Members of the OCTN family play an important role in L-carnitine transport in the placenta.

The magnitude of these deficiencies depends not only on the chemical reactions between drugs and nutrients, such as vitamins and minerals, but also on the dose and duration of treatment/exposure to the drug. Drugs can interfere with nutrient utilizations at several sites starting from the ingestion of the food to the final stage of excretion. Some of the nutrients that can be affected by common drugs are the B vitamins folacin and pyridoxine, Vitamin C and fat-soluble vitamins A and D, and minerals such as calcium and zinc. Effects of angiotensin-converting enzymes inhibitors (ACE) on zinc metabolism in patients with heart failure reveals higher urine zinc levels and lower concentrations of zinc in serum suggesting that treating heart failure with ACE inhibitors may result in zinc deficiency [38].

Phenytoin (and possibly carbamazepine) interferes with the intestinal conjugase allowing folate absorption and results in teratogenicity secondary to folate deficiency and megaloblastic anemia. Another example is isoniazid, which uses B6, the vitamin required for the heme synthesis via delta-ALA synthetase, for its metabolism and therefore can cause sideroblastic anemia. The supplementation of B6 in these conditions is recommended.

Food Intake

Many drugs can cause anorexia, alter taste and smell, cause nausea and vomiting and ultimately affect overall food intake. For example, medications such as methylphenidate (Ritalin), which influences the central nervous system, may reduce appetite. This medication is often prescribed for hyperactive young children who are in their rapid growth phase. Long term use of this drug may cause growth retardation in these children. Therefore, when this drug is prescribed to young children, their food intake must be monitored. On the other hand, some anorectic drugs are used for weight loss and to treat obesity by reducing appetite. Examples are adrenergic and serotoninergic agents, which cause satiety, reduce appetite, and increase energy expenditure leading to weight loss. Amphetamines are good examples of adrenergic drugs that stimulate secretion of norepinephrine and reduce food intake [39]. Serotoninergic drugs, such as fenfluramine and dexfenfluramine, inhibit the reuptake of serotonin, stimulate satiety, and therefore reduce food intake. However, these drugs were found to have adverse effects on the cardiovascular system and were withdrawn from the market in the United States in 1997. There are other drugs for treating obesity such as the appetite suppressant, sibutramine (also as antidepressant),

Table 12.5 Examples of drugs that change taste perception

Acetyl sulfasalicylic acid	Griseofulvin
Allopurinol	Lidocaine
Amphetamines	Lithium carbonate
Amphotericin B	Meprobamate
Ampicillin	Methicillin sodium
Amylocaine	Methylthiouracil
Benzocaine	Metronidazole
Captopril	Nifedipine
Chlorpheniramine	Maleate D-Penicillamine
Clofibrate	Phenindione
Diltiazem	Phenytoin
Dinitrophenol	Probucol
5-Fluorouracil	Sulfasalazine
Flurazepam (Dalmane)	Triazolam (Halcion)

Data from [15]

and orlistat (lipase inhibitor), and some new biological compounds such as bombesin and neuropeptide Y which also affect satiety.

Taste and smell are very important factors that influence food intake and can subsequently affect the nutritional status of individuals. Zicam, a homeopathic cold remedy which contains zinc as an active ingredient, was recalled in 2009 due to claims of loss of smell by over 800 customers [40]. Taste alteration (dysgeusia or hypogeusia) due to medications is very common. Some hypoglycemic agents such as glipizide, the antimicrobials amphotericin B, ampicillin, and antiepileptic phenytoin are among the medications that alter taste perception. Other examples are given in Table 12.5 [15].

Cisplatin and other cytotoxic agents commonly used in the treatment of cancer cause nausea and vomiting, which reduces food intake as a result. Attempts to increase food intake, decrease nausea and vomiting by diet modifications, such as colorless, odorless meals for cancer patients should be considered in order to increase the food intake in these patients.

Weight Gain

Several groups of drugs such as anticonvulsants (carbamazepine and VPA), antihistamines (cyproheptadine hydrochloride- Periactin), psychotropic drugs (chlordiazepoxide hydrochloride-Librium, diazepam-Valium, chlorpromazine hydrochloride-Thorazine, meprobamate-Equanil), and corticosteroids (cortisone, prednisone) may increase appetite and consequently lead to weight gain. A synthetic derivative of progesterone, medroxyprogesterone acetate or megestrol acetate, used for the treatment of hormone-sensitive breast and endometrial cancer, may increase appetite, food intake, and weight gain.

The use of second-generation antipsychotics (SGAs) is associated with metabolic side effects including weight gain, diabetes mellitus, and an atherogenic lipid profile. These adverse effects are not only the risk factors for cardiovascular disease, insulin resistance, and diabetes mellitus, leading to increased morbidity and mortality but may also impair the patient's adherence to treatment. SGAs in particular are associated with significant weight gain with clozapine and olanzapine carrying the highest risk, whereas newer agents, such as risperidone and aripiprazole, are considered to be less prone to cause weight gain [41]. A review of psychotropic drug-induced weight change found amitryptiline and nortriptyline to have one of the highest antidepressant incidences of weight gain followed by imipramine. Mirtazapine, an antidepressant used specifically for weight gain in the treatment of anorexics, must be carefully monitored due to its association with neutropenia [42]. In contrast, bupropion was associated with weight reduction. Regarding mood stabilizers and anticonvulsants, a marked gain in weight with lithium and sodium valproate was reported frequently. With gabapentin and vigabatrin a slight to moderate gain in weight was found. Treatment with topiramate and felbamate were reported to lead to weight loss. The atypical neuroleptics clozapine and olanzapine were frequently related to a strong gain in weight followed by risperidone [43].

The formulation of drugs in lipid emulsion (e.g., in 10% soybean), such as propofol, contributes to a significant amount of additional energy (kilocalories) intake. Other drugs such as lorazepam and morphine may change the bodyweight by decreasing the body's energy expenditure [44].

Weight gain could be therapeutically favorable in some cases such as in cancer and acquired immunodeficiency syndromes (AIDS)-related cachexia. Anabolic steroids, nandrolone, corticosteroids, cyproheptadine, hydrazine sulfate, megestrol acetate, and oxandrolone are prescribed in some cases to promote weight gain.

As well, dronabinol, a cannabis derivative, is used to address nausea and vomiting caused by cancer chemotherapy and anorexia and cachexia in HIV/AIDS [45, 46].

Nutrient Absorption

Several mechanisms may affect nutrient absorption due to the presence of drugs. Drugs can damage the intestinal absorptive surfaces including villi, microvilli, brush border enzymes, and the transport system. Drugs can also influence the absorption of nutrients by changing the gastrointestinal (GI) transit time or the overall GI chemical environment, such as changing the pH of the stomach. Absorption of micronutrients, vitamins, and minerals as well as macronutrients, protein, and fat, are affected by the type, dosage, and strength of some drugs. A review on the intestinal lipase inhibitor, Orlistat, revealed interference with a number of drugs (warfarin, amiodarone, ciclosporin, and thyroxine) as well as the fat-soluble vitamins, adversely affecting both their bioavailability and effectiveness. In addition, the use of Orlistat has been associated with rare cases of acute kidney injury, linked possibly

to increased fat malabsorption resulting from the inhibition of pancreatic and gastric lipase, leading to the formation of soaps with calcium and increased free oxalate absorption and enteric hyperoxaluria [47]. Bile, an emulsifier, is required for the metabolism of fat and also as an aid in the absorption of fat-soluble vitamins such as A, D, E, and K. Some bile-sequestering resins such as cholestyramine, therefore, interfere with the fat metabolism and absorption and may result in deficiency of the essential fatty acid linoleic acid and impair the synthesis of arachidonic acid. Lipids are important components of cell membrane structure. Individuals who are taking these types of medications should therefore be monitored for any deficiencies of essential fatty acids and/or fat-soluble vitamins.

GI damage can come from over-the-counter drugs such as aspirin and other acidic drugs, or from antibiotic neomycin or laxatives. The resulting changes in the mucosal lining interfere with optimum absorption of nutrients such as iron, calcium, fat (including some fat-soluble vitamins), protein, sodium, and potassium. Colchicines, anti-inflammatory drugs, *para*-aminosalicylic acid, antituberculosis, trimethoprim*, antibacterial*, and sulfasalazine, antiinflammatory (antiarthritic) *are* known to interfere with the intestinal transport mechanisms. They can impair the absorption of B vitamins, B12 and folic acid.

Many laxatives, mineral oil, and cathartic agents reduce transit time in the GI and may cause steatorrhea and loss of fat-soluble vitamins, A and E, and possibly calcium and potassium. Drugs containing sorbitol, such as theophylline solutions may induce osmotic diarrhea and therefore, shorten the transit time. Antacids change the pH of the stomach and cause chelating with some minerals consequently reducing their absorption. Higher pH in the stomach reduces the absorption of iron, calcium, zinc, and magnesium.

Nutrient Metabolism

Some of the important functions of vitamins and several minerals are their roles as coenzymes/cofactors in metabolic processes in the human body. Therefore, certain drugs are targeted to these coenzymes (antivitamins) in order to reduce the activity of some enzymes in related metabolic reactions. Good examples of these drugs are methotrexate (MTX) for treating leukemia and rheumatoid arthritis, and aminopterin, and pyrimethamine used for treating malaria and ocular toxoplasmosis. Dihydrofolate reductase activates folic acid into a tetrahydrofolate (THF) used as a carbon donor. THF is required to make thymine from uracil, and to build purines, adenine, and guanine. Folate is therefore critical for replication and gene expression. Drugs like methotrexate, trimethoprim, and pyrimethamine block the enzyme and decrease the available THF, reducing cell division and maturation. Prescription for supplements for these patients should be cautioned and monitored. Another example is the anticoagulant drug, Coumadin, which is a vitamin K antagonist. Dietary vitamin K can interact with anticoagulant drugs and it changes the safety and therapeutic efficacy of these drugs [48]. Therefore, many

patients are advised to avoid foods, such as vegetables, high in vitamin K. Patient nutrition education and monitoring of blood levels is necessary in order to include some vegetables in their daily diets without changing the efficacy of these drugs. As stated in Sect. “Pharmacodynamic Phase: The Enhancement and Inhibition of Drugs”, some patients with *unstable* response to Coumadin, actually respond better when their vitamin K levels are maintained at a constant level through supplementation rather than diet, so careful monitoring must be observed for individual differences [16–19].

MAOIs (moanmine oxidase inhibitors) such as a group of antidepressant drugs, antimicrobials, and antineoplastic drugs, interact with the biologically active pressor amines in foods very strongly. There are two different isoforms of MAO enzymes: MAO-A is found anywhere, including gut and liver and metabolizes tyramine from foods, but also norepinephrine and serotonin; MAO-B is found primarily in the brain and metabolizes dopamine, but not tyramine, norepinephrine, or serotonin. Tyramine is a releaser of norepinephrine, which can result in blood vessel constriction and consequently, high blood pressure, tachycardia, chest pain, and severe headache, particularly if its gut and liver metabolism are prevented by the coadministration of MAO-A inhibitors (phenelzine, tranylcypromine). Patients taking these medications must avoid foods high in tyramine (vasoactive amine) such as hard cheeses, smoked or pickled fish, broad beans, Chianti or vermouth wines, meat and yeast extracts, dry sausage, and beer and ale. The amines in these foods usually deaminate very rapidly by monoamine and diamine oxidases and therefore they cause no adverse effects. However, in the presence of the inhibiting drugs, bioavailability of tyramine is increased, its blood levels increase and in severe cases can cause intracranial hemorrhage from hypertensive crisis, cardiac arrhythmias, and cardiac failure. Table 12.6 lists the foods that one should monitor while taking oral MAOIs [49].

Nutrient Excretion

Competitive binding and altered reabsorption are the two recognized mechanisms that may cause drugs to induce nutrient excretion. D-Penicillamine chelates with intended toxic metals, but it may also bind with other metals such as zinc, eliminating it via urine. Ethylenediaminetetra-acetic acid (EDTA) has been shown to cause urinary excretion of zinc. Some diuretics, such as furosemide, ethacrynic acid, and triamterene, reduce the reabsorption of electrolytes and minerals such as potassium, magnesium, zinc, and calcium and increase renal excretion of these elements. Sodium loss in the urine is common with thiazide and loop diuretics. Potassium-sparing diuretics spare potassium and magnesium loss but augment urinary sodium loss [50]. Depletion of magnesium is associated with chemotherapeutic agents such as cisplatin. Therefore, magnesium supplement often is recommended between the chemotherapy treatments for these patients.

Table 12.6 The tyramine–restricted diet

Foods high in tyramine must be avoided	Foods should be used with caution	Foods low in tyramine, no restriction
Cheese	Avocado	Fresh fish
Smoked or pickled fish	Raspberries	Canned figs
Nonfresh meats, livers	Soy sauce	Mushrooms
Chianti and vermouth wines	Chocolate	Cucumber
Broad beans	Red and white wines, port wines	Sweet Corn
Banana peels	Distilled spirits	Fresh Pineapple
Meat extracts	Peanuts	Worcestershire sauce
Yeast extracts/brewers yeast	Yogurt and cream from unpasteurized milk	Salad dressings
Dry sausage		Yeast bread
Sauerkraut		Raisins
Beer and ale		Tomato juice
		Curry powder
		Beet root
		Junket
		Boiled egg
		Coca Cola
		Cookies (English biscuits)
		Cottage cheese
		Cream cheese

Data from [49]

Conclusions

Many nutrient–drug and drug–nutrient interactions, and the impact of these interactions on overall health have been identified and many more are being investigated. Healthcare professionals need to keep abreast of the new findings in this area and recognize that these interactions do occur, especially when a drug is used over a long period of time. Nutrient interactions are not unique to prescription drugs. Over-the-counter drugs, because of their increasing availability, are used by many including the older adult population and may impair nutritional status by interfering with bioavailability of many critical nutrients.

Consumers should consult with physicians about potential interactions, pharmacists for instructions on taking drugs, and with registered dietitians to assess nutritional status while taking medications. Food is essential for good health as well as are medications which enable people to enjoy better health, but they also bring side effects and risks that need to be addressed.

References

1. Thomas JA. Drug–nutrient interactions. Nutr Rev 53:271–282 (1995).
2. Kirk JK. Significant drug–nutrient interactions. Am Family Physician 51:1175–1182 (1995).

3. Sultana N, Arayne MS, Furgan H. In vitro availability of lomefloxacin hydrochloride in the presence of essential and trace elements. Pak J Pharm Sci 18(3):59–65 (2005).
4. Bennett WM. Drug interactions and consequences of sodium restriction. Am J Clin Nutr 65(Suppl 2):678S–681S (1997).
5. Houlihan CA, Allen TJ, Baxter AL, Panangiotopoulos S, Casley DJ, Cooper ME, Jerums G. A low-sodium diet potentiates the effects of losartan in type 2 diabetes. Diabetes Care 25(4):663–71 (2002).
6. Ameer B and Weintraub RA. Drug interaction with grapefruit juice. Clin Pharmacokine 33:103–121 (1997).
7. Li P, Callery PS, Gan LS, Balani SK. Esterase inhibition by grapefruit juice flavonoids leading to new drug interaction. Drug Metab Dispos 35(7):1203–08 (2007).
8. Dresser GK, Bailey DG. The effects of fruit juices on drug disposition: a new model for drug interactions. Eur J Clin Invest 33(Suppl 2):10–6 (2003).
9. Wagner D, Spahn-Langguth H, Hanafy A, Langguth P. Intestinal drug efflux: formulation and food effects. Adv Drug Deliv Review 50(Suppl 1):513–531 (2001).
10. de Castro WV, Mertens-Talcott S, Derendorf H, Butterweck V. Grapefruit juice and its components inhibit P-glycoprotein (ABCB1) mediated transport of talinolol in Caco-2 cells. J Pharm Sci 96(10):2808–17 (2007).
11. Sica DA. Interaction of grapefruit juice and calcium channel blockers. Am J Hypertens Med 19(7):768–73 (2006).
12. Kiani J, Imam SZ. Medicinal importance of grapefruit juice and its interaction with various drugs. Nutr J 6:33 (2007).
13. Karpman HL. Is grapefruit juice harmful? Internal Medicine Alert 23:1–4 (2001).
14. Noreddin AM, El-Khatib W, Haynes V. Optimal dosing design for antibiotic therapy in the elderly: a pharmacokinetic and pharmacodynamic perspective. Recent Patents Anti-Infect Drug Disc 3(1):45–52 (2008).
15. Pronsky, Z, Crowe, J. Assessment: Food-Drug Interactions. In: Mahan LK and Escott-Stump S, eds. Krause's food and nutrition therapy. Philadelphia: Saunders, 2008:432–453.
16. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 109(6):2419–23 (2007).
17. Reese AM, Farnett LE, Lyons RM, et al. Low dose vitamin K to augment anticoagulation control. Pharmacotherapy 25:1746–1751 (2005).
18. Fork SK, Misita CP, Shilliday BB, et al. Prospective study of supplemental vitamin K therapy in patients on oral anticoagulants with unstable International Normalize Ratios. J Thromb Thrombolysis 24:23–27 (2007).
19. Rombouts EK, Rosendaal FR, Van Der Meer FJ. Daily vitamin K supplementation improves anticoagulant stability. J Thromb Haemost 5:2043–2048 (2007).
20. Lamson, DW, Brignall MS. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. Altern Med Rev 4:304–329 (1999).
21. Norman H, Butrum R, Feldman E, Heber D, Nixon D, Picciano M, Rivlin R, Simopoulos A, Wargovich M, Weisburger E, Zeisel S. The role of dietary supplements during cancer therapy. J Nutr 133:3794S–3799S (2003).
22. Chen J, Power KA, Mann J, Cheng A, Thompson LU. Flaxseed alone or in combination with tamoxifen inhibits MCF-7 breast tumor growth in ovariectomized athymic mice with high circulating levels of estrogen. Exp Biol Med 232(8):1071–80 (2007).
23. Sacco SM, Chen J, Power KA, Ward WE, Thompson LU. Lignan-rich sesame seeds negates the tumor-inhibitory effect of tamoxifen but maintains bone health in a postmenopausal athymic mouse model with estrogen-responsive breast tumors. Menopause 15(1):171–9 (2008).
24. Ju YH, Doerge DR, Allred KF, Allred CD, Helferich WG. Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. Cancer Res 62(9):2474–2477 (2002).
25. Messina MJ, Loprinzi CL. Soy for breast cancer survivors: a critical review of the literature. J Nutr 131(11 Suppl):3095S–3108S (2001).

26. Doerge DR, Chang HC. Inactivation of thyroid peroxidase by soy isoflavones, in vitro and in vivo. J Chromatogr B Analyt Technol Biomed Life Sci 777: 269–79 (2002).
27. Jabbar MA, Larrea J, Shaw RA. Abnormal thyroid function tests in infants with congenital hypothyroidism: the influence of soy-based formula. J Am Coll Nutr 16:280–2 (1997).
28. Messina, M et. al. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid 16(3):249–58 (2006).
29. Khanna D, Park GS, Paulus HE, Simpson KM, Elashoff D, Cohen SB, Emery P, Dorrier C, Furst DE. Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. Arthritis Rheum 52(10):3030–8 (2005).
30. Chladek J, Simkova M, Vaneckova J, Hroch M, Chladkova J, Martinkova J, Vavrova J, Beranek M. The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during the remission-induction period of treatment for moderate-to-severe plaque psoriasis. Eur J Clin Pharamacol 64(4):347–55 (2008).
31. Genser D. Food and drug interaction: consequences for the nutrition/health status. Ann Nutr Metab 52(Supp 1):29–32 (2008).
32. Lamy PP. Effects of diet and nutrition on drug therapy. J Am Geriatr Soc 30:S99-S112 (1982).
33. Akamine D, Filho MK, Peres CM. Drug-nutrient interactions in elderly people. Curr Opin Clin Nutr Metab Care10(3):304–10 (2007).
34. Alonso-Aperte E, Varela-Moreiras G. Drug –nutrient interaction. Eur J Clin Nutr 54(Supple 1): s69–74 (2000).
35. Roe DA. Effects of drugs on nutrition. Life Science 15:1219–34 (1974).
36. Thomas JA and Markovac J. Aspects of neural tube defects: a mini review. Toxic Substances J 13: 303–12 (1994).
37. Hirano T, Yasuda S, Osaka Y, Asari M, Kobayashi M, Itagaki S, Iseki K. The inhibitory effects of fluoroquinolones on L-carnitine transport in placental cell line BeWo. Int J Pharm 351(1–2):113–8 (2007).
38. Trasobares E, Corbaton A, Gonzalez-Estecha M, Lopez-Colon JL, Pratas P, Olivan P, Sanchez JA, Arroyo M. Effects of angiotensin-converting enzyme inhibitors (ACE i) on zinc metabolism in patients with heart failure. J Trace Elem Med Biol 21(Suppl 1):53–5 (2007).
39. Atkinson RL. Use of drugs in the treatment of obesity. Ann Rev Nutr 17:383–404 (1997).
40. O'Rourke M. Smell no evil. Risk Management. 56(6):16 (2009).
41. Tschoner A, Engl J, Laimer M, Kaser S, Rettenbacher M, Fleischhacker WW, Patsch JR, Ebenbichier CF. Metabolic side effects of antipsychotic medication. Int J Clin Pract 61(8):1356–70 (2007).
42. Treatment recommendations for patients with eating disorders. Am J Psychiat 163(7): 5 (2006).
43. Drieling T, Biedermann NC, Scharer LO, Strobl N, Langosch JM. Psychotropic drug-induced change of weight: a review. Fortschr Neurol Psychiatr 75(2):65–80 (2007).
44. Mirenda J and Broyles G. Propofol as used for sedation in the ICU. Chest 108:539–548 (1995).
45. Navari R. Pharmacological Management of Chemotherapy-Induced Nausea and Vomiting: Focus on Recent Developments Drugs. 69(5): 515–534 (2009).
46. Adams L, Shepard N, Caruso R, Norling M, et al. Putting Evidence Into Practice®: Evidence-Based Interventions to Prevent and Manage Anorexia. Clin J Oncol Nurs. 13(1): 95–102 (2009).
47. Filipattos TD, Derdemezis CS, Gazi IF, Nakou ES, Mikhailidis DP, Elisaf MS. Orlistat-associated adverse effects and drug interactions: a critical review. Drug Saf 31(1):53–65 (2008).
48. Couris RR, Tataronis GR, Dallal GE, Blumberg JB and Dwyer JT. Assessment of healthcare professionals' knowledge about warfarin-vitamin K drug-nutrient interactions. J Am Coll Nutr 19:439–45 (2000).
49. Simpson GM and Gratz SS. Comparison of the pressor effect of tyramine after treatment with phenelzine and moclobemide in healthy volunteer. Clin Pharmacol Therap 52:286–291 (1992).
50. Nicholls MG. Interaction of diuretics and electrolytes in congestive heart failure. Am J Cardiol 65:17E (1990).

Related Websites

"FDA Public Health Advisory of possible interaction between Hypericum perforatum (St. John's Wort) and Indinavir, a protease inhibitor used to treat HIV infection" http://www.fda.gov/cder/drug/advisory/stjwort.htm

MedicineNet-Etidronate (Didronel) "Learn how the medication works to strengthen bone and explore its dosage, side effects, and interactions with food and other medicines."
http://www.FocusOnMedications.com/script/main/art.asp?articlekey=738

MDAdvice.com-Cholestyramine "Description of the antihyperlipidemic agent's uses, dosage, and side effects includes details about its interactions with foods and medications." http://www.mdadvice.com/library/drug/drug113.html

Food Medication Interactions "Find a table of contents and sample page of "HIV Medications-Food Interactions Handbook. Resource offers info on food and drug interactions." http://www.foodmedinteractions.com/

FDA –Zemplar Consumer Information "Medication, also known as paricalcitol, is used to treat high parathyroid hormone levels. Learn about its side effects and drug interactions." http://www.fda.gov/cder/consumerinfo/druginfo/Zemplar.htm

InteliHealth-Phenelzine Sulfate (Nardil) "Discover how the medication works to relieve depression and investigate its food, drug, and disease interactions. http://www.intelihealth.com/IH/ihtIH/WSIHW000/19689/11728/214201.html?rbrand=Nardil

Thyroid Drugs: Food, Drug and Supplement Interactions "Discover which foods, supplements, and drugs interact with thyroid medications." http://www.thyroid-info.com/articles/thyroid-drug-faq.htm

Chapter 13
Pharmacokinetic and Pharmacodynamic Interactions Between Alcohol and Other Drugs

A. Wayne Jones

Abstract Adverse drug–alcohol interactions represent a major problem in today's society because of the increasing use of prescription medication in the aging population and the recreational use and abuse of alcoholic beverages throughout adult life. Heavy drinking and drunkenness are major public health problems and ethanol is the drug most frequently encountered in poisoning deaths either alone or together with other substances. Drugs and alcohol can interact in a number of ways, such as by competition for binding sites on hepatic enzymes, which opens the possibility for a metabolic interaction. This is often reflected in a change in the blood or plasma concentration–time curve of alcohol and/or drug and a more rapid or slower rate of elimination from the body (pharmacokinetic interaction). The combined influence of alcohol and other drugs might occur at certain receptor sites or ion channels in the central nervous system and in this way modify behavioral response to drug treatment (pharmacodynamic interaction). This review is concerned with the biological background and the mechanism underlying pharmacokinetic and pharmacodynamic interaction between ethanol and other drugs. Examples are given of ethanol–drug interactions involving common medications (e.g., acetaminophen, benzodiazepines, and other sedatives) as well as drugs of abuse, such as cocaine and GHB.

Keywords Drug • Alcohol • Interactions

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Introduction

Knowledge about the disposition and fate of drugs in the body owes much to the efforts of early pioneers in pharmacology and organic chemistry, mainly from German speaking countries [1]. When benzoic acid, which was considered a potential treatment for gout, was administered to animals and man, hippuric acid (aryloglycine) was identified in the urine [2]. This chemical transformation of one substance into another, namely the conjugation of an aromatic carboxyl group with an endogenous amino acid was the first pathway of drug metabolism to be discovered in man [1, 2].

Before the end of the nineteenth century most of the major pathways of drug metabolism were discovered including synthetic conjugation reactions resulting in acetylation, glucuronidation, and sulfation [3]. The oxidative metabolism of drugs as exemplified by the conversion of benzene into phenol (stage I), followed by conjugation of the aromatic hydroxyl group with sulfate (stage II) represented a key discovery. An initial phase 1 reaction (oxidation, reduction, hydrolysis), followed by a phase II conjugation reaction emerged as an important concept in drug metabolism. In this way a lipophilic substance was converted into a more water-soluble metabolite, which facilitated removal of the drug from the body by excretion via the kidneys into the urine [1–3].

Francis Edmund Anstie was among the first to investigate the fate of ethanol in the body and he did this using a reliable analytical method (chemical oxidation with dichromate + sulfuric acid) for quantitative analysis of ethanol in body fluids [4]. Only a small fraction of the total amount of alcohol consumed could be recovered unchanged in breath and urine leading to the conclusion that alcohol was "burnt-up" in the body in the same way as ordinary foodstuff [5]. Somewhat later, Neubauer [6] discovered a nonoxidative metabolite of ethanol, which was identified in the urine as ethyl glucuronide [6]. The results from these early studies verified that >90% of the alcohol ingested underwent oxidation, first to acetaldehyde then to acetic acid [5]. Batelli and Stern discovered the endogenous factor responsible for the oxidation of ethanol and they named it "alcoholase" which today is better known as alcohol dehydrogenase (ADH) [2].

Undesirable drug–alcohol interactions are a common concern in clinical medicine because of the widespread use and abuse of alcoholic beverages throughout adult life [7]. The combined effects of heavy drinking and concomitant use of psychoactive drugs have caused many fatal poisonings, both accidental and in deliberate suicide attempts [8–10]. Adverse drug–alcohol interactions represent a constant concern for the pharmaceutical industry whenever a new drug is being developed. This possibility needs to be carefully explored during clinical trials before a new pharmaceutical product is registered and marketed [11–13].

Most people drink alcohol in moderation but for about 10–15% of the population, especially among men, ethanol is a drug of abuse and overconsumption leads to considerable morbidity and mortality worldwide [14, 15]. Alcohol has been referred to as the Jekyll and Hyde of the drug world because social drinking is relatively harmless, whereas excessive drinking and abuse wrecks people's lives and costs the health care system billions of dollars annually [16]. Alcohol is a legal drug, although purchasing it requires a minimum age, such as 18 y.o. in most countries (21 y.o. in the USA). Teenage drinking is a fact of life and is virtually impossible to

control. The enforcement of a 21 y.o. age limit as in the USA has been effective in reducing alcohol-related fatal crashes involving newly licensed drivers [17].

The danger of combining alcohol with a prescription drug is verified by inspecting the casualty records for visits to hospital emergency departments to treat cases of poisoning [18–20]. Interactions between alcohol and drugs also deserve consideration when skilled tasks, such as driving are performed. Statistics show that 20–50% of drivers killed in road-traffic crashes were under the influence of alcohol at the time [21–23]. The ready availability and consumption of alcoholic beverages along with the popularity of recreational drugs creates a heightened risk for an adverse drug–alcohol interaction [24–26].

The concentration of alcohol determined in a person's blood has important ramifications in forensic science and legal medicine because punishable limits of blood–alcohol concentration (BAC) are enforced for driving a motor vehicle: 0.08 g/100 mL in the USA and Canada compared with 0.05 g/100 mL in most EU nations [27]. If a man with a body weight of 70 kg has a BAC of 0.10 g/100 mL (1.0 g/L) a Widmark calculation shows that about 50 g 100% ethanol (1.0×70×0.7) are absorbed and distributed in all body fluids and tissues, where 0.7 is the distribution volume of ethanol for men [27]. This exceeds, by several orders of magnitude, the usual dose of an illicit or a prescription drug, such as 10 mg diazepam or morphine or 500 mg for aspirin or acetaminophen.

After oral administration, the concentration of a drug in blood or plasma depends on interplay between absorption, distribution, metabolism, and excretion (ADME) processes. The ADME for ethanol is illustrated schematically in Fig. 13.1. A drug and alcohol can interact during absorption from the gastrointestinal tract [28], first-pass metabolism (FPM) in the gut or liver [29], by competition for phase I and phase II hepatic enzymes [30, 31], and also during urinary excretion via the kidney and in the case of volatile substances when these are exhaled through the lungs [32].

The intensity and duration of drug action is closely related to the concentration in the blood and the rate of metabolic degradation of the parent compound, which usually represents the pharmacologically active substance [33–35]. Important in this connection is the activity and turnover of microsomal (P450) drug metabolizing enzymes [36]. Because most drugs are metabolized in the liver, competition for binding sites on hepatic enzymes becomes a key consideration for drug–drug or drug–alcohol interactions [37, 38]. People suffering from liver dysfunction, as a result of chronic heavy drinking (hepatitis, cirrhosis) or other medical condition, are likely to metabolize drugs more slowly compared with those with normal liver function [39]. Care is needed when drugs are prescribed to geriatric patients because body composition and proper functioning of the liver and the kidneys decrease during aging. This enhances the risk of experiencing an adverse drug interaction [40–43].

Ethanol is a small neutral molecule that easily crosses the blood–brain barrier and its pharmacological effects depends on the dose, the speed of drinking, and the concentration gradient between the blood and the brain. Ethanol is classified as a central nervous system (CNS) depressant and mediates its effects in various ways but primarily via the $GABA_A$ receptor complex [44, 45]. Accordingly, medicinal drugs that interact at the same receptor (e.g., sodium oxybate, barbiturates, and benzodiazepines) are likely to enhance the psychoactive effects produced by a given dose of ethanol [46, 47]. Also important for the effect of drugs or alcohol is the

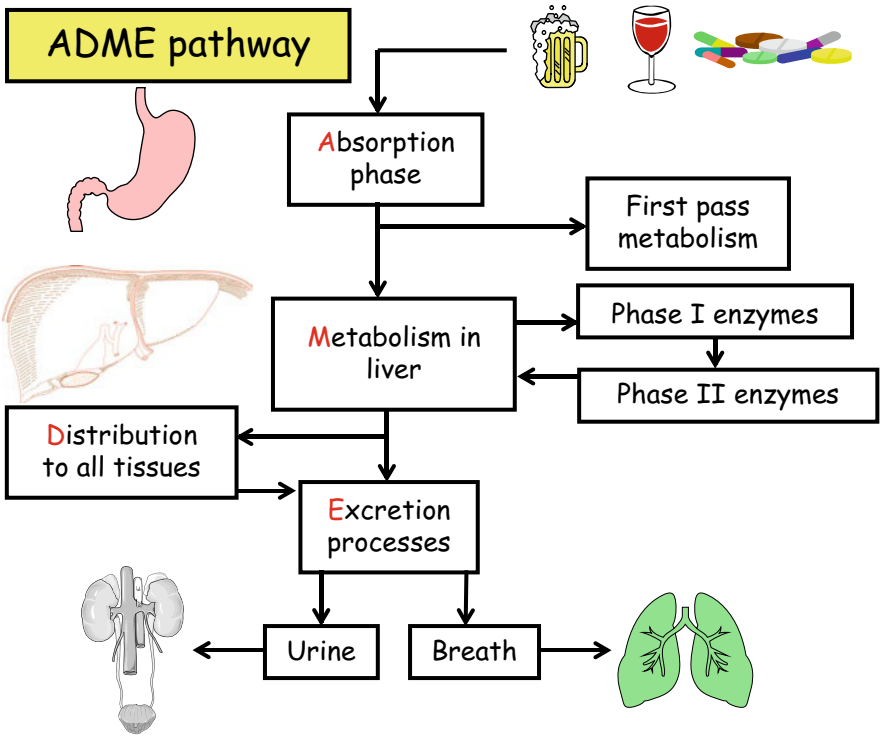


Fig. 13.1 Schematic diagram illustrating the fate of alcohol and drugs in the body showing possible sites of interaction on absorption, distribution, metabolism, and elimination (ADME) pathways. First-pass metabolism might take place in the gastric mucosa or the liver, phase I enzymes introduce or remove a functional group and phase II enzymes synthesize a more water soluble metabolite for excretion via the kidney in the urine

extent of prior exposure and whether the individual has developed some degree of tolerance [48–50]. Functional tolerance implies that larger amounts of alcohol are necessary to produce the same degree of effect caused by exactly the same dose of alcohol taken on earlier occasions [49]. Metabolic tolerance implies a faster rate of metabolism, which is associated with an induction of drug metabolizing enzymes in the liver as a result of chronic exposure [51].

The various sites and mechanisms of interaction, both pharmacokinetic and pharmacodynamic, between ethanol and other drugs are listed in Table 13.1.

Considerable thought is necessary when designing experiments to investigate drug–alcohol interactions. Factors such as the dose of alcohol and/or drug, the dosage form, the route and timing of administration relative to consumption of ethanol are all important considerations. Much depends on whether a single acute dose of alcohol and/or drug was administered or if the individual concerned was habituated to alcohol after a period of chronic heavy drinking. Also the results might differ for a single dose or multiple doses of a medication when steady-state plasma concentrations are reached before administration of ethanol.

Table 13.1 Pharmacokinetic and pharmacodynamic interactions between alcohol and other drugs indicating some of the possible sites and underlying mechanisms

Pharmacokinetic interactions	Pharmacodynamic interactions
Absorption	Nerve transmission at synapses
Gastric motility	Partition into lipids
Gastric pH	Receptor binding
First-pass metabolism	Release of neurotransmitters
Hepatic blood flow	Altered configuration of receptor proteins
Distribution	Opening or blocking ion channels
Ratio of blood flow to tissue mass	Drug transport proteins
Competition for protein binding	Transcription factors
Body mass index	Altered behavioral response
Adiposity	Tolerance development
Metabolism	Stimulation
Induction of metabolizing enzymes	Reinforcement
Inhibition of metabolizing enzymes	Craving
Excretion	Prolonged or diminished therapeutic effect
Enhanced or diminished diuresis	Impairment of body functions
Urinary pH more acid or alkaline	Respiratory depression
	Toxicity

Drug–alcohol interactions can be subdivided into four broad categories:

- The effect of acute or chronic consumption of alcohol on the absorption, distribution, metabolism, and excretion of a particular drug or medication.
- The effect of acute or chronic consumption of alcohol on the dynamics of drug action, that is, the action of the drug, particularly in the central nervous system (CNS) at receptor binding sites or ion-channels that mediate neuronal activity.
- The effect of a particular drug or other chemical agent after single or multiple doses on absorption, distribution, metabolism, and excretion (ADME) of ethanol as reflected in the blood or plasma concentration, compared with a placebo or no-drug treatment.
- The effect of a drug or chemical substance after single or multiple doses on the signs and symptoms of alcohol influence, such as a person's behavior and performance of skilled tasks, often related to driving.

Studies on drug–alcohol interactions involve human dosing experiments [52], various animal models [53], as well as in vitro experiments [54, 55]. Most attention in this review is given to human dosing studies, especially those with direct relevance to forensic science, legal medicine, and toxicology.

The first monograph dealing with the interaction between alcohol and other drugs appeared in 1968 [56] and another in 1978 [57]. Since then other books have focused on how the combined effects of alcohol and a drug might alter a person's performance and behavior, especially in relation to driving and the risk of a motor vehicle crash [58, 59]. Antidepressants, antihistamines, anticonvulsants, antipsychotics, opiates, and sedative–hypnotics have been tested for their potential interaction with alcohol using a battery of cognitive, behavioral, and psychomotor tests [60–64].

Lane et al. [65] presented a comprehensive review of the effects of alcohol on the metabolism of drugs and the formation of metabolites, distinguishing between short-term and long-term administration of ethanol. In a more recent survey, Fraser [66] looked at the interaction between alcohol and drugs with main focus on first-pass metabolism (FPM) of ethanol. Other investigators have concentrated on over-the-counter (OTC) medication or food supplements and whether there are negative effects if taken together with alcohol [67]. Weathermon and Crabb [68] presented a comprehensive review of adverse effects of drug–alcohol combinations on the disposition of drugs as well as their neuropharmacological effects mediated via receptor binding or the opening or blocking of ion channels. Havier [69] reviewed drug–alcohol interactions including the metabolic and CNS effects for a wide range of drugs often encountered in forensic science and legal medicine.

In experiments aimed at investigating drug-related effects on impairment of skilled tasks, the volunteer subjects should to be tested before and at various times after administration of the alcohol or drugs [70]. The pretreatment results provide baseline scores, which are then compared with measurements made on the same battery of tests after taking the drug alone or together with alcohol [71, 72]. If hangover or residual effects of drug treatment are of interest, then the battery of tests should be run in the morning after volunteers sleep overnight [73]. Whenever feasible, experiments should be done double blind with a randomized cross-over design so that each subject acts as his or her own control [74, 75].

The control arm of the study should include a placebo treatment, although the choice of placebo is problematic when it comes to administration of alcohol [76]. Some investigators give the dose of alcohol mixed with an alcohol-free drink in glasses of different size, shape, and color in an attempt to mask the nature of the liquids inside [77, 78]. Volunteers might be expected to consume the alcoholic drink from a closed container through a straw in order to mask the smell. Others sprinkle a few drops of alcohol on the surface of a placebo alcohol-free drink before giving this to the volunteers to drink as a bolus dose [70].

In human studies of drug–alcohol interactions, typical variables investigated are heart rate, blood pressure, various kinds of eye movements, mental arithmetic, word recall, body sway, simple and choice reaction time, tracking tasks, and divided attention tasks [70, 71]. It seems that divided attention is particularly sensitive to the impairment effects of alcohol and/or CNS active drugs [79]. As already emphasized, the battery of tests should be administered before treatment with the drug to establish baseline scores and also during a “dry-run” after placebo or a no-drug control treatment. The dry-run is useful to investigate the magnitude of learning effects on the various tasks performed because the subjects improve their performance after a number of practice sessions [70–75]. Widely available today are computer-driven performance tasks that are designed to measure various types of psychomotor impairment [80, 81]. Some investigators have constructed highly sophisticated driving simulators that mimic real-world conditions in terms of weather, speed, traffic intensity, and conditions of the road [81].

The *International Council on Alcohol, Drugs and Traffic Safety* (*ICADTS*) is an organization devoted to research and studies on the negative influence of alcohol and/or drug use on driver behavior and the risk this poses for traffic safety. Their website should be consulted for further details (www.icadts.org). Regarding drugs and driving legislation, more and more countries have enacted zero-tolerance laws, which implies that a person might be prosecuted for this offence if any amount of a banned scheduled substance is identified in a sample of blood [82, 83]. A useful literature resource is a special edition of the journal *Forensic Science Review*, which contained articles dealing with the effects of common recreational drugs on human performance and behavior [84].

This chapter gives an update of the material contained in the first edition of this book by reviewing pharmacokinetic and pharmacodynamic interactions between alcohol and other drugs. Alcohol is a legal drug and is used throughout adult life, which means that unwanted drug–alcohol interactions are a growing concern considering polypharmacy in today's society [85–89].

Fate of Alcohol in the Body

The disposition and fate of alcohol and/or drugs in the body is usually considered and discussed in terms of absorption, distribution, metabolism and excretion (ADME) processes as illustrated in Fig. 13.1. Alcohol (ethanol) is a small uncharged molecule completely miscible with water, which allows it to pass easily through biological membranes, including the blood–brain barrier [90]. After absorption from the gut, molecules of ethanol reach the portal vein and travel in the bloodstream being eventually distributed throughout the total body water space [90]. There is no evidence that ethanol binds to plasma proteins to any appreciable extent [90]. The solubility of ethanol in fat and bone is negligible compared with solubility in water and the water content of body fluids and tissues is therefore a major determinant of the concentration of ethanol at equilibrium [91]. The fate of ethanol or some other drug in the body is usually depicted by plotting the concentrations determined in samples of blood or plasma as a function of time after administration [92]. The resulting shape of the concentration–time profile of ethanol represents interplay between absorption, distribution, metabolism, and elimination.

The concomitant intake of another drug might delay or accelerate the rate of absorption of ethanol depending on whether the drug influences gastric emptying rate. The C_{max} and t_{max} of the BAC curve are markedly influenced by the rate at which the stomach contents pass through the pyloric sphincter into the small intestine [93, 94]. A quantitative evaluation of BAC profiles is usually done by defining a set of parameters, which allows making comparisons between and within individuals with or without administration of another drug (Fig. 13.2).

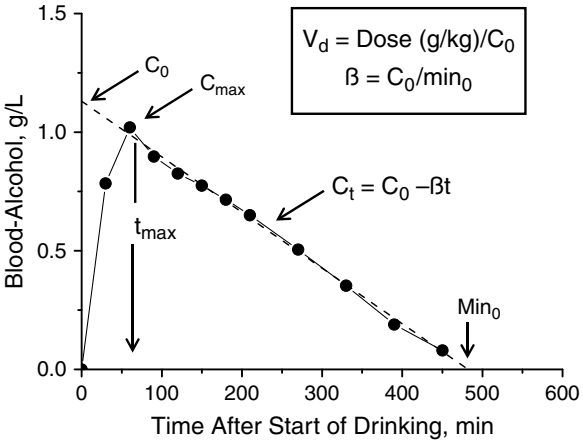


Fig. 13.2 Blood–alcohol concentration (BAC) time profile in one male subject after 0.68 g ethanol per kilogram body-weight was taken on an empty stomach. Quantitative parameters of the pharmacokinetics of ethanol are defined on this graph. C_{max} and t_{max} are the peak BAC and time of its occurrence; C_o is the theoretical BAC at the time of starting to drink; min_o is the extrapolated time to reach zero BAC, AUC is area under the concentration–time profile; β is the rate of disappearance of alcohol from the bloodstream

Absorption

Absorption of alcohol begins already in the stomach and the peak BAC (C_{max}) is usually reached between 10 and 120 min after the end of drinking [95]. Absorption occurs by diffusion through mucous surfaces in the gut in accordance with Fick's law along a concentration gradient [96]. The rate of absorption is faster from the duodenum, owing to the larger surface area provided by the microvilli covering the intestinal surface. A host of factors influence the rate of uptake of ethanol from the gut including the time of day, the drinking pattern, e.g., bolus intake or repetitive drinking over several hours [97–99]. The dosage form (beer, wine, or spirits) and the concentration of ethanol in the beverage consumed determine to some extent the speed of uptake of ethanol into the blood and the resulting C_{max} of the BAC curve [100–102].

The single most important factor leading to a delayed gastric emptying is the presence of food in the stomach before drinking starts [103–107]. In a human dosing study, stomach and duodenum contents were sampled and the remaining concentration of ethanol determined. This was done at various times after subjects had eaten a meal before drinking a moderate dose of ethanol [108]. The results showed that some of the ethanol remained unabsorbed in the stomach for several hours after dosing. This finding was verified in a rat model which showed that ethanol could bind to food particles in the stomach for much longer than was hitherto appreciated, hence delaying absorption into the bloodstream [109].

Figure 13.3 compares the BAC profiles in 9 healthy men who drank a moderate dose of ethanol (0.80 g/kg) and a smaller dose (0.30 g/kg) under fed and fasted

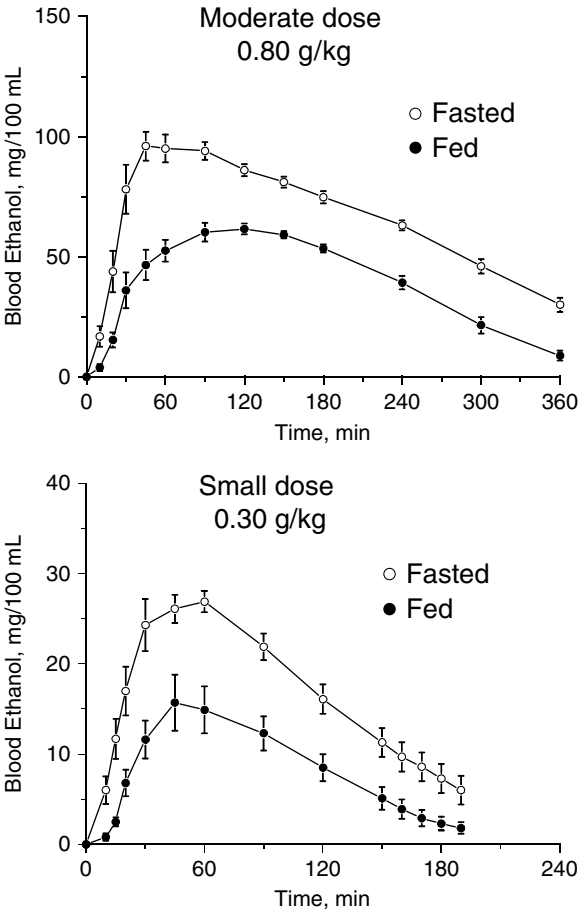


Fig. 13.3 Mean BAC curves in $N=9$ subjects after they drank a moderate dose (0.8 g/kg) and smaller dose (0.3 g/kg) of ethanol on an empty stomach or after eating a standardized breakfast

conditions [110]. One arm of the study involved drinking alcohol in 30 min after an overnight (10 h) fast and in the other arm the subjects had eaten a standardized breakfast before drinking the same dose of alcohol. Eating breakfast before drinking meant that C_{max} of the BAC curve was lowered by as much as 40% [110]. The nutrient composition of the food, in terms of its protein, fat, and carbohydrate content, was shown to be less important than the size of the meal and the closeness in time to drinking the alcohol [111–114]. Areas under the BAC curves were always less in the fed state compared with drinking on an empty stomach, and interestingly the time to reach zero BAC was shortened by 1–2 h in the fed state (Fig. 13.3).

This gives the impression that a smaller dose of alcohol was taken after eating breakfast but this was not the case. It appears then that the oxidative metabolism of ethanol is faster in the well-nourished organism, probably because of optimal activity of hepatic metabolizing enzymes. The enhanced rate of metabolism seems to occur primarily during the first 2 h postdosing (absorption phase), because the BAC curves

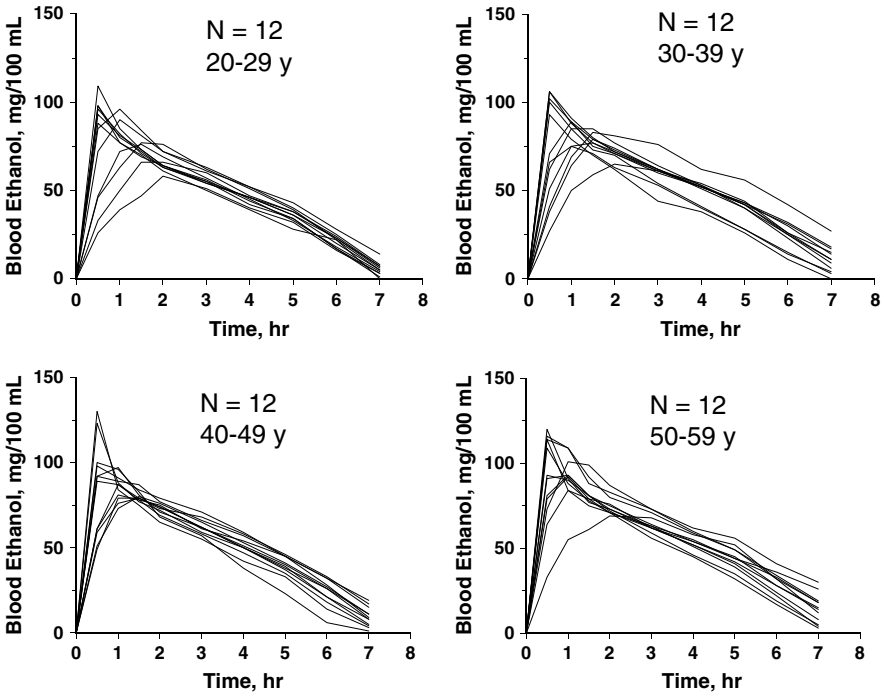


Fig. 13.4 Interindividual variations in blood-concentration time profiles of ethanol in four age groups of healthy men (20–29 y, 30–39 y, 40–49, and 50–59 y) after they drank 0.68 g/kg as neat whisky on an empty stomach (Redrawn from Jones and Neri [120])

thereafter ran parallel with approximately the same slope (Fig. 13.3). Another explanation for a smaller AUC in the fed state might be a more efficient first-pass metabolism, either in the gastric mucosa or the liver or both locations when absorption is delayed by food (see later in this chapter). Hepatic blood flow is also increased after eating a meal, which might permit a more efficient contact between hepatic enzymes and substrate.

Interindividual differences in the absorption rate of ethanol are significant even when drinking conditions are standardized and the dose is adjusted for variations in body weight [115–117]. The parameters C_{max} and t_{max} vary more between subjects than within subjects as might be expected from individual differences in gastric emptying [118, 119]. If absorption occurs by diffusion (Fick's law) one expects that beverages with higher concentrations of ethanol, such as vodka or whisky (40% v/v), are absorbed faster than weaker ones (beer or wine, 5–10% v/v), but this is not always the case [102]. Drinking neat spirits (40–50 vol.% ethanol) tends to irritate gastric surfaces in some people leading to a pyloric spasm, which retards stomach emptying and slows ethanol absorption resulting in a lower C_{max} and a later occurring t_{max} compared with drinking weaker alcoholic beverages [116].

Figure 13.4 gives an example of the magnitude of interindividual variations in absorption kinetics of ethanol in experiments with 48 men subdivided into 4 age

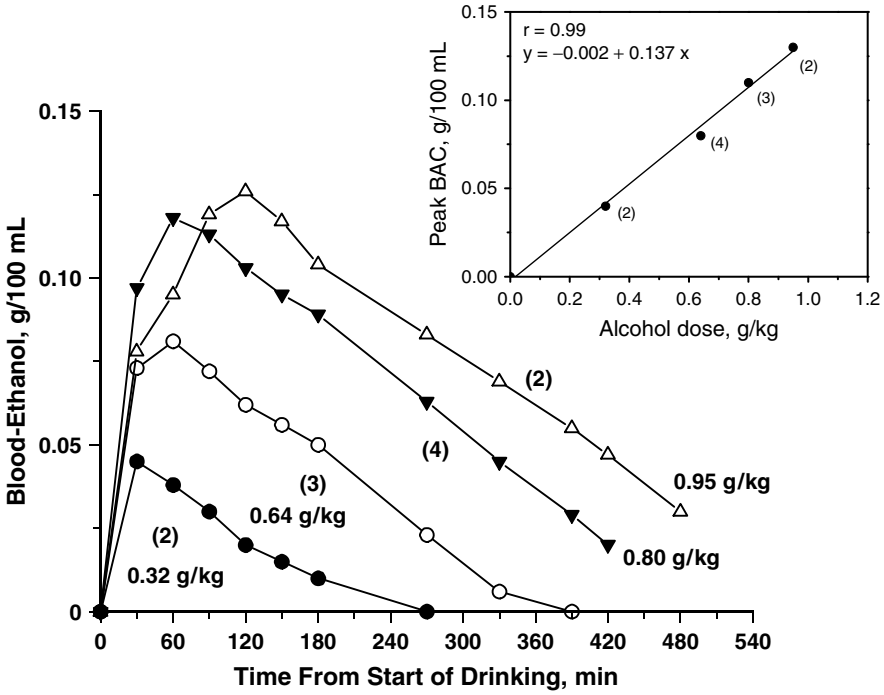


Fig. 13.5 Blood-concentration time profiles of ethanol after increasing doses as neat whisky on an empty stomach. The insert graph shows a high correlation between C_{max} and dose of alcohol administered ranging from 0.32 to 0.95 g/kg body weight (Jones, unpublished work)

groups: 20–29 y, 30–39 y, 40–49 y, and 50–59 y [120]. Under strictly controlled conditions, the men drank ethanol (0.68 g/kg) as neat whisky (2 mL per kg) in 20 min after an overnight fast [120]. The large intersubject variation despite standardized conditions underscores the need to include large numbers of subjects in experiments designed to investigate any drug-induced effect on the absorption kinetics of ethanol.

When alcohol is consumed on an empty stomach (overnight fast) the concentration–time profiles sometimes resemble those seen when ethanol is given by intravenous (i.v.) infusion [121]. Under these conditions, the alcohol is absorbed from the gut faster than the blood can distribute the alcohol to all body fluids and tissues. The BAC curve contain an overshoot peak with a higher C_{max} than expected for the dose administered, which is immediately followed by a diffusion plunge, during which time alcohol becomes distributed into all body fluids and tissues, a process taking about 30–60 min for completion [121].

The parameters C_{max} and t_{max} depend to a large extent on the dose of ethanol administered, both parameters increasing with increase in dose as shown in Fig. 13.5. In this study healthy volunteers drank 4 doses of ethanol as neat whisky on an empty stomach (0.32 g/kg, 0.64 g/kg, 0.80 g/kg, and 0.95 g/kg). The insert plot shows a

strong correlation between C_{max} and the dose administered ($r = 0.99$). When the dose of ethanol was above 1.0 g/kg as neat whisky and consumed in 25 min, many of the volunteers vomited, which ruined the experiment.

Other factors influencing gastric emptying include time of day, being faster in the morning when blood sugar is lowest [122]. Smoking a cigarette was shown to delay gastric emptying of solid and liquid meals and the C_{max} of the blood–alcohol curve was lower and occurred later in smokers [123, 124]. In subjects who had undergone gastric by-pass surgery for morbid obesity, the pylorus valve is no longer functional and as expected this resulted in much faster uptake of alcohol from the gut and more pronounced effect on the individuals [125].

Distribution

After absorption from the gut alcohol molecules are transported in the bloodstream to all parts of the body and distribute into the water space without binding to plasma protein or other endogenous molecules [90, 97]. This suggests that alcohol will not participate in displacement reactions with drugs that might bind to plasma proteins [126]. Accordingly, the absorbed alcohol distributes into the total body water and when equilibrium is reached the concentration in all body fluids and tissue will be proportional to their water content [127].

Because body water in women represents 50–55% of body weight compared with 55–62% in men, a gender-related difference in volume of distribution (V_d) can be expected for such a hydrophilic drug as ethanol [128]. Studies have shown that the average V_d for ethanol is 0.70 L/kg for nonobese males and 0.60 L/kg for nonobese females, but considerable variations exist within the sexes depending on age and relative proportions of fat to lean body mass [129]. When the dose of alcohol is administered per kg of body water or per kg lean body mass, the gender-related differences are abolished. The phase of the menstrual cycle in women and whether they use oral contraceptive steroids have been suggested to impact pharmacokinetic parameters of ethanol but the experimental results supporting these notions remain equivocal [130–133].

In the field of forensic toxicology and legal medicine, drugs and poisons, including alcohol, are almost always analyzed in specimens of whole blood and not in plasma or serum, which are the specimens of choice in clinical laboratories [97]. Whole blood contains 78–80% w/w water and plasma and serum are 91–93% water, which means that the concentration of alcohol is higher in plasma and serum compared with whole blood [134]. In the vast majority of people, the plasma/whole blood distribution ratio of ethanol ranges from 1.10 to 1.20, depending on the hematocrit of the blood sample [135]. A lower packed cell volume means more plasma and therefore more water per unit volume of whole blood. Plasma/blood and serum/blood ratios of ethanol were the same [136]. An uneven distribution of ethanol between plasma and erythrocytes has implications in pharmacokinetic studies when the volume of distribution of ethanol is calculated as the ratio dose/C_o. If the

concentrations of ethanol had been plotted for serial samples of plasma or serum, the C_o would have been 10–15% higher and the V_d correspondingly lower. Similar considerations apply to drugs other than alcohol that are unevenly distributed between plasma and erythrocytes. Diazepam in a blood sample is mostly bound to the plasma proteins and the plasma/whole blood ratio is about 1.9:1 [137].

Total body water per kilogram body weight decreases during aging, which means that elderly individuals receive a proportionally higher dose of alcohol per kg lean body mass or per kg body water [138, 139]. This difference is reflected in the shape of the BAC profile after a given dose of alcohol/kg body weight. The BAC curve for a young person will have a lower C_0 parameter and the V_d parameter (dose/C_0) will be proportionally higher compared with an elderly individual [120]. Alcohol dilution can be used to determine total body water by evaluation of the resulting blood–alcohol curves after subjects drink alcohol on an empty stomach or after intravenous administration. The results from these studies with ethanol as a marker substance compare well with methods to determine TBW by isotope dilution techniques [140, 141].

Another physiological aspect of drug distribution is the existence of differences in concentration between the venous and arterial blood circulation [142]. Ethanol is not evenly distributed in the vascular system and higher concentrations are present in arterial blood (A) during the absorption phase for about 90–100 min postdosing [143, 144]. The A–V difference is zero at about 90–100 min after end of drinking, which corresponds to the time of complete equilibration of ethanol in all body fluids and tissues [145]. Speed of equilibration of alcohol between the blood and body organs and tissues depend on the ratio of blood flow to tissue mass. This ratio is lowest for resting skeletal muscle and greatest for brain and kidney. Studies have shown that A–V differences for ethanol are more pronounced during the absorption phase prior to equilibration of alcohol in all body fluids [145]. During the postabsorptive phase, the concentration of alcohol in venous blood emerging from skeletal muscle and returning to the heart has a slightly higher concentration than arterial blood, owing to clearance of some of the alcohol by metabolism during passage through the liver [146]. This makes the slope of the declining phase of the BAC profile slightly steeper when sampling arterial blood compared with venous blood [145].

The different body composition of men and women (e.g., ratio of fat to lean tissue) is reflected in gender difference in volume of distribution of ethanol [147, 148]. The distribution volume of ethanol (Widmark's rho factor) might vary by a factor of 2 from as low as 0.45 L/kg in an obese female to 0.90 L/kg in a muscular male. More attention should be given to the degree of obesity in the individual and how this might impact on the distribution volume of water soluble drugs such as ethanol [149].

Some investigators have suggested a gender-related difference in gastric first-pass metabolism of ethanol to account for higher C_{max} and larger AUC observed in female drinkers [150–153]. Support for this came from analysis of ADH activity in the gastric mucosa by taking biopsies from women and men. The lower gastric ADH in women suggests that the female gender has less potential for presystemic metabolism of ethanol in the stomach. However, the significance of gastric ADH in metabolism of ethanol has been strongly challenged in favor of the liver as the primary site of first-pass metabolism [154–157].

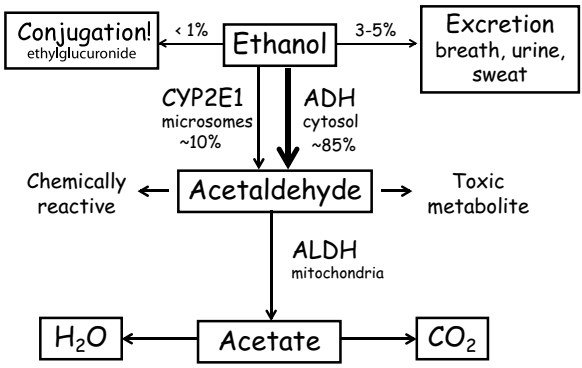


Fig. 13.6 Scheme showing the relative proportions of alcohol that undergo oxidative and nonoxidative metabolism as opposed to being excreted unchanged in breath, urine, and sweat

Elimination

Between 90% and 98% of the dose of ethanol administered undergoes hepatic metabolism and the remaining 2–10% is excreted unchanged in breath, urine, and sweat [158–161]. A very small fraction (<1%) is conjugated with glucuronic acid and sulfuric acid. These nonoxidative metabolites are then excreted in the urine [162–164]. Increasing the output of urine by drinking water or taking diuretic drugs is not a very effective way to accelerate the elimination of ethanol from the body, owing to the relatively small amounts excreted via the kidney.

The enzymes responsible for ethanol metabolism are alcohol dehydrogenase (ADH), which is located in the cytosol fraction, and CYP2E1 a part of the smooth endoplasmic reticulum [165, 166]. Both enzymes convert ethanol into its toxic metabolite acetaldehyde, which is rapidly converted into acetate by the action of mitochondrial low k_m aldehyde dehydrogenase (ALDH) [166]. The acetate produced in this reaction undergoes further oxidation via acetyl CoA mainly in peripheral tissues to give the end products carbon dioxide and water [167]. A schematic illustration of the fate of ethanol in the body is shown in Fig. 13.6.

The pharmacokinetics of ethanol has been studied extensively since the 1930s and the basic features of BAC curves are well characterized by defining a set of parameters, the so-called Widmark parameters [168–174]. These are defined and explained in Table 13.2. Results from hundreds of controlled alcohol dosing studies verify that the rate of elimination of alcohol from blood might range from 0.01 to 0.035 g/100 mL per h. Lower rates of alcohol elimination (0.01–0.015 g% per h) are usually seen when drinking on an empty stomach (10 h fast) and higher rates after a period of chronic heavy drinking, such as in alcoholics during detoxification [175, 176]. Both genetic and environmental factors influence the activity of alcohol metabolizing enzymes in the liver [177].

Table 13.2 Pharmacokinetic parameters of ethanol obtained from the evaluation of blood–alcohol profiles determined from controlled drinking experiments

Parameter	Symbol	Normal values	Comments
Peak concentration in blood or plasma	C_{max}	Dose of 1 g/kg gives ~0.15 g/100 mL	Depends on dose administered, gender, and speed of gastric emptying
Time to reach the peak concentration	t_{max}	5–120 min postdrinking in most instances (median 60)	Depends on gastric emptying and whether ethanol was consumed on an empty stomach or together with food
Disappearance rate of alcohol from blood	β or k_o	0.009–0.025 g/100 mL/h for most people	Depends on fed-fasting state and genetic factors. Values are low in malnutrition and protein deficiency and high in binge drinkers. The BAC clearance rate is slightly faster in women compared with men
Distribution volume	V_d or rho	Women 0.6–0.7 L/kg Men 0.7–0.8 L/kg	Depends on factors influencing ratio of water in body to water in blood such as age, gender, body composition (obesity), etc.
Hourly elimination rate from the body	B_{60}	0.08–0.15 g/kg/h	This parameter does not depend on gender but is directly proportional to k_o and V_d

Alcohol Metabolizing Enzymes

The hepatic enzymes responsible for the oxidative metabolism of ethanol have been studied extensively and their amino acid sequences, three-dimensional structures, and kinetic properties have been established [178, 179]. Class I ADH was extracted and prepared in a crystalline form from horse liver in 1948 and this research led to the development of a new biochemical assay for quantitative analysis of alcohol in body fluids [180, 181]. The second stage in the catabolism of alcohol involves the oxidation of acetaldehyde to acetate and this is accomplished by low k_m aldehyde dehydrogenase (ALDH) located in mitochondria of liver cells [182]. The major biochemical properties of the enzymes ADH and ALDH involved in the oxidative metabolism of ethanol are summarized in Table 13.3 [183].

Alcohol Dehydrogenase (ADH)

The class 1 hepatic ADH involved in the catabolism of alcohols exists in three molecular forms denoted ADH1, ADH2, and ADH3. The latter two alleles are polymorphic encoding three ADH2 peptides and two ADH3 peptides, respectively [184, 185].

Table 13.3 Some characteristic features of the alcohol metabolizing enzymes in humans

Characteristic	Alcohol dehydrogenase ADH	Aldehyde dehydrogenase ALDH
EC number	*EC* 1.1.1.1	*EC* 1.2.1.3
Enzyme subclass	*EC* 1.1 oxidoreductase acting on the group -CHOH	*EC* 1.2 oxidoreductase acting on aldehyde or oxo groups with NAD^+ or $NADP^+$ as acceptors
Genes encoding human enzyme	Seven human genes identified on chromosome 4 (*ADH1, ADH2, ADH3, ADH4, ADH5*). *ADH1A*, *ADH1B*, *ADH1C* (protein subunits previously known as α, β, and γ), produce homo- or heterodimers, *ADH4* (gastric ADH).	*ALDH* (18 human genes in 11 families and 13 subfamilies)
Active site	$Zinc^{2+}$, Histidine, Cysteine	Cysteine, Glutamate, Aspartate
Cofactor	Nicotinamide adenine dinucleotide, NAD^+	Nicotinamide adenine dinucleotide, NAD^+
Subcellular localization	Cytoplasm	Cytoplasm (ALDH1A1) and low K_m (ALDH2) in mitochondria
Organ distribution	Liver, gastric mucosa, kidney, lung, and other tissues	Liver, gastric mucosa, kidney, brain, and other tissues
Substrates	Primary and secondary alcohols (oxidation), aldehydes and ketones (reduction)	Aldehydes (oxidation and reduction)
Polymorphisms	ADH1B*1, ADH1B*2, and ADH1B*3 (earlier β_1, β_2, and β_3) and ADH1C*1 and 1C*2 (earlier γ_1 and γ_2)	ALDH2*1 and ALDH2*2 the latter enzyme is associated with a high incidence of facial flushing and nausea in East Asians after they drink alcohol

The K_m of class I liver ADH is only 0.005–0.01 g/100 mL, which means that the enzyme is saturated with substrate after the first couple of drinks. A class IV ADH located in the gastric mucosa has a higher K_m for oxidation of ethanol and is the enzyme mainly responsible for gastric first-pass metabolism.

The low K_m of hepatic ADH has implications for the pharmacokinetic profile of ethanol, which differs from most other licit and illicit drugs. After moderate social drinking (BAC 0.05–0.10 g%) the postabsorptive phase of the BAC curve decreases at a constant rate per unit time in accordance with zero-order kinetics. When the BAC drops below 0.02 g/100 mL, the metabolizing enzymes are no longer saturated with substrate and the velocity of the enzymatic reaction becomes proportional to the substrate concentration in accordance with first-order kinetics [186]. The entire post-absorptive period of the ethanol C–T profile is best described by saturation kinetics and the C–T data can be fitted to the Michaelis–Menten (M–M) equation. The entire BAC profile looks more like a hockey stick rather than a straight line [187].

More sophisticated pharmacokinetic models have been proposed to describe the C–T profiles including multicompartment models [187]. Because of saturation kinetics the relationship between the dose administered and the area under the concentration time profiles (AUC) is not a linear function [186]. The AUC increases more than proportionally with an increase in dose as expected for drugs that obey M–M kinetics. The existence of M–M elimination kinetics also explains the large variability in BAC profiles after volunteers consume small amounts of ethanol (0.1–0.3 g/kg).

The rate of gastric emptying controls the speed at which ethanol molecules make contact with hepatic enzymes and when absorption is slow and intermittent ethanol is easily cleared from the portal venous blood, which impacts on the systemic availability of the dose administered. The kinetic parameters C_{max} and t_{max} are highly sensitive to rate of absorption of ethanol from the gut. After small doses of ethanol (<0.3 g/kg) the BAC profiles obtained are not suitable for calculating elimination rates of ethanol from blood, because the metabolizing enzymes are not operating at full capacity. The postabsorption part of the C–T profile must be defined unequivocally to permit a reliable calculation of the elimination rate of ethanol from blood by curve fitting and linear regression analysis.

Drugs That Interact with ADH

Trace amounts of ethanol and methanol (~1 mg/L) are produced naturally in the body by fermentation of dietary sugars, mainly by microorganisms in the colon, and also in some metabolic reactions involving biosynthesis of acetaldehyde [188, 189]. The small amounts of ethanol synthesized in the gut are cleared from the portal venous blood as it passes through the liver for the first time. This probably represents one of the physiological functions of hepatic ADH to protect our ancestors from the alcohol produced by fermentation of the sugars in overripe fruits or honey in the search for food and survival [190].

Pyrazole Derivatives

After the isolation and purification of ADH from horse liver in the early 1950s, it was not long before the catalytic properties of the enzyme were characterized in detail [191, 192]. Theorell and Yonetani [193] studied heterocyclic compounds containing nitrogen atoms, such as pyrazole and found these to be potent inhibitors of liver ADH enzyme in vitro, especially the 4-methyl derivative [194]. The inhibition of ADH by pyrazole and its derivatives was later verified in both humans and rats and 4-methyl pyrazole (4-MP), which was less toxic than pyrazole itself, was developed into a therapeutic agent (fomepizole registered as Antizol®) for treatment of poisoned patients [195–197].

The drug Antizol® is now used clinically as an antidote for the treatment of patients poisoned with methanol or ethylene glycol [198]. This drug treatment is preferable to the traditional use of ethanol as a competitive inhibitor for two

principal reasons. First, ethanol is a powerful depressant of the CNS and should not be given to children or adults who might have liver dysfunction from previous abuse of alcohol. Ethanol needs to be given intravenously to reach a BAC of 0.1–0.12 g% and to maintain this level over many hours during which time the more toxic alcohols can be eliminated in breath and urine or removed from the blood by hemodialysis [199].

The administration of Antizol® blocks the oxidation of short-chain alcohols and prevents the formation of toxic metabolites formic acid, from methanol, and oxalic acid from ethylene glycol [200]. After administration of 4-MP to healthy subjects the concentration of endogenous ethanol in peripheral blood increased verifying this alcohol was a normal constituent of the body [201].

Methanol and Ethylene Glycol

Hepatic ADH exhibits a broad substrate specificity and catalyzes the oxidation of monohydroxy (methanol, ethanol, n-propanol, isopropanol) and dihydroxy (ethylene glycol, diethylene glycol, and butan-1,4-diol) alcohols [202]. The affinity of the enzyme differs for different substrates depending on the carbon chain length and especially the amount of branching, as exemplified by t-butanol, which is not oxidized by ADH. Moreover, studies have shown that the specificity of class I ADH is ~10 times higher for oxidation of ethanol compared to methanol and, as discussed earlier, this has found useful clinical applications in the treatment of methanol poisoning [203]. A scheme showing the metabolism of ethanol and methanol into their corresponding aldehydes and carboxylic acids is shown in Fig. 13.7. The enzymes and coenzymes involved are shown as well as the structural formulae of drugs (enzyme inhibitors) that block ADH (fomepizole or 4-methyl pyrazole) and ALDH (disulfiram).

Treatment of people poisoned with methanol or ethylene glycol requires intravenous administration of ethanol (8–10% v/v) to reach and maintain a BAC of about 0.12 g% [204]. After ethanol reaches the bloodstream, the liver ADH enzyme diverts its attention from oxidation of methanol toward oxidation of ethanol, the metabolites of which are much less toxic [204]. Depending on the concentration of methanol in blood and the amount of time that elapses after ingestion the patient might require hemodialysis to remove methanol metabolites (formaldehyde and formic acid) from the bloodstream [198, 199]. The formic acid metabolite formed during oxidation of methanol results in a state of metabolic acidosis, which is treated by giving bicarbonate [196].

The competitive inhibition of methanol oxidation by ethanol is exemplified in Fig. 13.8 in two alcoholic patients during detoxification [205, 206]. Note the very high starting BAC of 4.5 g/L (0.45 g/100 mL) in the male patient (upper trace) and 3.5 g/L (0.35 g%) in the female patient (lower trace) when detoxification began. The methanol in blood in these patients remained more or less constant during the time that ethanol was being metabolized. Moreover, in this example, the methanol concentration was not dangerously high, being only 10–15 mg/L arising from endogenous production and trace quantities of methanol as a congener in the alcoholic beverages

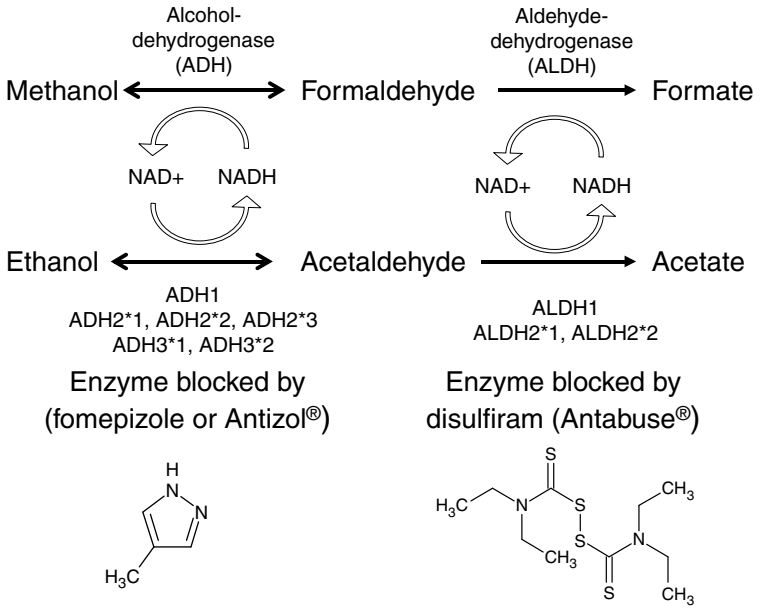


Fig. 13.7 Comparison of the oxidative metabolism of ethanol and methanol to metabolites, acetaldehyde and formaldehyde, respectively, and competitive inhibition for binding sites on Class I ADH. The oxidized and reduced forms of the coenzyme NAD^+ and NADH are shown along with the structural formulae of enzyme inhibitors of ADH (4-methyl pyrazole) and aldehyde dehydrogenase (disulfiram)

consumed. Methanol is eliminated by first-order kinetics (half-life 3–4 h) only after the blood–ethanol concentration drops below 0.02 g/100 mL, that is, when ADH is no longer saturated with its preferred substrate [207, 208].

Chloral Hydrate

Chloral hydrate (2,2,2-trichlorethane-1-1-diol) is the oldest sedative–hypnotic drug and its pharmacological properties were discovered already in 1869. Indeed, this pharmaceutical is registered in the USA as Noctec® and is in liquid form often prescribed for treatment of sleep disorder in children and elderly patients, who might have difficulty swallowing tablets [209]. Chloral hydrate is not appropriate for people with alcohol-use disorder because sedative effects are enhanced by concomitant use of alcohol [210].

After ingestion, chloral hydrate is rapidly hydrolyzed ($t_{½}$ = ~4 min) to chloral, which is then reduced by ADH to the pharmacologically active trichlorethanol [211]. Detoxification of 2,2,2-trichlorethanol occurs by conjugation with glucuronic acid (~52%) to give urochloralic acid and oxidation via ADH to trichloroacetic acid, which is an inactive metabolite excreted in urine. The metabolism of chloral hydrate is depicted in Fig. 13.9.

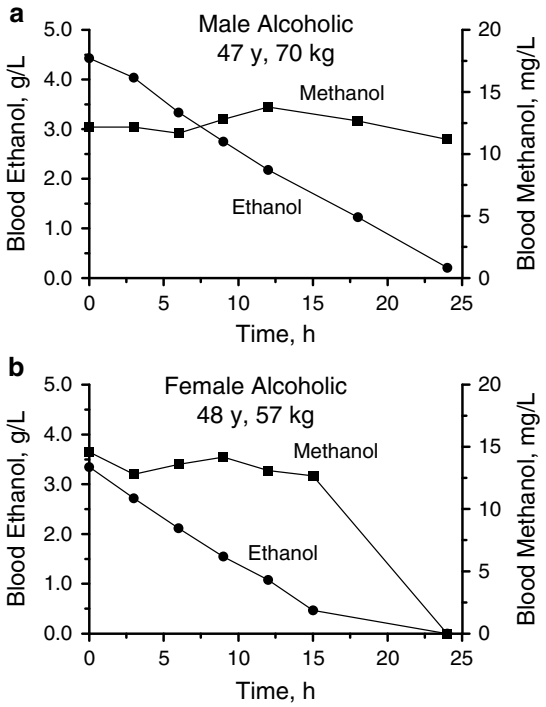


Fig. 13.8 Metabolic interaction between ethanol and methanol in two alcoholic after they entered a detoxification clinic. Note the high initial blood–ethanol in both patients who had probably been drinking for days or weeks. The concentration of methanol in blood (~10 mg/L) remains on a constant level during the 24 h period of detoxification, the metabolism being blocked by the ethanol (Redrawn from Jones and Sternebring [207])

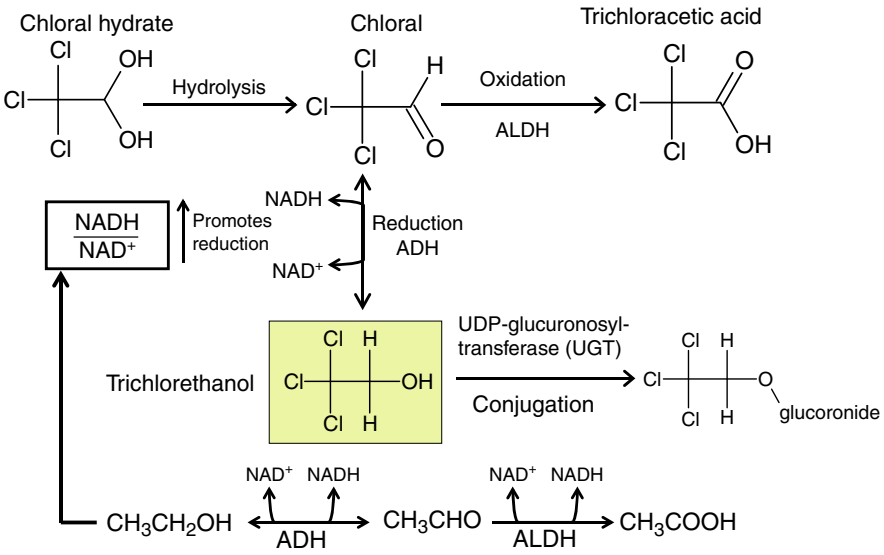


Fig. 13.9 Drug-drug interaction between the metabolism of ethanol and formation of trichlorethanol from chloral hydrate. The ratio NADH/NAD$^+$ increases during oxidation of ethanol, which promotes reduction of chloral to its pharmacologically active metabolite trichloroethanol

During the catabolism of ethanol the ratio NADH to NAD^+ in hepatocytes increases appreciably, which favors the reductive pathway from an aldehyde (chloral) to an alcohol (2,2,2-trichloroethnaol), which is the mechanism thought to explain the pharmacokinetic interaction between chloral hydrate and ethanol [212].

A mixture of alcohol and chloral hydrate gained notoriety as knockout drops or a "Mickey Finn" slipping a Mickey [213]. Evidently a bar owner in Chicago had the habit of giving his customers this drug combination mixture before robbing them [214]. The sleep-inducing or soporific effects of trichloroethanol are mediated via the $GABA_A$ inhibitory receptor, which is also a target for benzodiazepines, barbiturates, and also ethanol (see later). Accordingly, the sedation effects of chloral hydrate are likely to be more intense and prolonged if used together with other drugs having a similar pharmacodynamic mechanism of action.

1,4-Butanediol (1,4-BD)

The aliphatic diol 1,4-butanediol (b. pt. 230°C) is widely used as an organic solvent in industry and also for laboratory synthesis. After ingestion, one of the hydroxyl groups is oxidized first to an aldehyde and then a carboxylic acid [215]. Hence a prominent metabolite of 1,4-BD is γ-hydroxybutyrate (GHB), which has gained increasing popularity as a recreational drug of abuse and a depressant of the central nervous system [216–218]. GHB is a scheduled substance in most countries although the precursor drugs 1,4-BD and γ-butyrolactone (GBL) have proved much more difficult to classify, because of their industrial usage [219].

After oral administration 1,4-BD is rapidly converted to GHB by the class I ADH enzymes, which opens the possibility for a competitive inhibition if a person also drinks alcohol and the mechanism of this interaction is shown in Fig. 13.10 [220].

The co-administration of ethanol and 1,4-BD under controlled conditions has, to my knowledge, not been reported in human experiments. However, one study looked at the interaction between ethanol (0.6 g/kg) and GHB (50 mg/kg as sodium oxybate) in 16 healthy subjects [221]. The pharmacokinetic profiles plotted in Fig. 13.11 show that C_{max}, t_{max}, and AUC were remarkably similar when the drugs were taken alone or in combination. This does not support any pharmacokinetic interaction between ethanol and GHB. However, in the ethanol–GHB arm of the study, 6 subjects vomited and 2 suffered from hypotension, which suggests adverse pharmacodynamic interaction between the two alcohols [222]. 1,4-butanediol is sometimes used for intoxication purposes as a substitute for GHB [223]

Aldehyde Dehydrogenase (ALDH)

The proximate metabolite of ethanol oxidation is acetaldehyde, which is a highly reactive chemical substance and the –CHO group can bind to proteins and other endogenous molecules [224]. Acetaldehyde might undergo condensation reactions

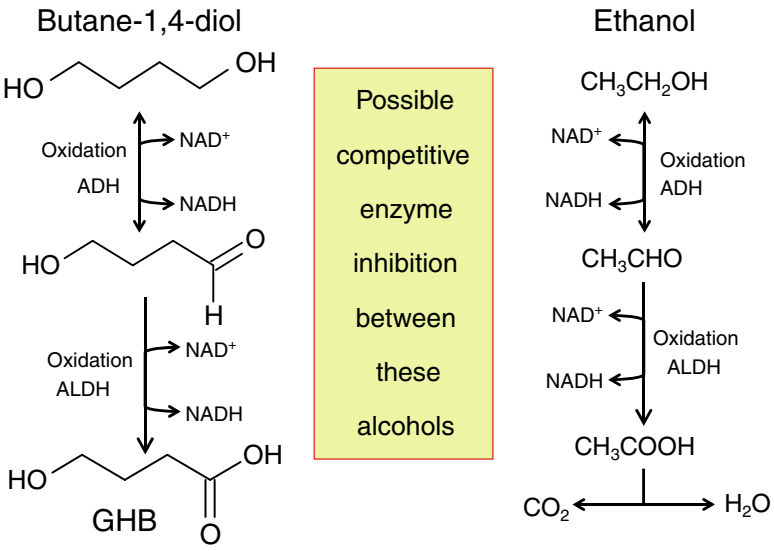


Fig. 13.10 Metabolic pathways showing the potential for competitive inhibition between ethanol and 1,4-butanediol a precursor of the recreational drug γ-hydroxybutyrate

with neurotransmitters, such as dopamine and serotonin to form alkaloid-like compounds such as isoquinolines and salsolinol that are potentially dependence producing [225]. An elevated concentration of acetaldehyde in blood causes vasodilatation, increased skin temperature, facial flushing, bronchoconstriction, lowered blood pressure, and sometimes nausea and headache [226]. These adverse effects are thought to arise from several biologically active compounds, such as catecholamines, opiate peptides, histamine, and/or prostaglandins [227].

The body needs to rapidly and effectively remove acetaldehyde from the blood stream and this is accomplished by the enzyme aldehyde dehydrogenase (ALDH). The most important form of ALDH is the low k_m variant located in the mitochondria (ALDH-2), although there is also a high k_m enzyme (ALDH-1) in the cytoplasm [228]. ALDH enzymes are also present in erythrocytes, in brain tissue, as well as the gut.

Two main factors help to regulate the concentrations of acetaldehyde produced in the liver during the oxidation of ethanol. One is the activity of hepatic ADH, which represents the slowest step in the overall oxidation reaction of ethanol to acetate [227, 229]. The faster the oxidation of ethanol the more acetaldehyde is produced and the greater are the untoward effects on the individual [230]. People with ADH2*2 or ADH3*1 alleles are likely to generate higher concentrations of acetaldehyde during oxidation of ethanol [231]. The second and most important factor controlling the level of acetaldehyde in the blood is the activity of ALDH, which transforms acetaldehyde into acetate [232].

Many people of Asian descent, such as Japanese experience unpleasant effects after they drink small amounts of alcohol, which is a direct consequence of an accumulation of acetaldehyde in the bloodstream [233]. These individuals have inherited a defective

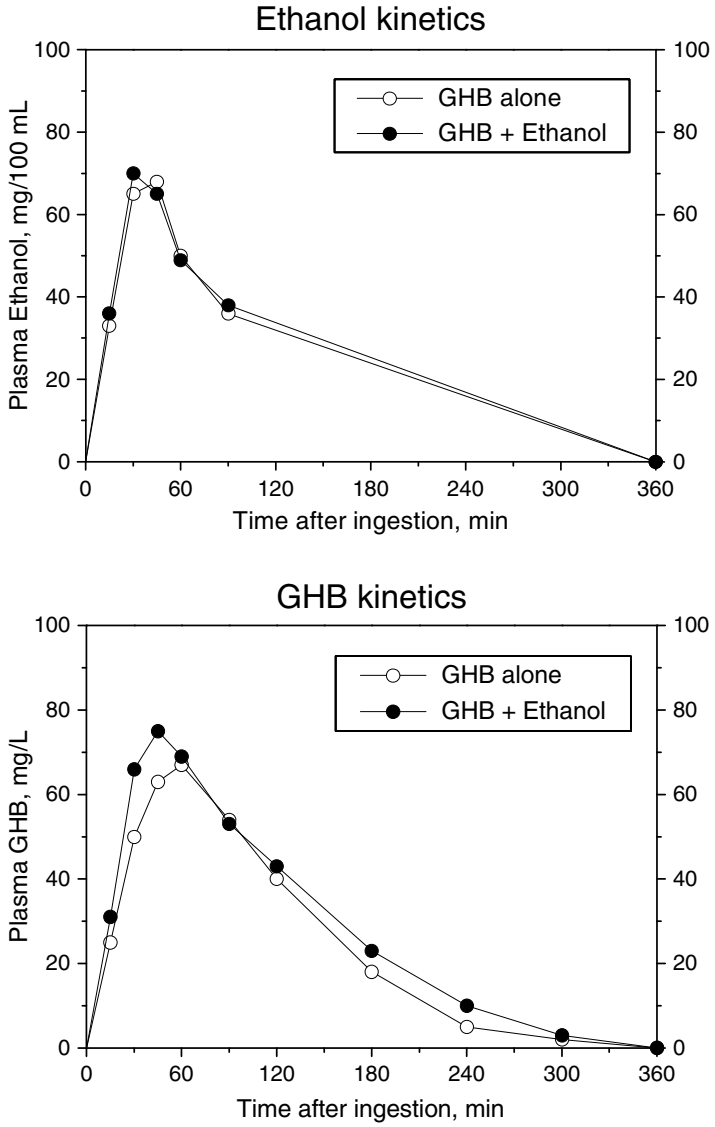


Fig. 13.11 Concentration–time profiles of ethanol in blood (*upper graph*) and γ-hydroxybutyrate in blood (*lower graph*) after co-administration of ethanol (0.3 g/kg) and sodium oxybate (4.5 g) (Redrawn from Thai et al. [222])

form of ALDH making them highly sensitive to consumption of alcohol. In short, they are genetically equipped with a natural aversion to alcohol because of the polymorphism of the ALDH2 enzyme, which regulates oxidation of acetaldehyde to acetate [234]. Asians and other ethnic groups with the ALDH2*2 allele are hypersensitive to alcohol because they cannot metabolize acetaldehyde as effectively as those with the

ALDH2*1 allele. People homozygous for the ALDH2*2 allele are extremely sensitive to acetaldehyde and as such are protected from developing alcohol-related problems, such as arrests for drunkenness, alcohol-impaired driving, hospital treatment for alcoholism, liver cirrhosis, and other social-medical problems which are rare or not seen at all [234–236].

Drugs That Interact with ALDH

Acetaldehyde has been incriminated in many of the untoward effects of heavy drinking, including organ and tissue damage and indirectly in addiction and dependence [236]. In Caucasians and others with normal hepatic ALDH activity, the concentration of free acetaldehyde in the peripheral blood during metabolism of ethanol is vanishingly low [227]. Using a reliable headspace gas chromatographic method to determine volatiles in blood, the concentration of acetaldehyde was close to the limits of quantitation [238, 239]. Many older publications using less reliable methodology reported artificially high concentrations of acetaldehyde in blood. It seems that to a large extend the acetaldehyde reported was generated by spontaneous oxidation of ethanol in vitro after the blood was sampled [237, 238].

The biochemistry and enzymology of ALDH has been extensively studied in East Asians because many of these individuals generate abnormally high concentrations of acetaldehyde after drinking small amounts of alcohol [240]. A defective enzyme thus furnishes a biological protection from dependence on alcohol and this phenomenon has understandably attracted considerable interest in biomedical alcohol research [241].

Antabuse®

Many useful therapeutic agents are discovered by accident and disulfiram or Antabuse® is certainly no exception. In the late 1940s, scientists in Denmark were interested in medication for eradicating intestinal worms [242, 243]. They tested the drug on themselves to investigate possible side effects and experienced unpleasant sensations when they drank a few beers after work. They soon realized there had been an untoward interaction between alcohol and the new drug they had taken, which was an organic sulfur-containing compound with the empirical formula $C_{10}H_{20}N_2S_4$. This serendipitous discovery led to the production and marketing of disulfiram (tetraethylthiuram disulfide) or Antabuse® a new alcohol-sensitizing drug approved worldwide for treatment of alcoholism [242].

Antabuse® is a potent inhibitor of the low k_m ALDH enzyme so when a person drinks alcohol after taking the drug, the concentration of acetaldehyde in the circulating blood increases. This triggers unpleasant physiological effects, such as tachycardia, nausea, sweating, and also a pronounced flushing in the face and neck [242]. Another drug used to treat people suffering from alcohol problems with a similar mechanism of action is cyanamide or calcium carbimide (Temposil®) [244].

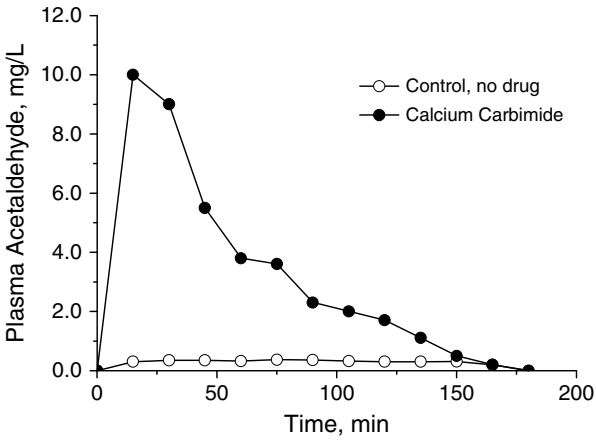


Fig. 13.12 Concentration–time profiles of acetaldehyde in blood in one subject who drank 0.25 g ethanol per kg body weight after taking the drug calcium carbimide, a potent inhibitor of low k_m aldehyde dehydrogenase, or a placebo treatment

When the inky-cap mushroom was mistakenly eaten along with consumption of alcohol it caused an antabuse-like reaction. The active substance in the mushroom was later identified as coprine, which is a naturally occurring inhibitor of hepatic ALDH [245].

Figure 13.9 shows a plot of the plasma concentration of acetaldehyde, estimated indirectly by analysis of breath, in one subject who participated in two drinking sessions [246]. The man drank the same small dose of ethanol (0.25 g/kg) with or without pretreatment with the ALDH inhibitor calcium carbimide (50 mg) given 60 min before drinking. After the placebo control treatment, the concentrations of acetaldehyde in plasma were barely measurable, whereas after blocking ALDH the concentrations were raised about 50-fold for several hours afterward. The subjects in this experiment complained of headache, tachycardia, and difficulties in breathing and these symptoms as well as a pronounced flush of the face lasted for several hours after the end of drinking [246] (Fig. 13.12).

The untoward cardiovascular effects of the Antabuse® reaction with alcohol were abolished after administration of 4-methyl pyrazole (4-MP), because this treatment prevented continued production of acetaldehyde in the liver [247]. Aversion therapy using drugs such as Antabuse® is controversial because a number of deaths have occurred when people take this medication and also consume massive amounts of alcohol [248]. A fatality was reported in a Japanese subject with ALDH2*2 genotype, owing to the abnormally high concentrations of acetaldehyde in blood after this person drank alcohol, evidently in a suicide attempt [249].

Oral Hypoglycemic Agents

A number of prescription drugs were found to sensitize people to ethanol and were thought to act as inhibitors of the ALDH enzyme [250]. For example, oral hypoglycemic agents, such as chlorpropamide and tolbutamide, used for treatment

of adult-onset type-2 diabetes, were found to interact with the low k_m ALDH enzyme [251]. People taking this medication should therefore be warned about drinking alcohol. The sulfonylurea derivatives compete with acetaldehyde for binding sites on ALDH so as to increase blood acetaldehyde after drinking alcohol. The degree of facial flushing, hypotension, and nausea after this medication was, however, much less intense than after alcohol was taken by patients treated with Antabuse® [252].

The classic drug for treating angina and heart failure, namely nitroglycerine, serves as a substrate for ALDH and this enzymatic reaction is regarded as the mechanism triggering release of free nitric oxide, which relaxes vascular smooth muscle [253].

Metronidazole

Metronidazole (Flagyl®), an effective agent for treating anaerobic bacterial infections, has hitherto been considered unsafe to use when people drink alcohol, owing to a purported antabuse-like flush reaction [254]. This undesirable effect of the medication was attributed to metronidazole inhibiting hepatic ALDH leading to elevated concentrations of acetaldehyde in blood. A number of case reports supported this example of an adverse drug–alcohol interaction and one death was apparently caused by combined influences of ethanol and metronidazole [255].

Notwithstanding these reports, a seemingly faultless study was published that cast doubt on the existence of an adverse interaction between metronidazole and ethanol [256]. In a carefully controlled double-blind study, 12 healthy men drank ethanol (0.4 g/kg) after treatment with metronidazole or a placebo for 5 days. No measurable blood acetaldehyde concentration was seen in either the test or control groups and the blood–ethanol profiles were also similar. Moreover, objective evidence of an alcohol-antabuse reaction (e.g., elevated skin temperature, increased blood pressure, and heart rate) was absent. Neither did the volunteers experience any untoward subjective feelings of nausea compared with the placebo treatment. The authors question whether metronidazole was indeed an inhibitor of ALDH. Instead they suggested that there might be subgroups of people who were allergic to the drug and reacted with symptoms similar to an Antabuse® reaction [256].

Cytochrome P450 Enzymes

The oxidative metabolism of drugs and endogenous substances occurs via an important group of enzymes located within the smooth endoplasmic reticulum structure of the liver cell, particularly the microsomal fraction [257–259]. The cytochrome P450 enzymes constitute a broad family of proteins that catalyze the oxidation, reduction, and hydroxylation of many drugs and xenobiotics, including ethanol [260]. The major pathway for metabolism of ethanol is by oxidation with ADH in

the cytosol, although the microsomal enzyme, denoted cytochrome P4502E1 or CYP2E1, is also involved [261]. The contribution of the CYP2E1 pathway to overall ethanol metabolism depends on the underlying BAC and therefore the dose of alcohol ingested [262].

When small amounts of alcohol are consumed (BAC < 0.05 g%), Class 1 ADH is the dominant enzyme, but as more alcohol is consumed and BAC increases above 0.08 g/100 mL, CYP2E1, becomes more and more involved. The k_m of CYP2E1 for ethanol as its substrate is reported to be 8–10 mM (0.04–0.05 g/100 mL), which means that the enzyme plays a more important role after a period of heavy drinking [263].

The clinical response to medication is closely related to the blood or plasma concentration of the parent drug reaching the site of action [264]. When moderate doses of ethanol are taken (BAC > 1.0g/L) a competition occurs with other drugs for CYP450 enzymes, particularly CYP2E1. As a consequence, metabolism of the drug is hampered, which means that its pharmacological effect is prolonged [265].

On the other hand, drinking large amounts of alcohol daily causes induction of CYP2E1, which enhances a person's capacity to metabolize some medicinal drugs and environmental chemicals [266, 267]. More of the drug is needed to achieve the same therapeutic effect, because the active substance (parent drug) is more rapidly cleared from the blood stream [268]. Alcoholics often require larger doses of general anesthetics (volatile hydrocarbons) prior to surgery because of their induced CYP2E1 enzyme [268]. The improved capacity for oxidative metabolism is not indefinite and after sobering-up for a few days the rate of metabolism of ethanol returns to normal, owing to re-synthesis of the enzyme [269, 270].

Drug Interactions Involving CYP2E1

The hepatic cytochrome P-450 enzymes constitute the body's main defense against chemical attack from xenobiotics that enter the organism with the air breathed or with the food eaten. These toxic constituents are rendered less dangerous by the action of P450 enzymes [271]. The CYP450 enzymes also accomplish the oxidative metabolism of a multitude of endogenous compounds (steroids, bile acids, fat soluble vitamins, prostaglandins, and fatty acids) besides exogenous substances, such as pharmaceutical products, organic solvents, and environmental carcinogens [272].

The particular isoform of P450 that oxidizes ethanol is denoted CYP2E1 and this enzyme is also involved, at least in part, with the detoxification of a number of organic solvents, anesthetic gases, and prescription medications [273, 274]. One oxygen atom from molecular oxygen reacts with the coenzyme nicotinamide-adenine dinucleotide phosphate (NADPH) to give one molecule of water and the other oxygen atom enters the drug molecule which becomes oxidized as shown below:

$$\text{Drug} + \text{NADPH} + \text{H}^+ + \text{O}_2 \rightarrow \text{NADP} + \text{H}_2\text{O} + \text{Drug} - \text{OH}$$

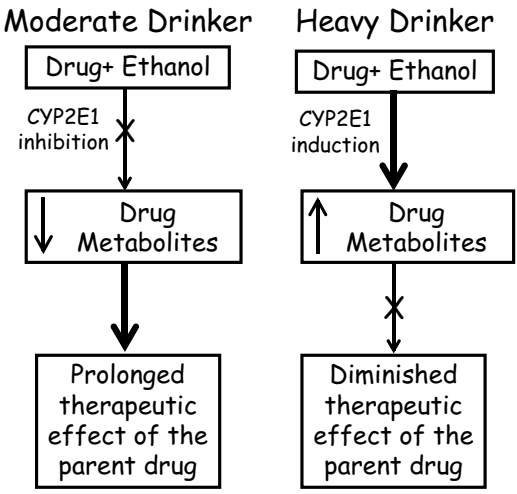


Fig. 13.13 Drug–alcohol interaction via CYP2E1 showing diminished or prolonged effect of the parent drug. The left diagram illustrates the situation in a moderate drinker where there is a competitive inhibition between ethanol and the drug for CYP2E1 enzymes. The right diagram shows the situation in a heavy drinker or alcoholic with higher CYP2E1 activity as a result of enzyme induction after chronic heavy drinking

Some recent work indicates that besides CYP2E1 other P450 enzymes might play a role in the oxidation of ethanol (e.g., CYP3A4 and CYP1A2), which suggests that ethanol treatment can interfere with metabolism of drugs that utilize these other P450 systems besides CYP2E1 [275].

Figure 13.13 illustrates two ways in which alcohol and another drug might interact [166]. After an acute dose of ethanol there is a competition with drug molecules for binding sites on CYP2E1 enzymes. As a consequence, the therapeutic effect of the parent drug is prolonged. However, if a person consumes large amounts of alcohol daily for weeks or months this leads to an induction of CYP2E1 enzymes and some therapeutic drugs are also oxidized faster. The parent drug, which is normally pharmacologically active, is metabolized into inactive metabolites causing a diminished therapeutic effect and higher dosages are needed [276]. This becomes a serious problem if the drug metabolites are toxic, as exemplified by the widely used analgesic and antipyretic drug acetaminophen.

Acetaminophen

Acetaminophen (*N*-acetyl-*p*-aminophenol) is an OTC analgesic and antipyretic drug widely used worldwide by people of all ages, including infants [277]. This ubiquitous OTC and prescription drug, known as paracetamol in Europe, is used to relieve headache, fever, muscle pain, and other ailments. Overdose with acetaminophen is often unintentional but this drug is also widely used for self-poisoning and an extensive literature exists pertaining to its toxicity and the effectiveness of the antidote N-acetylcystine [278]. In correct doses of 3–4 g per day there are no ill effects of acetaminophen, although after a single overdose or excessive repeated doses or too frequent therapeutic doses there is a risk of hepatotoxicity and death by irreversible liver damage [279].

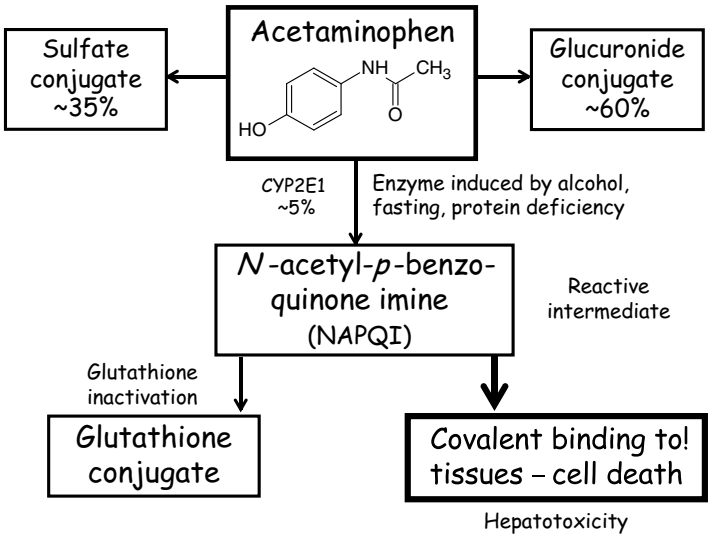


Fig. 13.14 Metabolism of acetaminophen (paracetamol) and formation of inactive conjugates (glucuronide and sulfate) and the toxic oxidative metabolite (*N*-acetyl-*p*-benzoquinone imine) formed by the action of CYP2E1

Metabolism of acetaminophen occurs primarily by phase II conjugation of the aromatic hydroxyl group with glucuronic acid (~60%) and sulfuric acid (~30%) and a much smaller fraction (~5%) is oxidized by CYP2E1 into the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI) [280]. Normally, the NAPQI metabolite is either reduced back to acetaminophen or inactivated by conjugation with glutathione, a scavenger of free radicals, and then excreted in urine after further phase II metabolism to produce cysteine and mercapturic acid [281]. A schematic diagram of the metabolism of acetaminophen in the body is shown in Fig. 13.14.

After a massive acute dose of acetaminophen, the hepatic glutathione stores soon become depleted and the reactive NAPQI intermediate starts to accumulate in the blood and attack the liver tissue [282]. The chemically reactive metabolite NAPQI binds covalently to vital constituents of the cell causing impairment of calcium homeostasis, oxidative stress, and cell death. The liver tissue, where the metabolite is produced, is especially vulnerable to these adverse effects [283]. Other contributing factors to toxicity of acetaminophen are food deprivation, such as a prolonged fast, protein deficiency, malnutrition, and binge drinking [284]. Because of enzyme induction of CYP2E1 in alcoholics on a drinking binge these individuals produce an excess of the toxic metabolite NAPQI [285]. Alcoholics should therefore be cautious about taking acetaminophen even in therapeutic doses, owing to the added risk of toxicity and cell death from the metabolite [286]. Heavy drinkers also have a reduced antioxidant capacity in the liver because of depletion of glutathione stores thus making alcoholics even more susceptible to the toxic effects of acetaminophen

Table 13.4 Drugs that compete for binding sites on enzymes involved in the metabolism of ethanol

Alcohol dehydrogenase (ADH)	Aldehyde dehydrogenase (ALDH)	Microsomal P450 system (CYP2E1)
Pyrazole	Disulfiram (Antabuse®)	Acetaminophen (paracetamol)
Fomepizole (4-methyl pyrazole) Antizol®	Cyanamide (calcium carbimide) Temposil®	Acetone (fasting)
Cimetidine (Tagamet®)	Coprine, contained in inky-cap mushroom	Phenobarbital (Luminal®) and other barbiturates
Ranitidine (Zantac®)	Metronidazole (Flagyl®)	Meprobamate (Milttown®)
Acetylsalicylic acid (Aspirin®)	Chlorpropamide (Diabinese®)	Disulfiram (Antabuse®)
Methanol and other aliphatic alcohols	Tolbutamide (Mobenol®)	Phenylbutazone
Ethylene glycol	Nitroglycerine	Anesthetic gases (enflurane. halothane, etc.)
Trichloroethanol (metabolite of chloral hydrate)	Nitrefazole (Altimol®)	Chlorocarbons (CCl_4 $CHCl_3$, CH_2CCl_3)
1,4-butanediol	Cephalosporin antibiotics, e.g., cefamandole and cefoperazone	Organic solvents (aniline, benzene, toluene, xylene)

[287]. Moreover, many alcoholics do not eat a proper diet and their daily calories to a large extent come from metabolism of alcohol. Many suffer from malnutrition and hypoglycemia making them more vulnerable to the toxic effects of acetaminophen [288]. Hypoglycemia (low blood sugar) is a predisposing factor in the toxicity of acetaminophen because glucuronidation of drugs is less effective under these circumstances [289].

The treatment strategy for people poisoned with acetaminophen depends on how much time has elapsed after the drug was taken and the concentration remaining in the blood. A rapid and specific determination of the plasma concentration of the analgesic is important and dictates the course of treatment necessary [290]. Shortly after overdosing, gastric lavage or induction of emesis is an effective way to remove unabsorbed drug and administration of activated charcoal to bind drug molecules can help to prevent further absorption [291]. If the time elapsed after overdosing with the drug is unknown, treatment with the antioxidant N-acetylcysteine is always recommended to replenish glutathione stores and aid in detoxification of formed NAPQI [292]. As long as sufficient glutathione is present, the poisoned patient is protected from liver failure but without this antidote necrosis occurs and the only lifesaving treatment is to perform a liver transplant [293].

When two drugs compete for binding sites on the same metabolizing enzyme, this creates a potential for a pharmacokinetic interaction depending on the relative affinity of enzyme for its preferred substrate [294]. Table 13.4 lists examples of drugs and/or medication known or suspected to compete with ethanol for binding to the enzymes involved in oxidative metabolism of ethanol. Note that some substances, such as disulfiram, might bind to two different enzymes (e.g., ALDH and CYP2E1).

First-Pass Metabolism of Ethanol

First-pass metabolism (FPM) refers to the metabolic degradation of an orally administered drug during its first passage through the gut and liver. Metabolism in or exhalation of the drug as the pulmonary blood passes through the lungs is also considered presystemic elimination [295]. FPM lowers the systemic availability of the drug and this should be considered when dose and dose interval are decided, because the parent drug is pharmacologically active [296]. The therapeutic efficacy of the drug is lowered, sometimes appreciably, because less of the active substance reaches target organs and tissues and/or binds to receptor sites [297].

A reduced bioavailability caused by FPM needs to be considered when blood concentrations vs. dose calculations are made using the Widmark equation [27]. Articles appeared in leading medical journals, New England Journal of Medicine and Journal of the American Medical Association (JAMA), reported that a "significant portion" of ingested ethanol was metabolized by enzymes in the gastric mucosa [153, 298]. This presystemic gastric metabolism of ethanol meant that a small fraction of the dose reached the central compartment and C_{max} was lower and there was less exposure of organs and tissues to the active metabolite acetaldehyde. Taking a drug that blocked the activity of gastric ADH would mean that the person was exposed to more of the ethanol compared with not taking the drug [151].

The structure and enzymatic properties of gastric ADH (class IV) differed from the hepatic enzyme (class I) in having a higher k_m for oxidation of ethanol [299]. Thus, gastric ADH is effective for oxidative metabolism of ethanol at the higher concentrations found in the stomach after drinking alcoholic beverages [152]. The activity of gastric ADH was also shown to differ depending on ethnic group, age, gender, and degree of habituation to alcohol [153, 300]. Gastric metabolism of ethanol was much less or abolished completely when people had undergone a gastrectomy [301]. But this finding is confounded by the fact that the rate of absorption of ethanol is much faster in people with abnormal gut, as verified in women after gastric-bypass operation for morbid obesity [124].

Some commonly used drugs, such as Aspirin®, Tagamet®, and Zantac®, blocked the activity of the gastric ADH enzyme under in vitro conditions and whether the same occurred in vivo attracted a lot of attention. Taking this medication along with alcohol would mean that a larger fraction of the dose administered reaches the portal venous blood by escaping metabolism in the gastric mucosa. The activity of gastric ADH was lower in women compared with men and also less in alcoholics compared with moderate drinkers [153]. Individuals with lower gastric ADH activity might be more vulnerable to the untoward effects of ethanol and its metabolites, which needs consideration when these people are prescribed drugs that block gastric ADH [302–304].

The clinical significance of gastric ADH in ethanol metabolism became highly controversial attracting many proponents and critics [155]. Some considered that the gastric ADH functioned as a protective barrier against the toxic effects of alcohol, whereas others considered its role was insignificant [155]. Many experiments

supporting the role of gastric ADH in alcohol metabolism were criticized because of the particular experimental design (too few subjects), inferior analytical methodology (breath alcohol not blood–alcohol), and the way blood–alcohol curves were evaluated [305–307]. The effect of the drug treatment seemed to be greatest when very small doses (0.15–0.30 g/kg) of ethanol were consumed about 1 h after eating a fat-rich meal [308]. Even in the control experiments without any drug treatment, the resulting BAC profiles were highly variable and not easy to interpret [309].

Greater effects of drugs on FPM and bioavailability of ethanol were seen if ethanol was consumed in divided doses over several hours rather than as a single bolus dose [308]. This observation was significant because repetitive drinking resembles more closely the drinking pattern under real-world situations. The amount of FPM of ethanol seemed to depend on the fed-fasted state of the individual and was greatest after small doses of ethanol were consumed corresponding to one glass of wine (25 g) after breakfast [156]. Other studies showed that C_{max} as well as AUC depended on gastric residence time and the duration of exposure of ethanol to gastric ADH [157].

Metabolism of ethanol obeys a dose-dependent saturation kinetics, which means bioavailability of the drug cannot be determined by comparing AUC after oral and intravenous administration of the same dose [106, 154, 186]. This follows because AUC does not increase linearly with the dose of alcohol ingested as would be expected for a drug with first-order kinetics [186]. Instead, the AUC increased more than proportionally with the dose, which is proof of the existence of saturation kinetics [186]. Moreover, when rate of absorption is slow and intermittent, the amounts of ethanol reaching the portal blood are more easily cleared by enzymes in the liver during the first passage of blood through the organ [311, 312]. This implies that FPM might just as well be caused by hepatic ADH as gastric ADH, and their relative contribution has not been possible to resolve [312].

Thus, FPM of ethanol is highly variable and depends on many factors particularly the dose ingested, the drinking pattern, the speed of drinking, and the fed-fasted state of the subject. Stomach emptying exhibits large inter- and intrasubject variations depending on a person's age, gender, anatomy of the gut, disease states, time of day, blood sugar level, and not least the use of prescription drugs [313–315]. A particularly convincing study of FPM in men and women concluded that only a small fraction (<6%) of an ethanol dose of 0.3 g/kg occurred by presystemic metabolism either in the gut or liver or both organs and that gender-related differences were minor [316]. Some investigators are adamant that the liver is the predominant site for FPM of ethanol and not the gut for the simple reason that enzyme (ADH) activity in the liver vastly exceeds that in the gastric mucosa [156, 309, 310].

Gastric Emptying and First-Pass Metabolism

Gastric emptying is an important determinant of the rate of absorption of many drugs including ethanol [317–320]. Drugs that accelerate or delay the emptying of

the stomach are likely to impact on the absorption kinetics of ethanol [317]. If a part of the dose of ethanol was metabolized by FPM in the gastric mucosa or the liver the bioavailability of ethanol is lowered, which should be considered when blood–alcohol calculations are made for forensic purposes [27].

Drug-related effects on metabolism of ethanol are not easy to differentiate from an effect on gastric emptying [321]. Some published papers claim that a certain drug treatment boosted the rate of ethanol metabolism but a closer examination of the results shows that a lower C_{max} and smaller AUC can be explained by a delayed gastric emptying [322]. One way to resolve this dilemma would be to give the drug orally and the ethanol intravenously and avoid drug-induced effects on rate of absorption of ethanol from the gut [321–323].

A recently used experimental design in studies of the effect of drugs on rates of ethanol metabolism is known as breath clamping and depends on zero-order kinetics [324–326]. Ethanol is administered intravenously to reach and maintain a certain steady-state concentration in the blood, estimated indirectly by analysis of breath at 5-min intervals [324]. The test drug or treatment is then applied, such as eating a meal, and the influence this has on the rate of ethanol metabolism is seen from the need to maintain steady-state concentration of ethanol in blood [326]. If the rate of infusion of ethanol needs to be increased to keep the steady-state level, then the treatment has boosted the rate of ethanol metabolism.

With the above study design, Ranchandanni et al. [112] found that alcohol was eliminated faster after eating a meal regardless of the protein, fat, and carbohydrate composition. Some authors have speculated that the activity of alcohol-metabolizing enzymes is optimal in the fed state and that a meal leads to an increase in liver blood flow and thus more exposure of ethanol for metabolizing enzymes [327].

Aspirin

Aspirin® (acetylsalicylic acid) is one of the most widely used drugs worldwide. Studies in vitro showed that aspirin blocked the activity of gastric ADH, which raised the question of whether similar effects might be expected in vivo [328]. Roine et al. [305] investigated the effect of aspirin (1 g) on BAC profiles after ethanol (0.3 g/kg body weight) was consumed 1 h after subjects had eaten a standard breakfast. The higher C_{max} and AUC of the BAC curves after aspirin pretreatment were significantly greater compared with no-drug treatment. The authors interpreted this to mean a decreased first-pass metabolism because aspirin blocked the action of gastric ADH. However, inspection of the BAC profiles in the aspirin and control groups showed that in reality the major influence of the drug treatment was on speed of absorption of alcohol and not on FPM, because the BAC curves reached zero at the same time.

Melander et al. [329] found that BAC curves were not significantly different in terms of C_{max}, t_{max}, and AUC with and without aspirin pretreatment. However, women were used as the volunteer subjects and other published work found that gastric ADH activity in women was lower than in men [153, 330]. No effects of

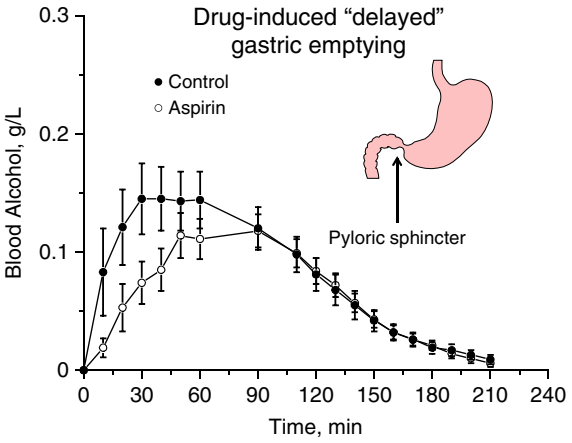


Fig. 13.15 Effect of pretreatment with low dose aspirin, which delays gastric emptying, on blood–alcohol profiles after an ethanol dose of 0.30 g ethanol per kg body weight in a cross-over design study (Redrawn from Kechagias et al. [332])

aspirin treatment on BAC profiles were observed when moderate doses of ethanol were administered (0.8 g/kg) as might be more realistic in drinking drivers [331].

The effect of low-dose aspirin (75 mg once daily for 7 days) on the pharmacokinetics of ethanol was studied by Kechagias et al. in a cross-over design experiment [332]. Low-dose aspirin is widely used as a prophylactic treatment for ischemic heart disease. The rate of absorption of ethanol from the gut was slower after pretreatment with aspirin as reflected in a lowered C_{max} and later occurring t_{max} (Fig. 13.15). After aspirin pretreatment, the BAC increased more slowly and did not reach the peak until 90 min postdosing. Thereafter the two BAC curves coincided and decreased toward zero BAC at the same rate. This observation suggests that aspirin treatment slows gastric emptying rate and has little or no effect on first-pass metabolism. If aspirin inhibited the action of gastric ADH to prevent FPM, one would expect the BAC curve in the control situation to run on a lower level and reach zero BAC earlier compared with aspirin, but this was not the case. The effect of aspirin on delaying gastric emptying was verified by the acetaminophen absorption test by including this drug in both arms of the study [332]. Acetaminophen (pKa ~9.5) is unionized at gastric pH and becomes absorbed into the blood when the stomach contents empty into the duodenum and the small intestine [333].

Therapeutic doses of ibuprofen, a nonsteroidal anti-inflammatory drug, that blocked the enzyme prostaglandin synthetase, had no effect on the pharmacokinetic profile of ethanol in a controlled human study [334]. Blood–ethanol was estimated indirectly by analysis of exhaled breath. Neither C_{max} (0.095 ± 0.026 vs 0.095 ± 0.033 g/100 mL) nor rate of blood–ethanol clearance (0.018 ± 0.006 g/100 mL/h vs 0.017 ± 0.007 g/100 mL/h) showed any significant differences. In another study with 8 volunteer subjects, it was reported that the rate of ethanol elimination from blood was decreased by 10% after treatment with ibuprofen [335].

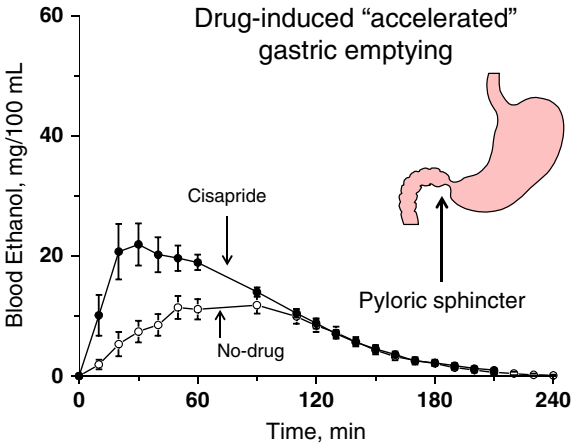


Fig. 13.16 Effect of pretreatment with cisapride, a drug that accelerates gastric emptying. on blood–alcohol curves after an ethanol dose of 0.30 g/kg body weight and a cross-over design (Redrawn from Kechagias et al. [340])

The same study also looked at the effect of the same drugs on various cognitive tasks and found a worsened performance when ibuprofen was combined with alcohol compared with a placebo control treatment [335]

Cisapride

Drugs used to treat stomach ailments might be expected to influence gastric emptying and the rate of absorption of ethanol into the bloodstream [336, 337]. Cisapride is a prokinetic drug prescribed for people with gastric reflux problems, because it enhances gastrointestinal motility indirectly via cholinergic transmission in the myenteric plexus [338]. Incidentally, cisapride (Propulsid®) is no longer registered in some countries because of the possible risk of cardiotoxicity. In one study, the rate of absorption of ethanol was compared in 5 healthy volunteers with or without pretreatment with cisapride (10 mg). Both C_{max} and $AUC_{0–4\,h}$ were higher after treatment with cisapride when the ethanol was ingested on an empty stomach but not when the same dose was ingested together with a meal [339]. However, the volunteer subjects took only two tablets of cisapride before they drank the ethanol and plasma concentrations of the medication were not measured or reported.

Kechagias et al. [340] gave 10 male subjects cisapride for 4 days (10 mg, 3 times daily before meals) to reach steady-state plasma concentrations as occurs in subjects prescribed this medication. Ethanol (0.3 g/kg body weight) was ingested 1 h after a meal and the mean peak blood-alcohol concentration rose 43% after cisapride compared with the no-drug control session (Fig. 13.16). However, the increase in BAC in absolute terms was only 0.01 g/100 mL, which is practically insignificant ($p < 0.05$). Gastric emptying was monitored simultaneously by the acetaminophen absorption test. It is well known that this drug is only taken up into the blood stream after the contents of the stomach empty into the duodenum and small intestine.

The serum concentration curves for this biomarker of absorption mirrored the changes in BAC after cisapride treatment verifying that the higher C_{max} and earlier t_{max} observed after treatment with cisapride was largely caused by accelerated gastric emptying [340].

Verapamil

The calcium channel blocker verapamil (Verelan®) is widely used for the treatment of angina, control of arrhythmias, and other cardiovascular diseases, such as hypertension [341–343]. Because ion channels and calcium transport might be related to ethanol's effects on the brain, it seemed reasonable to investigate a likely interaction with ethanol. Drugs that block calcium transport (verapamil and nifedipine) were evaluated for potential pharmacokinetic and pharmacodynamic interaction with ethanol [341, 342]. One study reported a significant pharmacokinetic interaction showing a 20% increase in the C_{max} of ethanol when combined with verapamil treatment (peak BAC 0.124 ± 0.024 vs. 0.106 ± 0.021 g/100 mL) [342]. However, the concentration–time profiles of ethanol in this study were not presented in the article to allow detailed evaluation. The higher C_{max} and AUC after verapamil treatment might have been caused by drug effects on absorption of ethanol from the stomach and not a faster rate of metabolism or FPM as speculated upon by the authors of the article in question [342].

In another study, verapamil was compared with nifedipine and a placebo treatment but no differences were found regarding pharmacokinetics of ethanol or subjective feelings of inebriation and psychomotor performance [343]. The effect of verapamil on pharmacokinetics of ethanol if any remains an open question.

Erythromycin

The widely used antibiotic erythromycin appears to increase the rate of gastric emptying, which might be expected to cause a higher C_{max} and AUC for ethanol [344]. The mechanism of action of erythromycin is believed to be as an agonist of the gastrointestinal peptide motilin thus increasing gastric motility [345]. An intravenous dose of erythromycin (3 mg/kg body weight) accelerated gastric emptying and caused a faster absorption of ethanol in 8 subjects who ingested 0.5 g ethanol per kg body weight immediately after eating a solid meal [346]. The mean C_{max} increased from 0.055 ± 0.004 (± SE) to 0.077 ± 0.004 g/100 mL ($p < 0.05$) and the mean $AUC_{0–330\,min}$ increased from 6.6 ± 0.27 to 7.6 ± 0.35 g/100 mL × min ($p < 0.05$).

Ranitidine

H_2-receptor antagonists, such as ranitidine (Zantac®), cimetidine (Tagamet®), famotidine (Pepcidine®), and nizatidine (Axid®), are widely used and are available OTC

for treatment of stomach ailments such as hyperacidity, gastritis, and ulcers [347]. These drugs, particularly ranitidine and cimetidine, were found to block the action of gastric ADH raising the potential for increasing the bioavailability of ethanol [348, 349].

The interaction between Zantac and alcohol was published in JAMA and, accordingly, attracted considerable attention from the news media [298]. The authors claimed that treatment with ranitidine meant that a larger fraction of the dose of alcohol consumed would reach the systemic circulation. This led to speculation that people regularly taking antacid drugs and who also consume alcohol are at a greater risk of organ and tissue damage after social drinking [298]. A faster absorption and higher ethanol C_{max} also meant a greater risk for accidents when skilled tasks, such as driving a motor vehicle, were involved.

A closer examination of the JAMA article showed that only 6 subjects were tested and the doses of ethanol were very low (0.15–0.3 g/kg) and the drinking took place 1 h after subjects had eaten a fatty breakfast [298]. Moreover, the blood–ethanol C_{max} was low and highly variable, which meant that finding a small absolute increase in BAC (e.g., 0.01 g%) leads to fairly large percentage changes in BAC between the test and control groups.

Amir et al. [349] recently confirmed that ranitidine (300 mg given every evening for 1 week) increased the bioavailability of ethanol but the mechanism was now attributed to a faster gastric emptying and not to inhibition of gastric ADH. The shorter residence of ethanol in the stomach after drug treatment gave less opportunity for presystemic metabolism to occur in the gastric mucosa. In many studies of this type, the investigators fail to separate the contribution of hepatic ADH from gastric ADH in FPM of ethanol.

Attempts by other research groups to replicate the results of the JAMA study were unsuccessful even under similar test conditions and when more volunteer subjects were included and increasing doses of ethanol 0.15, 0.3, and 0.6 g/kg [350]. Some effect was noted after the smallest dose (0.15 g/kg), but the investigators warned that under these conditions large intersubject variability in absorption kinetics of ethanol and first-pass metabolism in the liver might also explain the findings.

Another good study looked at the BAC profiles with and without drug treatment when a small dose of ethanol (0.3 g/kg) was administered in the morning, at midday, and in the evening in a well-designed randomized cross-over study [351]. The schedule for ranitidine administration was optimal to achieve therapeutic concentrations in blood before ethanol was consumed. The median BAC time profiles were remarkably similar regardless of treatment with antacid drug and the time of day – morning, afternoon, or evening.

Other studies failed to support the conclusions in the JAMA article [199], which were evidently much exaggerated. When this drug–alcohol interaction was investigated in Asians and Caucasians there were no statistically significant increases in either C_{max} or AUC after small doses of alcohol [352, 353].

Cimetidine

The first H_2-receptor antagonist marketed for treatment of hyperacidity was cimetidine (Tagamet®), and in vitro studies involving biopsies from gastric mucosa found that the drug inhibited activity of gastric ADH [352–355]. The chemical structure of cimetidine includes a 5-membered imidazole ring, which resembles that of pyrazole, a well-known inhibitor of hepatic ADH [193, 194].

Scores of studies tested the effect of cimetidine treatment on the pharmacokinetics of ethanol but the effects were small or negligible and can largely be explained by the intersubject variations in gastric emptying rate and the very small doses of alcohol administered [356–359]. One study looked at patients that suffer from duodenal ulcers and might normally be medicated with H_2-antagonists [360]. Other studies found a higher peak BAC after cimetidine treatment but no attempt was made to resolve whether this was caused by inhibition of gastric ADH or a faster stomach emptying [361].

Studies reporting positive effects of cimetidine treatment have invariably involved very small doses of ethanol consumed at 1 h after a fatty breakfast [355]. Drinking alcohol together with or after a meal is known to influence the rate and extent of absorption of ethanol into the bloodstream in a very unpredictable manner [156, 309, 310]. Seitz et al. [362, 363] found that C_{max} for plasma-ethanol was 0.086 g/100 mL after treatment with cimetidine compared with 0.078 g/100 mL after placebo, thus only a small absolute difference. When ethanol was administered by intravenous infusion to avoid any confounding influences of gastric emptying, the rate of clearance of alcohol from blood was the same as in a no-drug control group [363].

Feely and Wood [364] studied the effect of cimetidine on pharmacokinetics of ethanol and also recorded subjective feelings of ethanol-induced inebriation. The peak plasma ethanol concentrations (PAC) were within the range expected for the dose administered and the C_{max} was higher (0.163 g/100 mL) after cimetidine compared with placebo (0.146 g/100 mL). The authors considered this as showing a faster rate of absorption of ethanol after treatment with cimetidine and not a mechanism involving drug-induced effects on gastric ADH.

Webster et al. [365] found a negligible effect of cimetidine on absorption, distribution, and elimination of ethanol. These workers measured BAC indirectly by a breath-alcohol analyzer in 4 men and 3 women receiving cimetidine (200 mg three times daily), ranitidine (150 mg twice daily), or placebo for 2 days. The peak BAC and AUC were slightly higher after ranitidine but not after pretreatment with cimetidine or placebo. Dobrilla et al. [366] also failed to find any measurable effect of cimetidine on the pharmacokinetics of ethanol in a human study that also included testing ethanol-induced impairment.

Jönsson et al. [367] compared the effects of therapeutic doses of ranitidine, cimetidine, and omeprazole (a proton-pump inhibitor Losec®) on the pharmacokinetics of ethanol after subjects drank 0.8 g/kg in the morning after an overnight fast. The BAC profiles from this study are reproduced in Fig. 13.17 and the pharmacokinetic parameters C_{max}, t_{max}, k_o, and AUC are compared and contrasted in Table 13.5.

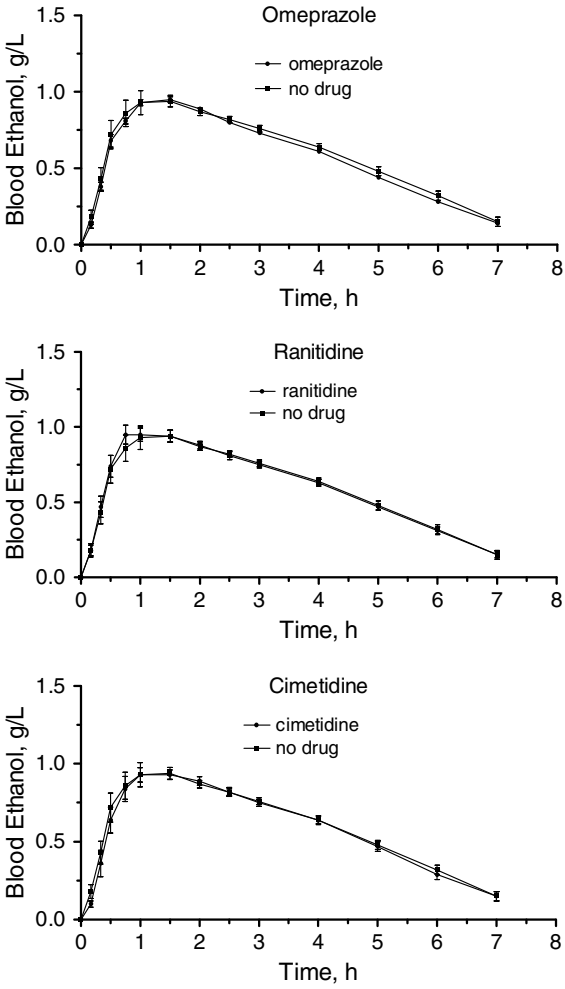


Fig. 13.17 Lack of effect of pretreatment with drugs for gastric hyperacidity, omeprazole (*upper plot*), ranitidine (*middle plot*), and cimetidine (*lower plot*), compared with a no-drug control treatment. Blood–alcohol profiles are shown for 12 volunteers who drank 0.8 g ethanol per kg body weight after an overnight fast (Redrawn from Jönsson et al. [367])

Table 13.5 Effect of pretreatment with cimetidine, ranitidine, omeprazole and a no-drug control treatment on the peak blood–alcohol concentration (C_{max}), time to reach maximum (t_{max}), rate of elimination of alcohol from blood (k_0), and area under the curve (AUC). Twelve healthy men participated in a randomized cross-over study [367]

Treatment	C_{max} g/100 mL mean (range)	t_{max} min median (range)	k_0 g/100 mL/h mean (range)	AUC g × h/100 mL mean (range)
Cimetidine	0.101 (0.094–0.108)	70 (52–88)	0.015 (0.014–0.016)	0.414 (0.376–0.451)
Ranitidine	0.103 (0.092–0.113)	64 (51–77)	0.014 (0.013–0.015)	0.436 (0.395–0.478)
Omeprazole	0.102 (0.091–0.113)	69 (53–84)	0.014 (0.013–0.015)	0.433 (0.380–0.487)
Control (no drug)	0.105 (0.092–0.118)	70 (49–91)	0.014 (0.013–0.015)	0.443 (0.387–0.500)

Because the same subjects participated in each arm of the study this kind of experimental design has a high power to detect any effects from the different treatments. However, neither treatment with H_2-receptor antagonists nor with omeprazole had any effects on BAC parameters compared with no-drug control treatment. The dose of ethanol (0.8 g/kg) used in the Jönsson et al. study [367] was higher than that used by other investigators but more in line with moderate social drinking. Also the dose of alcohol was ingested on an empty stomach to avoid any food-induced effects on the rate of ethanol absorption.

Several studies finding a higher C_{max} of ethanol after treatment with cimetidine or ranitidine have chosen to administer very low doses of ethanol (0.15–0.3 g/kg) and only 6–8 test subjects were included in the study design. Moreover, the relative importance of the stomach as opposed to the liver as site for FPM of ethanol was not resolved. This highlights some of the dangers of drawing too hasty conclusions from drug-interaction studies. Differences in experimental protocol and design, such as dose of ethanol, pattern of drinking, and especially the fed vs. fasted state of the volunteer subjects are very important.

Fraser [368] presented a balanced review of many published studies dealing with the interaction of ethanol and H_2-receptor antagonists. He arrived at the conclusion that except for special circumstances, such as drinking small doses of ethanol (0.15 g/kg) after eating a fat-rich meal, there was no evidence that this drug effect existed. Small doses of ethanol exaggerate intersubject variability in C_{max} and AUC making it virtually impossible to draw any conclusion about the effects of a concomitant drug treatment unless hundreds of subjects are used in the test and control groups. Highly variable stomach emptying, the effects of drug treatment, and the role of fed or fasted state complicate a proper interpretation of results. In an editorial on the subject of gastric FPM and its role in studies of ethanol pharmacokinetics, the author referred to the situation as mountain or molehill, suggesting that the effects of these types of drugs (H_2-receptor antagonists) on ethanol metabolism were insignificant [369].

Pharmacodynamic Aspects of Ethanol

Ethanol is unique among drugs of abuse in exhibiting two completely different actions on the body, one being metabolic and nutritional and the other depression of the CNS leading to sedation, impairment, and risk for dependence and addiction [190, 370, 371]. The complete combustion of ethanol liberates 7 kcal/g, making it intermediate between fats (9 kcal/g) and carbohydrates and proteins (4 kcal/g). Alcoholics derive much of their daily energy needs from the large amounts of alcohol they consume at the expense of other nutrients. The calories derived from oxidation of alcohol are referred to as empty calories because they are produced and utilized in the liver and cannot be stored in other forms, as glucose is stored as glycogen, for later use when needed. Moreover, alcoholic beverages lack the important micronutrients (vitamins and minerals) that are contained in ordinary foodstuffs [371].

When the liver is engaged in the metabolism of ethanol it cannot perform its normal metabolic functions, such as taking care of fats, carbohydrates, and proteins. Many of the metabolic disturbances as a consequence of heavy drinking depend on a shift in the redox state of the liver toward a more reduced potential [372]. The elevated $NADH/NAD^+$ ratio in the hepatocytes during ethanol oxidation causes a shift from pyruvate to lactate resulting in lactic acidosis. Moreover, removal of an important substrate from gluconeogenesis tends to cause fasting hypoglycemia. The competition of lactate with urate for excretion can lead to hyperuricemia and gout attacks [373]. Other NAD-dependent reactions involving carbohydrate and fat metabolism are perturbed during hepatic oxidation of ethanol. Among other things, this leads to an accumulation of fat in the liver and a dangerous state of hypoglycemia might develop if intake of food is restricted [371–373].

Ethanol-Induced Impairment

Ethanol is a relatively weak psychoactive substance compared with most other drugs of abuse when one considers that 25–50 g must be consumed to produce feelings of mild euphoria [374, 375]. The mechanism of action of ethanol on the brain and CNS was for a long time thought to involve nonspecific interaction with the membrane lipids in the same way as organic solvents (e.g., ether and chloroform) and general anesthetic gases such as N_2O, enflurane, and halothane [376–378]. Solubility of drugs in lipid membranes is a key factor determining potency of anesthetics, as predicted by the Meyer–Overton theory, which makes ethanol a very weak narcotic agent owing to its high water solubility [378].

Ethanol passes easily through biological membranes, between and within neurons, changing the microenvironment and electrical signaling and the configuration of receptor proteins embedded in the cell membrane [379]. In vitro studies with isolated tissue and brain slices found that very high concentrations of ethanol were necessary to bring about fluidization of membrane lipids. The concentrations required far exceeded the BAC that resulted in intoxication under in vivo condition, which suggests that other mechanisms are involved in the central nervous effects of ethanol.

Ethanol has a wide spectrum of pharmacological effects including euphoria, altered mood and behavior, impairment of motor coordination, arousal, and cognition [380–389]. The best candidate for ethanol's brain receptor is the major inhibitory neurotransmitter γ-aminobutyric acid (GABA), particularly the $GABA_A$ subtype [380, 381]. This same receptor subtype mediates many of the effects of other depressant drugs including benzodiazepines and barbiturates [388]. This receptor complex is made up of a number of subunits arranged symmetrically to form an ion channel as shown diagrammatically in Fig. 13.18. When the receptor is activated (e.g., by a GABA agonist) the ion channel opens and chloride ions flow into the cell. The negative charges of the ions hyperpolarize the neuron's membrane potential, effectively inhibiting its electrical activity. GABA binds to the β-subunit of the receptor and

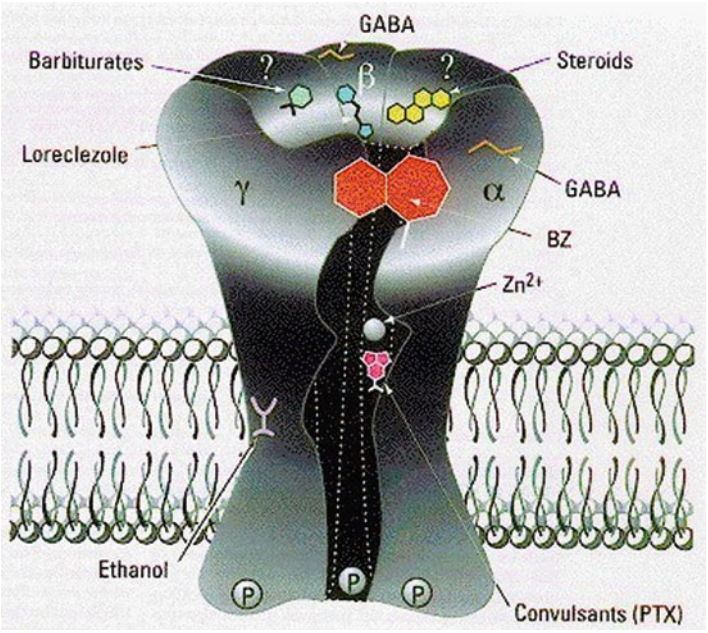


Fig. 13.18 Schematic representation of a receptor ($GABA_A$) for the major inhibitory neurotransmitter γ-aminobutyric acid (GABA) showing the chloride ion channel and binding sites for GABA, benzodiazepines, barbiturates, and ethanol. The receptor molecule is formed from five protein subunits and when activated chloride ions flow into the cell resulting in a pharmacological response (Reproduced with permission from National Institute on Alcohol Abuse and Alcoholism, Washington DC, USA)

when ethanol or other depressant drugs are within the membrane the agonist action of the neurotransmitter is supplemented [384–387].

Yet another proposed receptor site for the action of ethanol in the brain is the excitatory neurotransmitter glutamate [389]. Ethanol seems to antagonize the NMDA (*N*-methyl-*D*-aspartate) glutamate subtype receptor, which can also account for some of the diverse effects of ethanol on memory and learning. The mechanism involves an altered flux of sodium and calcium ions through the receptor channel and activation of a second messenger leading to a physiological response. Antagonism of NMDA receptors was also suggested as a possible mechanism to account for some of the antisocial and aggressive behaviors seen in drunken people [388]. The pleasurable effects of ethanol (euphoria and disinhibition) experienced at fairly low BAC occur on the rising phase of the curve and are thought to involve interference with receptors for dopamine [390].

Ethanol is classified as a CNS depressant, which means that concomitant use of other depressant drugs (e.g., barbiturates and benzodiazepines) can lead to adverse effects and a pharmacodynamic interaction [391–393]. The euphoric effects of ethanol are felt almost immediately after the start of drinking verifying rapid transport of the drug from

the gut and its ease of passage over the blood–brain barrier. The dose of ethanol and the speed of drinking are critically important for the effects produced on the drinker.

When the BAC is relatively low (~0.03 g/100 mL) people become talkative and experience mild euphoria [387]. These pleasurable and rewarding effects of small doses of ethanol are especially evident on the ascending limb of the alcohol curve [390]. As drinking continues and BAC rises to reach 0.10 g/100 mL, a person's judgment is impaired and some become emotionally unstable. At even higher BAC (0.15–0.20 g/100 mL) speech is slurred and incoherent, balance is seriously impaired and reaction time is slowed, especially in choice situations [51]. However, moderate drinkers rarely reach such high BAC of 0.15–0.2 g%, owing to the nausea they experience and many will vomit.

For those who continue drinking alcohol, impairment becomes progressively worse and they eventually lose the inability to stand or walk without support. On reaching still higher BAC (>0.3 g/100 mL), the narcotic action of ethanol predominates with subjects showing a lack of response to pain stimuli and the individual reaches a comatose and unconscious state [388]. Drinking to reach even higher BAC causes a lethal impairment of the respiratory centers in the brain stem and death ensues through asphyxia and circulatory collapse [394, 395].

Tolerance Development

Human beings show an enormous variation in their response to the same amount of ethanol under the same drinking conditions. It is common knowledge that some individuals tolerate more alcohol than others [51]. Tolerance is defined as a diminution of the effects of a drug after repeated exposure and this phenomenon is often represented by a shift in the dose–response curve toward the right [396]. When the BAC rises rapidly to reach 0.15 g/100 mL this is likely to trigger a vomit reflex in the brain, which has doubtless saved the lives of many inexperienced drinkers. However, use of certain medication or repetitive drinking over several hours allows a person to tolerate 0.15 g/100 mL without vomiting. A common cause of death in inexperienced drinkers is asphyxia by aspiration of stomach contents (vomit) when in a deeply comatose state [394, 395].

For approximately 100 years, it has been known that after a single acute dose of ethanol the subjective feelings of intoxication as well as objective measures of impairment are more pronounced during the absorption phase before reaching the peak BAC [51, 397]. A marked recovery in the signs and symptoms of drunkenness occur when the BAC enters the postabsorptive phase and any remaining impairment effects can only be ascertained by highly sensitive tests [396, 397]. This phenomenon is called "the Mellanby effect" named after a British pharmacologist (Sir Edward Mellanby) who first made the observation during experiments with dogs [398]. Alcohol was administered by stomach tube and when the animals lost the ability to walk and stand on four legs their BAC was measured and once again when they regained the ability to stand and walk unaided. The BAC on the rising

limb of the alcohol curve (prepeak impairment) was lower than on the descending limb (postpeak recovery), hence the notion of acute tolerance during a single exposure to alcohol [398].

The phenomenon of acute tolerance is distinct from chronic tolerance, which develops after much longer periods of exposure to alcohol lasting days or weeks [399, 400]. Ethanol also exhibits cross-tolerance with other sedative–hypnotic drugs and CNS depressants such as barbiturates and benzodiazepines, hence the use of these substances to relieve the alcohol withdrawal symptoms [399]. Yet another kind of tolerance is referred to as metabolic or dispositional tolerance, which is concerned with variations in absorption, distribution, metabolism, and elimination (pharmacokinetic aspects) of the drug [400]. The mechanism underlying metabolic tolerance seems to be induction of microsomal enzymes (e.g., CYP2E1) increasing its capacity to oxidize ethanol after a period of continuous heavy drinking or medication with barbiturates or other drugs known to boost the activity of microsomal enzymes [166].

The development of acute tolerance to the effects of ethanol was demonstrated in a classic study from Finland [401]. Four doses of alcohol were administered according to body weight (0.5 g/kg, 0.75 g/kg, 1.0 g/kg, and 1.25 g/kg) as a bolus dose (finished in 5 min) and consumed on an empty stomach. The test subjects were police officers or prison inmates and venous blood samples were taken at various times postdosing. The subjects were examined before drinking by physicians who administered various psychomotor and cognitive tests to determine baseline scores. The subjects were examined again by the same physicians using the same battery of tests at various times after drinking when a sample of blood was taken for quantitative analysis of ethanol. The relationship between symptoms of alcohol influence and the average BAC after a dose of 1.0 g/kg is plotted in Fig. 13.19.

This plot shows that C_{max} of the BAC curve was reached about 1 h after the end of drinking, whereas the peak symptoms of alcohol influence occurred shortly before C_{max} was reached. The BAC then continued to decrease at a more or less constant rate per unit time although the symptoms of alcohol influence dropped off much more rapidly. At 5-h postdosing there was no longer any observable symptoms of alcohol influence but the mean BAC was still elevated and above the legal limit for driving in most countries [401].

Some apprehended drivers tolerate BAC as high as 0.4 g% and a few have exceeded 0.5 g% without loss of life. This is hard to rationalize when some authorities in legal medicine maintain that the median BAC for acute alcohol poisoning is 0.36 g% [402, 403]. People who drink to reach such high BAC have consumed alcohol more or less continuously for days or weeks and have chronic tolerance for the drug effects [396]. These very high BACs are seemingly tolerated without the need for emergency hospital treatment for alcohol poisoning [404–406]. By contrast, starting from zero BAC and drinking the amounts of alcohol needed to reach a BAC of 0.4 g% would result in gross intoxication, stupor, coma and death by respiratory arrest and circulatory failure [407].

Table 13.6 summarizes the results of clinical tests of drunkenness in apprehended drunken drivers in Sweden, who were examined by the same physician [97]. Using

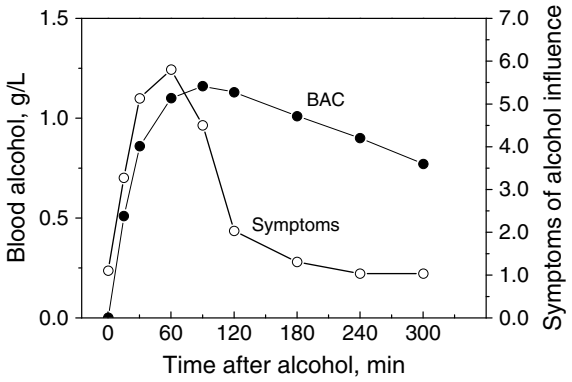


Fig. 13.19 Concentration–time course of alcohol in blood and symptoms of alcohol intoxication measured at various times after consumption of ethanol (1.0 g/kg body weight) in 5 min after an overnight fast (Redrawn from work published by Alha [401])

Table 13.6 Numbers of individuals diagnosed as being under the influence of alcohol according to examination by a physician in relation to their blood–alcohol concentration. The same physician examined 244 people apprehended by the police suspected of drunken drivers

Blood–alcohol, g/100 mL	N	Clinical diagnosis of under the influence of alcohol			
		None	Low	Moderate	High
0.00–0.049	29	3	26	–	–
0.05–0.099	39	2	37	–	–
0.10–0.149	54	2	41	10	1
0.15–0.199	47	1	24	17	5
0.20–0.249	47	–	20	22	5
0.25–0.299	25	–	7	11	7
0.30–0.359	3	–	1	1	1

a questionnaire and checklist to document and record clinical signs and symptoms associated with drunkenness, the physician formed an opinion whether the suspects were not under the influence of alcohol, or showed mild, moderate, or severe symptoms of alcohol influence. One notices that conclusions about degree of alcohol influence (none, low, moderate, or severe) differed widely within each 0.05 g/100 mL interval of BAC. Because the same person examined all suspects, the differences noted cannot be attributed to the experience and training of the physician concerned. Furthermore, some people have the ability to pull themselves together when under pressure and in a critical or compromising situation.

Toxicity of Ethanol

A group of experts from the United Kingdom, representing disciplines of pharmacology, psychology, and public health, developed a classification of the relative dangerousness of recreational drugs [375]. Overall, ethanol was considered more

dangerous than ecstasy and cocaine in terms of physical harm, dependence, and the social and medical consequences of abuse of this social drug. Considering that ethanol is a legal drug its acute toxicity must be considered high because the ratio of lethal dose to effective dose is only about 10:1 (BAC 0.5 g% compared to 0.05 g%). This is a relatively narrow margin of safety compared with many other therapeutic and illicit drugs.

The mean BAC at autopsy in deaths ascribed to acute alcohol poisoning was 0.36 g% but because of metabolism of ethanol until the time of death, the person must have experienced higher BAC earlier during life [402, 403]. The rate of elimination of ethanol from blood ranges from 0.01 to 0.025 g% per h for the vast majority of people and metabolism begins immediately after the start of drinking. What this means is that the BAC at autopsy is almost always a conservative estimate of the total amount of alcohol consumed [402].

Sampling and analysis of femoral blood is preferred to heart blood in postmortem toxicology because this minimizes risk of contaminating the specimen by diffusion of alcohol from gastric residue to the central blood compartment after death [407, 408]. Another aspect to consider when postmortem BACs are interpreted is the water content of the specimen analyzed in comparison with fresh whole blood (80% w/w water). Ethanol distributes into the blood's water fraction so analytical results might be corrected to a value of 80% w/w found in living subjects [407]. Another problem in postmortem alcohol analysis is the risk for production of ethanol after death by microbes utilizing glucose and other substrates [408]. This problem is not trivial especially if the body is decomposed and putrefaction processes have started. To some extent the validity of the BAC can be controlled and verified by sampling and analysis of ethanol in other body fluids, such as urine or vitreous humor [407, 408].

One of the physiological effects of drinking a large dose of ethanol is a lowering of core body temperature (hypothermia) because alcohol offsets central regulatory mechanisms in the medulla of the brain [409]. This adverse effect of ethanol is much exaggerated when the environmental temperature is also unusually low [410]. Accordingly, a very drunk person exposed to the cold, such as a skid row alcoholic sleeping outdoors in the winter, is likely to be found dead with a BAC that otherwise would have been easily tolerated [410–414]. Hypothermia-related deaths might be important to consider when the acute toxicity of alcohol is investigated as a function of the BAC [415]. One study reported a BAC at death of 0.36 ± 0.08 g/100 mL (range 0.21–0.70) in alcoholics ($N = 116$) not exposed to cold compared with 0.17 ± 0.09 g/100 mL (range 0–0.32) in another group ($N = 35$), which were classified as hypothermia deaths [414]

An oft-times overlooked factor in alcohol-related deaths is the role played by positional asphyxia, particularly if the person is obese and laying face-down with partial obstruction of the airway [415, 416]. Many heavy drinkers are also heavy smokers with impaired lung function and breathing difficulties caused by long-term use of cigarettes [417]. An elevated level of carbon monoxide in the blood from smoking might exaggerate alcohol-induced respiratory depression and hypoxia. Allowing a person in an alcoholic stupor or coma to "sleep-it-off" lying

in a compromising position so that breathing becomes restricted has often resulted in death [418].

Finally, the role of ketoacidosis as a cause of death in alcoholics is just beginning to be better understood [419]. Alcoholics not only drink a lot of alcohol, they also neglect to eat properly and hepatic glycogen stores soon become depleted. The combined influence of a hypoglycemic state and metabolic disturbances related to alcohol metabolism make alcoholics a risk group for ketoacidosis deaths [420]. This possibility should be considered when a known alcoholic or heavy drinker is discovered dead at home with zero or low BAC and nothing more remarkable found at autopsy apart from an enlarged and fatty liver [421]. The finding of elevated concentrations of β-hydroxybutyrate in postmortem blood in relation to acetoacetate and total ketone bodies was suggested as a useful biochemical test to support a diagnosis of ketoacidosis death [422, 423].

Another major factor influencing toxicity of ethanol is concomitant use of other drugs, especially sedative–hypnotics (barbiturates and benzodiazepines) that share similar mechanism of action via GABA neurotransmission [424]. The dose of alcohol and the BAC necessary to kill a person might be substantially lower after coingestion of other sedatives or hypnotics, such as barbiturates or benzodiazepines [424].

Toxicity of Drug-Ethanol Interactions

It is common knowledge that combinations of various drugs increase the risk of toxicity and this is especially so when they share the same mechanism of action at the cellular level. Drugs such as heroin, morphine, methadone, as well as other opiates have multiple actions depending on where in the body target receptors are located [425, 426]. Besides the relief of pain, opiate-like drugs also depress respiration making them particularly dangerous if and when taken together with a large dose of ethanol or some other CNS depressant, such as a benzodiazepine or barbiturate drug [427–429].

Propoxyphene

Propoxyphene (called dextropropoxyphene in Europe) was synthesized in 1953 and in terms of chemical structure and pharmacology is similar to methadone [430]. Propoxyphene (t½ 8–24 h) is prescribed for treatment of mild to moderate pain although a common side effect of this treatment is sedation. Shortly after propoxyphene became widely prescribed (~1957) there was also a rise in overdose fatalities and one common finding in these deaths was the liberal use of alcohol by the deceased and elevated BAC at autopsy [431, 432]. The danger of prescribing propoxyphene to alcoholic patients and heavy drinkers thus became well recognized and alternative strong analgesics emerged, such as tramadol [433].

The ratio between lethal and therapeutic concentrations of propoxyphene in blood is fairly narrow and prescribing of this dangerous drug has been restricted or banned in some countries [434]. The mechanism of this adverse drug–alcohol interaction is thought to involve $GABA_A$ and opiate receptors leading to enhanced depression of respiratory centers in the brain [435–437].

Sedative–Hypnotic Drugs

Sedative–hypnotic drugs have diverse chemical and pharmacological properties finding usefulness to treat anxiety, insomnia, and also as anticonvulsants or muscle relaxants. These drugs are among the most widely prescribed and are obvious candidates for interaction with ethanol, owing to the similar mechanism and sites of action in the brain, namely the GABA receptor complex [438]. Use of alcoholic beverages should be avoided by people who use sedative–hypnotic medication because of the risk of additive or supra-additive effects, such as more profound sedation and a worsened behavioral impairment and acute toxicity [439–441]. The fast acting hypnotic flunitrazepm seems to be particularly dangerous when used together with alcohol [440, 441].

Table 13.7 lists many examples of common sedative–hypnotic drugs that might be expected to participate in a pharmacodynamic interaction with ethanol by interfering with GABA neurotransmission. Both trade names and elimination half-lives are given.

Barbiturates

Barbituric acid was first synthesized in 1864 but proved not to be pharmacologically active. It was not until 1903 that the first therapeutically useful barbiturate drug became available in the form of 5,5-diethylbarbituric acid (barbital) or Veronal® and this pharmaceutical was widely prescribed as a sedative–hypnotic [442]. Thereafter hundreds of derivatives of barbituric acid were prepared and tested for their usefulness as therapeutic agents. The barbiturate group of drugs are often classified as ultra short acting (applications in anesthesia, e.g., thiopental), short to medium acting (sleeping pills or hypnotics, e.g., secobarbital), and long acting (sedatives and anticonvulsants, e.g., phenobarbital) [443]. Overdosing with barbiturates was early recognized as a problem, because of a narrow therapeutic index and many deaths occurred by accident and in suicide attempts [444]. For half a century, the barbiturates were the drugs of choice to relieve anxiety, insomnia, to treat epilepsy, and for self-poisoning (suicide). The ultra short-acting highly lipid-soluble sulfur-containing barbiturate thiopental is widely used as premedication before general anesthesia and also as a component of the drug cocktail used for lethal injection for execution of convicted murders [445].

The major clinical feature of barbiturate overdose is profound depression of the CNS leading to deep sleep and coma, which is exaggerated if the person has

Table 13.7 Examples of sedative–hypnotic drugs with strong potential for undergoing a pharmacodynamic interaction with ethanol, their trade names (US) and approximate elimination half-lives [319, 463]

Barbiturates (trade name), half-life ($t_{½}$)	Benzodiazepines (trade name), half-life ($t_{½}$)	Other depressants (trade name), half-life ($t_{½}$)
Amobarbital (Amytal®) 15–40 h	Alprazolam (Xanax®) 6–22 h	Chlormethiazole (Heminevrin®) 3–5 h
Aprobarbital (Alurate®) 14–34 h	Chlordiazepoxide (Librium®) 6–27 h	Chloral hydrate (Noctec®) 6–10 h
Butabarbital (Butisol®) 34–42 h	Diazepam (Valium®) 21–37 h	Ethchlorvynol (Placidyl®) 19–32 h
Hexobarbital (Sombulex®)	Flunitrazepam (Rohypnol®) 9–25 h	Glutethimide (Doriden®) 7–15 h
Mephobarbital (Mebaral®) 10–70 h	Flurazepam (Dalmane®) 1–3 h	γ-hyroxybuyrate GHB (Xyrem®) 0.3–1.0 h
Methohexital (Brevital®) 3–5 h	Lorazepam (Ativan®) 9–16 h	Meprobamate (Miltown®) 6–17 h
Pentobarbital (Nembutal®) 20–30 h	Midazolam (Versed®) 1–4 h	Methaqualone (Sopor®) 20–60 h
Phenobarbital (Luminal®) 48–120 h	Nitrazepam (Mogadon®) 17–48 h	Methyprylon (Noludar®) 7–11 h
Probarbital (Ipral®)	Oxazepam (Serax®) 4–11 h	Paraldehyde (Paral®) 3–10 h
Secobarbital (Seconal®) 15–40 h	Temazepam (Restoril®) 5–15 h	Zolpidem (Ambien®) 1.4–4.5 h
Thiopental (Pentothal®) 6–46 h	Triazolam (Halcion®) 2–4 h	Zopiclone (Imovane®) 0.5–6.5 h

Table 13.8 Concentrations (mean and range) of older sedative–hypnotic drugs in postmortem (PM) blood in drug-related deaths with and without elevated blood–alcohol concentration [448]

Drug	N[a]	Concentration (mg/L) without alcohol	N[a]	Concentration (mg/L) with alcohol	Blood–alcohol mean (range), g/100 mL
Phenobarbital	11	93 (51–183)	4	69 (46–90)	0.11 (0.05–0.23)
Pentobarbital	11	26 (9–59)	11	21 (6–51)	0.11 (0.02–0.21)
Secobarbital	6	25 (0.7–47)	10	15 (2–66)	0.12 (0.01–0.30)
Meprobamate	12	112 (34–258)	18	99 (39–220)	0.14 (0.02–0.25)

[a]Number of cases

consumed intoxicating doses of alcohol [446, 447]. Table 13.8 compares concentrations of some sedative–hypnotic drugs in autopsy blood in fatal poisonings with and without alcohol being present. Note that the blood concentrations of the barbiturates and other sedatives were lower when the victim also had an elevated BAC [448].

Chronic use of barbiturates causes an induction in microsomal enzymes including CYP2E1, which means that other drugs are metabolized faster under these conditions. Heavy drinking causes induction of CYP2E1, so alcoholics are capable of metabolizing barbiturates faster than moderate drinkers. But the most dangerous

adverse drug–alcohol interaction between barbiturates and ethanol is a pharmacodynamic one via voltage and ligand-gated ion channels that control neuronal activity [446]. The high abuse potential and toxicity of barbiturates in overdose means that they are seldom prescribed as sleeping aids today. The newer class of hypnotics, pyrazolopyrimidine derivatives, as exemplified by zolpidem, zopiclone, and zaleplon, are widely used today to treat insomnia and this medication has low toxicity when used as mono-therapy [449].

Benzodiazepines

The first benzodiazepines (chlordiazepoxide and diazepam) became available in the early 1960s and they soon dominated the market as a class of anxiolytic and sedative–hypnotic medication [450]. As a group these mild tranquilizers possess a much wider safety margin and they are less toxic in overdose compared with the barbiturates. Benzodiazepines are widely used to treat conditions such as anxiety, panic disorder, muscle spasm, alcohol withdrawal, epileptic seizures, and insomnia [451, 452]. The toxicity of some benzodiazepines should not be underestimated, especially the swifter acting hypnotics, such as midazolam, triazolam, and flunitrazepam [453–455]. These have been incriminated in many deaths especially when used together with other CNS depressants, such as opiates and ethanol [456, 457].

Although the acute toxicity of benzodiazepines is considerably less than the barbiturates, the class of drugs they replaced, they are still subject to abuse and care is necessary when prescribing to people with alcohol-use disorder. The clinical pharmacokinetics of benzodiazepines as therapeutic agents are extensively studied over the past 40 years [458, 459]. Most are absorbed rapidly after oral administration; they have low hepatic clearance and are highly bound to plasma proteins and metabolized in the liver by phase II conjugation reactions [460]. This makes it unlikely that they undergo metabolic interaction with ethanol via CYP450 enzymes [461].

Benzodiazepines interact with their own sites on the $GABA_A$ receptor complex. These receptors are widely distributed in brain regions that control anxiety, memory, sedation, and coordination [462]. The endogenous brain chemical that normally activates the same receptor complex is γ-aminobutyric acid (GABA), the most important inhibitory neurotransmitter. The benzodiazepine binding sites are distinct from the GABA site, which in turn is distinct from the binding site for barbiturates and ethanol. The interaction with ethanol is predominantly pharmacodynamic via the $GABA_A$ receptor [463]. Benzodiazepine receptors are denoted BZ1 and BZ2, whereas BZ1 binding correlates with the hypnotic action of the drugs and BZ2 stimulation is related to cognitive and psychomotor effects of the drugs. Figure 13.18 gave a schematic representation of the $GABA_A$ receptor complex showing the binding sites for ethanol, barbiturates, and benzodiazepines. Drugs of the benzodiazepine and barbiturate families act as agonists enhancing the effects of GABA and dampening brain activity resulting in a tranquilizing effect [464]. Depending on the dose and the concentration reaching the receptor, benzodiazepines

elicit anxiolytic, anticonvulsive, and anesthetic properties [465]. However, benzodiazepines are subject to abuse and care is needed when this medication is prescribed to people with alcohol or substance abuse disorders [465–467]. The $GABA_A$ receptor complex is the molecular target in the brain for the action of benzodiazepines, barbiturates, and ethanol [468].

Diazepam is a GABAergic agonist and binds to specific sites on the $GABA_A$ receptor to open an ion channel, which facilitates passage of chloride ions into the adjacent cell [469]. Ethanol also acts on the $GABA_A$ receptor but at a different binding site from diazepam. Both drugs are agonist at the same receptor and together exert a bigger influence on reducing nerve activity in the brain leading to deeper sedation effect. Many other sedative–hypnotic drugs listed in Table 13.5 are thought to act in one way or another via the $GABA_A$ or $GABA_B$ receptors and have the potential to interact pharmacodynamically with ethanol.

Chloral Hydrate

Chloral hydrate is the oldest synthetic drug (since 1869) and still available and used to some extent today as a sedative–hypnotic [470]. In liquid form, Noctec® is more palatable to geriatric patients and young children who often have difficulties swallowing tablets. The metabolic interaction between ethanol and chloral hydrate was discussed in section "Chloral Hydrate" and will not be repeated here. The active metabolite of chloral hydrate 2,2,2-trichlorethanol is structurally similar to that of ethanol, which opens the potential for a pharmacodynamic interaction as well. Indeed, this drug combination is known colloquially as knockout drops or a Mickey Finn and was allegedly used to incapacitate people for purposes of robbery or sexual assault. The pharmacodynamic interaction between ethanol and chloral hydrate involves a joint action at the $GABA_A$ receptor complex and its chloride ion channel leading to an enhanced sedation effect over and above that expected from the individual drugs alone.

Illicit Drugs

Any drug or chemical agent with psychoactive properties, which exerts an action on the brain also has the potential to alter the behavioral effects of ethanol. The entire range of drugs of abuse including CNS stimulants, such as cocaine, amphetamine, and methamphetamine, the opiates (heroin and morphine), cannabis and marijuana, as well as hallucinogens like LSD are candidates for interaction with ethanol at the cellular level. Many commonly prescribed medications such as antidepressants and antihistamines that modulate the uptake and/or release of neurotransmitters are often identified together with ethanol in postmortem blood samples from victims of overdose deaths and drug poisonings [471–474].

Polydrug use is widespread among drug-dependent individuals and combined use of the legal drug ethanol is no exception. An interesting example of the

combined influence of an illicit drug and a legal drug is the interaction between cocaine and ethanol, which leads to the synthesis of a new psychoactive substance called cocaethylene [475].

Cocaethylene

The epidemic of crack cocaine abuse in the USA meant that co-ingestion of cocaine and alcohol was a common occurrence and represented a new example of a drug–alcohol interaction. The combined use of alcohol and cocaine became popular in some circles because it allegedly gave more intense feelings of a high [476]. Cocaine also seemed to antagonize some of the learning deficits and the impairment of psychomotor performance after drinking ethanol [477]. Interestingly, it was observed that when cocaine and ethanol were used together a new pharmacologically active substance was produced called ethyl cocaine or cocaethylene [478].

Thus, cocaethylene is biosynthesized during the metabolism of cocaine in individuals who had been drinking and had elevated blood–ethanol concentrations [479]. Cocaine is metabolized by hydrolysis by various carboxyl esterases to produce its major metabolite benzoylecgonine and also cocaethylene [480]. Cocaethylene was shown to pass the blood–brain barrier and to exert its pharmacological effects through the dopamine receptor thus enhancing the feelings of euphoria [481]. Moreover, the elimination half-life of cocaethylene was longer than for cocaine, which prolonged the effects of the stimulant drug on the individual. Several studies suggested that when cocaine was taken together with ethanol the risk for cardiotoxicity was increased [482, 483].

Drugs Used in the Treatment of Alcoholism

Alcohol abuse and dependence exert enormous costs for the individual and society and substantial morbidity and mortality worldwide [484]. Early intervention and treatment of people susceptible to developing an alcohol-use disorder is an urgent task for family physicians [485]. A person's drinking habits are often investigated by use of various questionnaires (CAGE, MAST) but there is also a need for more objective ways to demonstrate risky drinking because many alcoholics deny they have a problem [486]. For this purpose, a battery of biochemical tests or biomarkers are in use to detect organ or tissue damage caused by chronic heavy drinking [487]. Such biochemical tests of excessive drinking include blood chemistry profiles, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase (ASAT, ALAT, GGT), mean corpuscular volume (MCV), and carbohydrate deficient transferrin (CDT), which are widely used in the clinic as biomarkers [488].

An effective pharmacological treatment for alcohol dependence represents a major goal for the pharmaceutical industry considering that 10% of men and somewhat less women consume alcohol in dangerously high amounts rendering them

dependent on this drug [489]. The ideal agent should reduce craving for alcohol and also block the reinforcing or pleasurable effects associated with the consumption of alcohol [490, 491]. The medication should also be free from side effects and not show any undesirable interaction with other medication the patient might be taking [492]. In recent years, considerable progress has been made in the search for effective pharmacotherapy to treat alcoholism with focus on drugs that interact with GABA neurotransmission [493, 494]. A number of controlled trials have demonstrated that pharmacotherapy for alcohol abuse gives best results if combined with some form of psychological counseling and regular follow-up of patients using clinical interviews [495].

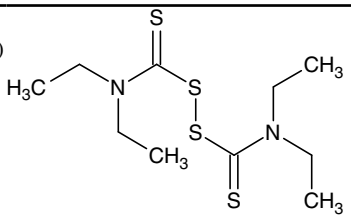
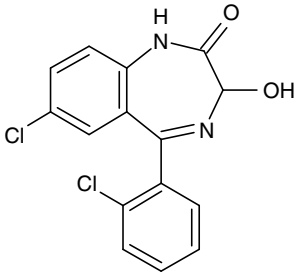
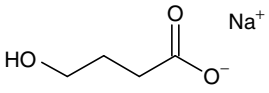
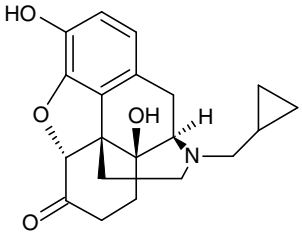
Table 13.9 lists examples of drugs already being used or being evaluated in clinical trials for treatment of alcohol abuse and dependence. A major problem in the clinical treatment of people addicted to alcohol is the high rate of relapse and drug treatment is often aimed at helping to maintain abstinence and improving quality of life [496, 497]. A diverse group of substances are represented as evidenced by their chemical structures and suggested mechanism of action. Benzodiazepines, such as diazepam or lorazepam, are useful to administer during the early phase of detoxification as a means to alleviate life-threatening withdrawal symptoms (delirium), whereas other drugs are needed more long term to reduce craving for alcohol during protracted abstinence [498].

Disulfiram represents the first and oldest pharmacotherapy for treatment of alcoholics and this drug was discovered in Denmark in the 1940s [242, 243]. Marketed as Antabuse® (antiabuse) this medication was quickly approved for clinical practice and is still widely used today as an aid to remain sober. This sulfur-containing drug works by blocking the activity of the liver enzyme ALDH that converts acetaldehyde to acetate. If a patient taking the medication should also drink alcohol, this would result in an accumulation of acetaldehyde in the bloodstream. This in turn triggers a range of unpleasant reactions, such as cutaneous flushing of the face and upper arms, palpitations, headache, hypotension, tachycardia, and breathing difficulties [496].

Treatment with Antabuse® is known as aversion therapy because it is intended to scare the patient from continuing to drink alcohol, owing to an otherwise unpleasant reaction [242]. To enhance compliance with this type of drug treatment, subcutaneous implants of antabuse tablets were developed but their effectiveness was called into question in controlled trials. Patients receiving this treatment did not develop higher concentration of acetaldehyde in blood compared with a placebo implant when both groups were challenged with a moderate dose of alcohol [495].

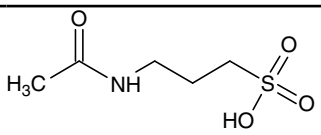
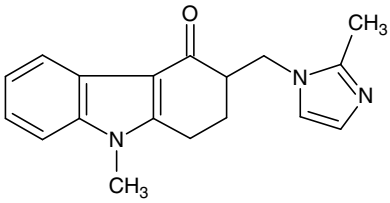
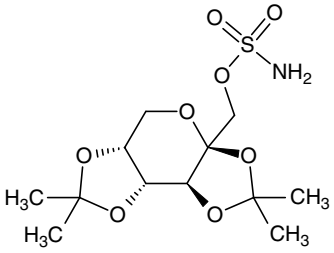
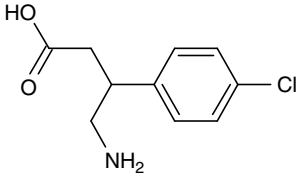
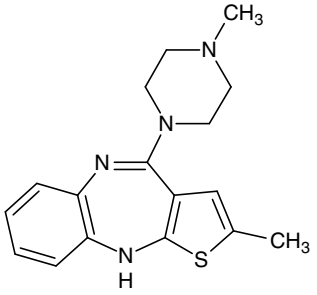
During the withdrawal phase after a period of chronic heavy drinking, people become anxious and restless and in extreme cases suffer from delirium and life-threatening epileptic seizures [497, 498]. To counteract these withdrawal signs, patients are given benzodiazepines, such as diazepam or lorazepam, during the initial stages of detoxification (first day or two). These drugs are sometimes referred to as “dry alcohol” indicating similarity in their mode of action in the brain with ethanol. Note that benzodiazepines are themselves dependence producing so care is needed not to replace one addictive drug (alcohol) with another (diazepam). If seizures

Table 13.9 Examples of drugs used in the treatment of alcohol dependence or during withdrawal to prevent relapse along with the chemical name, trade name, structural formulae, and mechanism of action

Drug (trade name)	Chemical structure	Mechanism of action
Disulfiram (Antabuse®)		Inhibitor of low k_m aldehyde dehdyrogenase blocking metabolism of acetaldehyde and causing a range of unpleasant effects; facial flushing, nausea, headache, palpitations, low blood pressure, tachycardia, etc. Treatment with Antabuse® is known as aversion therapy intended to scare the patient from drinking alcohol [242–244, 495]
Lorazepam (Ativan®)		One of several benzodiazepines ($GABA_A$ agonist) used during the initial phase of detoxification to counteract potentially life-threatening withdrawal symptoms, including cramps, convulsions, and deliriums [452, 464, 466]
γ-hydroxybutyrate (sodium oxybate), Xyrem®		Sodium oxybate is the sodium salt of the recreational drug gamma hydroxybutyrate (GHB) a $GABA_B$ receptor agonist. GHB is useful during initial stages of withdrawal and also in long-term rehabilitation of patients as an anticraving drug [501–504]
Naltrexone (ReVia®)		An orally active μ-opioid receptor antagonist was found to reduce craving for alcohol during abstinence and relapse rate was decreased. This treatment is more effective when combined with a program of social and psychological counseling [505–511]

(continued)

Table 13.9 (continued)

Drug (trade name)	Chemical structure	Mechanism of action
Acamprosate (Campral®)		A specific antagonist of the excitatory neurotransmitter glutamate, acting via the N-methyl-D-aspartate (NMDA) receptor. Blocking the receptor reduces the intensity of craving for alcohol and patients remain abstinent for longer. A program of psychological intervention helps to improves outcome after this drug treatment [512–514]
Ondansetron (Zofran®)		This drug represents a newer serotonin ($5HT_3$) antagonist and allegedly helps to diminish the rewarding effects of drinking ethanol by blocking the dopamine receptor [515]
Topiramate (Topamax®)		Topiramate is a drug increasingly used during alcohol withdrawal and protracted abstinence. Originally developed as an anticonvulsant for treatment of epilepsy and works by opening GABA-activated chloride channels and also inhibits excitatory neurotransmission through kainate and AMPA receptors [516–520]
Baclofen (Lioresal®)		Baclofen was developed as a muscle relaxant and functions as an agonist at the $GABA_B$ receptor. Patients with alcohol-related liver cirrhosis remained abstinent for longer when they received this drug and fewer relapsed to drinking compared with a placebo treatment [521, 522]
Olanzapine (Zyprexa®)		This atypical antipsychotic drug is approved for treating various psychiatric disorders and has also been evaluated as pharmaco-therapy for alcohol dependence. The drug acts as an agonist at the $5\text{-}HT_2$ and D_2 receptors and is claimed to help people remain abstinent from alcohol [523, 524]

and hallucinations become pronounced during several days of withdrawal patients should be treated with phenytoin or haloperidol medication [497].

Gamma-hydroxybutyrate (GHB) is both an illicit recreational drug and in the form of its sodium salt (sodium oxybate) is a pharmaceutical product (Xyrem®) registered for treatment of narcolepsy with cataplexy [499, 500]. The mechanism of action of GHB is via the $GABA_B$ receptor and this drug has proven useful for treating patients during alcohol withdrawal [501]. However, care is necessary because GHB is itself subject to abuse hence its popularity as a recreational drug among young people worldwide [502]. As a sedative–hypnotic drug, GHB helps to alleviate the withdrawal symptoms and to minimize the risk of relapse during protracted abstinence. When GHB is used for treatment of alcohol dependence, finding the optimal dose for effective therapy and close medical supervision are necessary, because GHB is also an abused drug [503, 504].

A more recent pharmacological treatment for alcohol abuse is the opiate antagonist naltrexone (ReVia®) [505–511]. This pure μ-opioid antagonist is orally active and helps to block feelings of reward and the desire to continue drinking weeks or months after the last drink. Opioid peptides stimulate dopamine release in the brain thus blocking these receptors would seem effective in eliminating some of the reinforcing effects of alcohol intoxication [506, 507]. However, a number of randomized controlled studies aimed at evaluating the effectiveness of naltrexone have yielded conflicting results. It seems that besides drug therapy there is also a need for psychological counseling and other types of social intervention, without which the effectiveness is less convincing [508–511].

Another fairly new pharmacotherapy for alcohol dependence, also registered by the FDA, is the drug acamprosate (calcium acetylhomotaurinate) registered in Europe as Campral® [512]. This treatment has proven more effective than placebo in delaying the time for relapse in abstinent alcoholics [513]. The drug works via several mechanisms affecting multiple neurotransmitters systems including antagonism of excitatory amino acids and reduction of calcium ion fluxes [514]. The drug is intended to treat alcoholics by helping them to maintain abstinence by reducing the craving and reward associated with alcohol consumption [514].

Ondansetron (Zofran®) blocks the serotonergic $5HT_3$ receptor and has been tested as a pharmacological treatment for alcohol dependence and withdrawal [515]. Taking this drug seems to regulate the release of dopamine into the nucleus accumbens thereby lowering the lust to continue drinking. In a placebo-controlled trial with mildly alcohol-dependent male outpatients, ondansetron helped to reduce alcohol consumption [515]. The anticonvulsant topiramate (Topamax®), which is both a GABA and glutamate receptor agonist, has attracted interest as pharmacotherapy for alcoholism [516, 517]. Treatment with this drug was shown to decrease the urge to drink in abstinent alcoholics and also improved the quality of life [518–520].

Baclofen was developed primarily as a muscle relaxant and anticonvulsant and also works as an agonist of the $GABA_B$ receptor complex via a second messenger. Treatment with this drug was found to attenuate the desire for drinking alcohol in animal models and has also shown promise in a number of randomized placebo-controlled human trials in patients with liver cirrhosis [521, 522]. Another drug

currently being tested for use in alcohol withdrawal is the antipsychotic drug olanzapine, which is said to reduce the urge to drink in abstinent alcoholics [523, 524].

Many other drug treatments have been investigated for their potential use as pharmacological aids including lithium, the drug of choice for treating bipolar disorder [525]. Selective serotonin reuptake inhibitors (SSRIs) as well as antipsychotics, such as the dopamine antagonist haloperidol have been considered for use as pharmacotherapy for alcohol abuse [492].

Sobering-Up Drugs

Sobering-up drugs are known as amethystic agents, derived from the Greek word "amethystos" meaning a remedy against drunkenness [526]. Two types of sobering-up drugs can be distinguished depending on pharmacokinetic or pharmacodynamic mechanism of action. The first type of treatment is aimed at accelerating the rate of elimination of alcohol from blood and thereby shortening the time necessary for BAC to drop below a threshold concentration, such as the legal blood–alcohol limit for driving [526, 527]. Another type of treatment might alleviate the impairment or incapacitating effects of alcohol in a similar fashion to naloxone, which is the drug of choice for reversing the effects of heroin or opiate overdose [26, 528].

An OTC sobering-up pill is likely to find a market among people who drive after drinking and would want to hasten the decrease in their BAC below some critical threshold, e.g., the legal alcohol limit for driving [529]. Accelerating the rate of elimination of alcohol from blood might also be useful in emergency clinics when patients undergo detoxification before starting any medical intervention or rehabilitation. The ideal sobering-up agent should (a) antagonize ethanol without itself altering physiology or behavior; (b) have no adverse or toxic effects; (c) have a rapid onset of action lasting long enough to eliminate ethanol from the body; (d) and not have any dependence producing properties [529].

Carbohydrates such as sucrose, glucose, and fructose have been extensively studied as to their ability to increase the rate of ethanol clearance from the bloodstream [530]. In some countries, small packets of fructose were made available at pubs and bars as a sobering remedy but their effectiveness has not been verified in proper controlled human studies [531]. Along the same lines, interest exists in developing a "hangover pill" that would alleviate unpleasant effects of an evening's heavy drinking and the resulting alcohol hangover [532]. However, the signs and symptoms of hangover show large inter- and intrasubject variation in intensity and duration and dose–response relationships have not been established. The mechanism behind the alcohol-induced hangover has not been established and few controlled studies exist because this is not seen as a medical problem in need of a treatment. Administration of fructose did not relieve the hangover symptoms in one controlled study [533]. Giving people a mixture of vitamins or salts to correct the water and electrolyte imbalance resulting from an evening's heavy drinking might have some benefit but no controlled studies have been published [534, 535].

Experiments designed to test the effectiveness of sobering-up agents should be done double blind and use a cross-over design so that within-subject comparison can be made. When the effect of fructose was tested, a large dose of this sugar together with ethanol delayed stomach emptying causing a retarded absorption of alcohol and a much lower C_{max} and a later occurring t_{max} [536]. A better designed study would require giving the fructose treatment after the absorption and distribution of ethanol is complete, that is in the postabsorptive declining stage of the BAC curve [114, 537]. Moreover, large doses of hypertonic sugar solutions exert an osmotic effect, thereby slowing intestinal absorption by retaining water and ethanol in the gastrointestinal tract for longer periods [538]. Great care is needed not to confuse the influences of the sugars on the absorption rate of ethanol as opposed to increasing the rate of oxidative metabolism [114, 537–539].

The mechanism of the fructose effect in increasing the rate of ethanol metabolism was suggested to involve a more effective re-oxidation of reduced coenzyme NADH back to NAD^+ which represented the slowest step in the ADH catalyzed enzymatic oxidation of ethanol [540]. However, in healthy well-nourished individuals administration of fructose failed to boost the elimination rate of ethanol from blood above rates normally observed, such as a range from 0.01 to 0.025 g% per h. In contrast, when subjects had fasted overnight (10 h) or were malnourished the treatment with fructose did increase the rate of metabolism by 25–100% compared with a placebo treatment [541]. Large doses of fructose tended to cause upper abdominal pains, nausea, and diarrhea and might also result in lactic acidosis and hyperuricemia, owing to metabolic shifts in the hepatic redox state of the liver [542].

The notion of finding a drug that abolishes the narcotic effects of ethanol without necessarily altering the rate of metabolism has also received some attention. However, an effective alcohol antagonist is not likely to be discovered because ethanol molecules penetrate all regions of the brain interfering with multiple neurotransmitter systems. Most attention has been given to drugs that interact with the receptor for the major inhibitory neurotransmitter GABA, especially the $GABA_A$ subtype. One substance that showed some initial promise in animal studies was a benzodiazepine antagonist denoted RO 15–4513 [543]. In rats immobilized by a large acute dose of ethanol, injecting the drug RO 15–4513 caused faster recovery times compared with placebo treatment [543]. Also the $GABA_B$ receptor antagonist phaclofen was able to modify some of the behavioral effects of ethanol, at least for a short time after administration [544].

Miscellaneous Substances

Literally hundreds of publications can be found that deal with the effects of coadministration of certain drugs together with a moderate dose of ethanol. A bibliography of early studies appeared in 1970 and this listed a plethora of substances and pharmacological treatments [545]. Inert substances such as sodium chloride [546],

oxygenated water [547], the artificial sweetener xylitol [548], vitamin mixtures [549, 550], ascorbic acid [551, 552], hormones and peptides [553], as well as various herbal medicines [554–556] have all been investigated without any effects. Central nervous stimulants exemplified by caffeine from coffee and tea [557, 558], nicotine from smoking tobacco [559], illicit stimulants such as methamphetamine [560] and cocaine (see section "Cocaethylene") have also been tested for interaction with ethanol.

Drugs that act on the CNS, such as antihistamines [561] and antidepressants including SSRI, have all been investigated in acute dosing studies for their potential interaction with alcohol [562]. Many drugs were tested without any prior theoretical basis that such an effect was feasible [563–568]. The marginal effects reported in some studies can be ascribed to the limited number of test subjects or some other aspects of the experimental design, such as demographics of the participants or their smoking, drinking, and dietary habits.

All-in-all, studies spanning back more than half a century, suggest that the co-administration of ethanol and other drugs is much more likely to alter the pharmacokinetics or pharmacodynamics of the drug rather than altering the disposition and fate of ethanol [569].

Concluding Remarks

Pharmacokinetic and pharmacodynamic interactions between ethanol and other drugs, whether licit and illicit, have become increasingly important in today's society because of the rise in polypharmacy, especially in elderly people [570–572]. Adverse drug–drug and drug–alcohol interactions are responsible for many acute poisonings requiring hospital admission for emergency treatment [573, 574]. Moreover, many drug-related fatalities have been documented involving alcohol and prescription drugs both accidental and self-poisoning in attempted suicide [575–577]. Blood samples taken at autopsy in drug-related poisoning deaths show a predominance of alcohol and other CNS depressants [8, 575]. Overconsumption of alcohol is a major public health problem worldwide and alcohol abuse is incriminated in many drug-related suicides [578].

Clear warnings from the physician and pharmacist are needed to minimize risks for adverse drug–alcohol interactions and some drugs should not be prescribed to people with an alcohol or substance abuse disorder [579]. A recent study reported a spike in fatal medication errors at the beginning of each month and this coincided with the time when many people received their government payment checks [580]. The implication being that it was at this time that the individuals increased their purchase of alcohol and prescription medication and that the cause of death was often related to substance abuse [581].

An adverse drug reaction has been defined in the following way [11].

> An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medical product, which predicts hazard from future administration and

warrants prevention or specific treatment, or alteration of the dosage regime or withdrawal of the product.

The more drugs a person combines the greater the risk for negative effects and risk of a drug-related fatality. Geriatric patients are especially susceptible to drug–drug interactions, not only because of polypharmacy in this population, but also because of the physiological changes that occur during aging. These changes include lowered metabolic rate and lean body mass, less total body water, excess fat, decreased cardiac output, altered liver mass and hepatic blood flow, and impaired kidney functioning [41]. These changes impact on the ADME of many drugs, which must be considered when medication is being prescribed. Inappropriate medications and adverse drug reactions in the elderly account for many hospital admissions and drug-related poisoning deaths [575–577]. Adverse drug reactions can arise from several mechanisms including idiosyncratic reactions, which are unpredictable reactions that have resulted in unexpected fatalities, often via active metabolites or immune response [582–584].

Some OTC drugs as well as prescription medications contain alcohol as one of the ingredients [585]. For example, many cough syrups (e.g., Nyquil is ~25% v/v ethanol) and the opiate antitussive medication ethylmorphine are dispensed mixed with ethanol (10% v/v). Also many mouth washes, vitamin tonics, and pick-me-ups are available and these contain 10–20% v/v ethanol, so like any alcoholic beverage, drinking these in excess can certainly raise a person's BAC [586].

Deaths from overdosing with alcohol and a barbiturate are classic in the annals of toxicology and among the poisons used for suicidal intent, barbiturates and carbon monoxide were predominant [587]. The barbiturates were clinically used as hypnotics and anticonvulsants making them particularly dangerous to use together with ethanol, which is also a CNS depressant. Combining two or more drugs with a similar mechanism of action obviously heightens the risk of an additive or synergistic effect [588]. In medical examiner cases, it is very common to find examples of deaths with no pathological causes but multiple therapeutic drugs detected in autopsy blood samples, albeit at therapeutic concentrations. Inadvertent dosing intervals with multiple drugs might lead to an unexpected respiratory depression and circulatory collapse and this deserves consideration when a cause of death is assigned [589].

The drugs most commonly identified in blood samples sent for analysis to a National Forensic Laboratory and representing medical examiner cases (autopsy) and drug-impaired drivers are shown in Table 13.10. One finds that in autopsy cases it is mostly prescription drugs that are identified whereas in impaired drivers illicit recreational drugs dominate: cocaine, amphetamine, and cannabis [590]. The legal drug alcohol was at the top of both lists, which underscores the importance of drug–alcohol interactions in modern society. The drugs identified in the medical examiner cases do not necessarily represent drug-poisoning deaths but instead they show the frequency of use and abuse of pharmaceutical agents throughout the country [589]. Moreover, diazepam (rank 4) has a very long elimination half-life (20–50 h), which means that it might be detected along with its metabolite (nordiazepam) for up to a week after last use [459].

Table 13.10 Examples of drugs most frequently identified in blood samples from impaired drivers and medical examiner cases (autopsy) in Sweden. Note that several different drugs were identified in many blood specimens including ethanol

Rank	Autopsy cases ($N=20{,}000$)[a]	Characteristic of the drug or medication	Rank	Impaired drivers ($N=7{,}052$)[b]	Characteristic of the drug or medication
1	Ethanol	Alcoholic beverages (social drug)	1	Ethanol	Alcoholic beverages (social drug)
2	Acetaminophen	Analgesic/antipyretic over-the-counter drug	2	Amphetamine	Illicit drug, central nervous system stimulant
3	Citalopram	SSRI antidepressant	3	THC[c]	Illicit drug, THC active constituent in cannabis and marijuana
4	Diazepam and nordiazepam	Anxiolytic, muscle relaxant + its desmethyl metabolite	4	Diazepam and nordiazepam	Anxiolytic, muscle relaxant + its desmethyl metabolite
5	Zopiclone	Fast acting hypnotic and sleeping aid	5	Alprazolam	Benzodiazepine anxiolytic for panic disorder
6	Morphine[d]	Strong analgesic	6	Morphine[d]	Strong analgesic
7	Codeine[d]	Analgesic/antitussive	7	Methamphetamine	Illicit drug central nervous system stimulant
8	Tramadol	Opioid analgesic	8	Codeine[d]	Analgesic/antitussive
9	Alimemazine	Antihistamine, sedative	9	Acetaminophen	Analgesic/antipyretic
10	Propoxyphene	Centrally acting analgesic	10	MDMA/Ecstasy	Illicit drug central nervous system stimulant
11	Mirtazapine	Antidepressant, antipsychotic	11	Flunitrazepam + 7-amino derivative	Benzodiazepine hypnotic and its primary metabolite
12	Carbamazepine	Anticonvulsant	12	Clonazepam	Benzodiazepine hypnotic
13	Amphetamine	Illicit central nervous stimulant	13	Nitrazepam	Benzodiazepine hypnotic
14	Sertraline	SSRI antidepressant	14	Zolpidem	Fast acting hypnotic and sleeping aid
15	THC[c]	Illicit drug active constituent of cannabis and marijuana	15	Tramadol	Opioid analgesic

[a]Femoral venous blood
[b]Cubital venous blood
[c]THC = tetrahydrocannabinol active metabolite of cannabis or marihuana
[d]Metabolite of heroin

The dangerousness of drugs, including ethanol, depends largely on the dose administered, the route of administration, development of tolerance, and the concentrations reaching brain receptors [591]. The latter cannot be measured directly so the concentrations in blood or plasma are used as surrogates [592]. Susceptibility to abuse of drugs includes a strong genetic component and personality traits, peer-group pressures and age at first intoxication play a role for future events. Sensation seeking behavior of the individual observed during adolescence is another risk factor for abuse of alcohol and/or drugs in later life [593–595].

Racial and ethnic differences in phase I drug metabolizing enzymes, especially polymorphic CYP2D6, CYP2C9, and CYP2C19 might account for adverse drug effects [596–599]. The particular genotype a person inherits can also explain much of the variability in plasma concentrations after a standard dose of the drug. Polymorphism in the major P450 enzymes has clinical consequences and after chronic dosing has sometimes caused drug-related toxicity and death [600–603].

The subject of pharmacogenetics of drug action and interaction has emerged as a hot research topic and the notion of manufacturing tailor-made drugs based on genetic profiling of the individual seems a future possibility [604–606]. If this becomes a reality adverse effects of drugs and undesirable drug–alcohol interactions might be reduced considerably [33, 607–609]. The alcohol-flush reaction in many Asians when they drink alcohol is a pharmacogenetic trait because they have an inactive form of the enzyme ALDH and they are protected from becoming heavy drinkers [37, 178, 610].

Much of the variability in pharmacokinetics of ethanol and other drugs can be explained by a combination of genetic and environmental factors [177, 611, 612]. Ethnic differences are particularly important when it comes to the metabolism of ethanol and acetaldehyde because many Asians inherit a defective ALDH enzyme, which renders them hypersensitive to alcohol compared with Caucasians or African Americans [608, 613–616].

Notwithstanding the many factors discussed above, the experimental design is a very important aspect of drug–alcohol interactions including route and timing of administration of ethanol relative to the test drug, the selection and allotment of subjects to the various treatments, washout times between treatments, and previous use of the drug and ethanol might influence the outcome of the study. More work is needed to investigate variability in alcohol–drug interactions under real-world situations with repeated intake of different kinds of alcoholic beverages without reference to body weight or previous exposure to drugs.

Confusion and controversy sometimes exist about the clinical or forensic significance of drug–alcohol interactions. Experiments in animals are mostly not very helpful in elucidating the problem and many of the older human studies purporting to find a significant interaction have not always withstood careful scrutiny. In many studies of drug–alcohol interactions, the volunteers are often young healthy males and not hospital patients or people suffering from the ailment or condition that the drug or medication is intended to treat.

A recent paper reported an investigation into the risk of an adverse drug–alcohol interaction for a new medication (mirodenafil) intended for treatment of erectile

dysfunction [617]. This drug works by inhibiting phosphodiesterase type 5 (PDE-5) and was tested in a single-dose, randomized-sequence, open-label, cross-over study in healthy male volunteers. Because people often consume alcohol before sex, the pharmaceutical company was aware and concerned about possible negative hemodynamic effects of this drug combination. The results showed that concurrent administration of mirodenafil and alcohol was not associated with any clinically significant hemodynamic changes in healthy male volunteers from Korea. Neither was there any pharmacokinetic interactions observed between these two substances [617].

Pharmaceutical companies are well aware of the potential problems if their candidate drug undergoes an adverse interaction with ethanol. Accordingly, drug–alcohol interaction studies are always included in clinical trials when new pharmaceutical products are evaluated. The results of such studies and the resulting publications in peer-reviewed journals are important to include among the masses of paperwork and other documentation submitted to the US Food and Drug Administration (FDA) or equivalent registering authorities in other countries before a new pharmaceutical product is approved for marketing.

References

1. Conti A and Bickel MH. History of drug metabolism Discoveries of the major pathways of the 19th century. Drug Metab Rev 6:1–50 (1977).
2. Bachmann C and Bickel MH. History of drug metabolism: the first half of the 20th century. Drug Metab Rev 16:185–253 (1985).
3. Williams RT. Detoxication mechanisms. London, Chapman & Hall Ltd, (1959).
4. Anstie FE. On the physiological and therapeutic action of alcohol. Lancet 343–5 (1865).
5. Anstie FE. Final experiments on the elimination of alcohol from the body. The Practitioner 13:15–28 (1874).
6. Neubauer, O. Uber Glukuronsaure paarung bei Stoffen der Fettreihe. *Arch Exp Pathol Pharmacol,* 46, 133 (1901).
7. Launiainen T, Vuori E and Ojanpera I. Prevalence of adverse drug combinations in a large post-mortem toxicology database. Int J Legal Med 123:109–115 (2009).
8. Carson HJ. Classes of drugs and their prevalence in multiple drug intoxication in suicides and accidents. Leg Med 10:92–95 (2008).
9. Koski A, Ojanperä I and Vuori E. Interaction of alcohol and drugs in fatal poisonings. Hum Exp Toxicol 22:281–287 (2003).
10. Koski A, Vuori E and Ojanperä I. Relation of postmortem blood alcohol and drug concentrations in fatal poisonings involving amitriptyline, propoxyphene and promazine. Hum Exp Toxicol 24:389–396 (2005).
11. Edwards IR and Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet 356:1255–1259 (2000).
12. Phillips DP, Barker GE and Eguchi MM. A steep increase in domestic fatal medication errors with use of alcohol and/or street drugs. Arch Intern Med 168:1561–1566 (2008).
13. Hickman M, Carrivick S, Paterson S, Hunt N, Zador D, Cusick L and Henry J. London audit of drug-related overdose deaths: characteristics and typology, and implications for prevention and monitoring. Addiction 102:317–323 (2007).
14. Roche AM, Watt K, McClure R, Purdi DM and Green D. Injury and alcohol: a hospital emergency department study. Drug Alc Rev 20:155–166 (2001).

15. Rivara FP, Mueller BA, Somes G, Menoza CT, Rushforth NB and Kellermann AL. Alcohol and illicit drug abuse and the risk of violent death in the home. JAMA 278:569–575 (1997).
16. Gibbons B. Alcohol – the legal drug. Nat Geographic 181:3–35 (1992).
17. Fell JC, Fisher DA, Voas RB, Blackman K and Tippetts AS. The impact of underage drinking laws on alcohol-related fatal crashes of young drivers. Alcohol Clin Exp Res 33:1–12 (2009).
18. Pirmohamed, M, James S, Meakin S and Green C, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329:15–19 (2004).
19. Juntti-Patinen L, Kuitunen T, Pere P and Neuvonen PJ. Drug-related visits to a district hospital emergency room. Basic Clin Pharmacol Toxicol 98:212–217 (2006).
20. Hall AJ, Logan JE, Toblin RL and Kaplan JA, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA 300:2613–2620 (2008).
21. Movig KL, Mathijssen MP, Nagel PH, and van Egmond T et al. Psychoactive substance use and the risk of motor vehicle accidents. Accid Anal Prev 36:631–636 (2004).
22. Jones AW, Kugelberg FC, Holmgren A and Ahlner J. Five-year update on the occurrence of alcohol and other drugs in blood samples from drivers killed in road-traffic crashes in Sweden. Forensic Sci Int 186:56–62 (2009).
23. Gonzalez-Wilhelm L. Prevalence of alcohol and illicit drugs in blood specimens from drivers involved in traffic law offences. Systematic review of cross-sectional studies. Traffic Inj Prev 8:189–98 (2007).
24. Ropero-Miller JD and Goldberger BA. Recreational drugs – current trends in the 90s. Clin Lab Med 18:727–746 (1998).
25. Britt GC and McCance-Katz EF. A brief overview of the clinical pharmacology of club drugs. Substance Use & Misuse 40:1189–1201 (2005).
26. Ricaurte GA and McCann UD. Recognition and management of complications of new recreational drug use. Lancet 365:2137–45 (2005).
27. Jones AW and Holmgren A. Age and gender differences in blood-alcohol concentration in apprehended drivers in relation to the amounts of alcohol consumed. Forensic Sci Int 188: 40–45 (2009).
28. Griffin JP. Drug interactions occurring during absorption from the gastrointestinal tract. Pharmacol Ther 15:79–88 (1981).
29. Baillie TA. Metabolism and toxicity of drugs. Two decades of progress in industrial drug metabolism. Chem Res Toxicol 21:129–37 (2008).
30. Ito K, Iwatsubo T, Kanamitsu S, Ueda K, Suzuki H and Sugiyama Y. Prediction of pharmacokinetic alterations caused by drug-drug interactions: Metabolic interactions in the liver. Pharmacol Rev 50:335–492 (1998).
31. Hines RN. The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Ther 118:250–67 (2008).
32. Offerhaus L. Drug interactions at excretory mechanisms. Pharmacol Ther 15:69–78 (1981).
33. Gardiner SJ and Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. Pharmacol Rev 58:521–90 (2006).
34. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 352:2211–21 (2005).
35. Eichelbaum M, Ingelman-Sundberg M and Evans WE. Pharmacogenomics and individualized drug therapy. Annu Rev Med 57:119–37 (2006).
36. Roberts DM and Buckley NA. Pharmacokinetic considerations in clinical toxicology: clinical applications. Clin Pharmacokinet 46:897–939 (2007).
37. Navarro VJ and Senior JR. Drug-related hepatotoxicity. N Engl J Med 354:731–9 (2006).
38. Senior JR. Monitoring for hepatoxicity: What is the predictive value of liver function tests. Clin Pharmacol Therap 85:331–334 (2009).
39. Schlatter C, Egger SS, Tchambaz L and Krähenbühl S. Pharmacokinetic changes of psychotropic drugs in patients with liver disease: implications for dose adaptation. Drug Saf 32: 561–78 (2009).
40. Mallet L, Spinewine A and Huang A. The challenge of managing drug interactions in elderly people. Lancet 370:185–191 (2007).

41. Herrlinger C and Klotz U. Drug metabolism and drug interactions in the elderly. Best Pract Res Clin Gastroenterol 15:897–918 (2001).
42. Shi S, Morike K and Klotz U. The clinical implications of ageing for rational drug therapy. Eur J Clin Pharmacol 64:183–99 (2008).
43. Klotz U. The elderly-a challenge for appropriate drug treatment. Eur J Clin Pharmacol 64: 225–226 (2008).
44. Koob GF. A role of GABA in alcohol dependence. Adv Pharmacol 54:205–229 (2006).
45. Cruz MT, Bajo M, Schweitzer P and Roberto M. Shared mechanisms of alcohol and other drugs. Alc Res Health 31:137–147 (2009).
46. Clapp P, Bhave SV and Hoffman PL. How adaptation of the brain to alcohol leads to dependence. Alc Res Health 31:310–339 (2009).
47. Krystal JH, Petrakis IL and Mason G. et al. N-methyl-D-aspartate glutamate receptors and alcoholism: reward, dependence, treatment and vulnerability. Pharmac Therap 99:79–94 (2003).
48. Spanagel R and Heilig M. Addiction and its brain science. Addiction 100:1813–22 (2005).
49. Kalant H, LeBlanc SE and Gibbins RJ. Tolerance to and dependence on some non-opiate psychotropic drugs. Pharmacol Rev 23:135–191 (1971).
50. Chesher G and Greeley J. Tolerance to the effects of alcohol. Alc Drugs Driving 8:93–106 (1992).
51. Brick J and Erickson CK. Intoxication is not always visible: An unrecognized prevention challenge. Alcohol Clin Exp Res 33:1–19 (2009).
52. Coleman MD. Human drug metabolism – an introduction. John Wiley & Sons, Chichester, (2005).
53. Shenton JM, Chen J and Uetrecht JP. Animal models of idiosyncratic drug reactions. Chem Biol Interact 150:53–70 (2004).
54. Li AP. Preclinical evaluation of drug-drug interactions using human in vitro experimental systems. IDrugs 1:311–314 (1998).
55. Li AP. Human-based in vitro experimental systems for the evaluation of human drug safety. Curr Drug Saf 2:193–9 (2007).
56. Forney RB and Hughes FW. Combined effects of alcohol and other drugs. Charles C. Thomas Publisher, Springfield (1968).
57. Pirola RC. Drug metabolism and alcohol. University Park Press, Baltimore (1978).
58. Milner G. Drugs and driving. S. Karger, Basel (1972).
59. Mattila MJ . Alcohol, drugs and driving. S Karger, Basel (1976).
60. Kuitunen T. Drug and ethanol effects on the clinical test for drunkenness: single doses of ethanol, hypnotic drugs and antidepressant drugs. Pharmacol Toxicol 75:91–98 (1994).
61. Mattila MJ, Kuitunen T and Plétan Y. Lack of pharmacodynamic and pharmacokinetic interactions of the antihistamine ebastine with ethanol in healthy subjects. Eur J Clin Pharmacol 43:179–184 (1992).
62. Kuitunen T, Mattila MJ, Seppälä T, Aranko K and Mattila ME. Actions of zopiclone and carbamazepine, alone and in combination, on human skilled performance in laboratory and clinical tests. Br J Clin Pharmacol 30:453–461 (1990).
63. Kuitunen T, Mattila MJ and Seppala T. Actions and interactions of hypnotics on human performance: single doses of zopiclone, triazolam and alcohol. Int Clin Psychopharmacol 5(2):115–130 (1990).
64. Mattila M, Mattila MJ, Vrijmoed-de Vries M and Kuitunen T. Actions and interactions of psychotropic drugs on human performance and mood: single doses of ORG 3770, amitriptyline, and diazepam. Pharmacol Toxicol 65:81–8 (1989).
65. Lane EA, Guthrie S and Linnoila M. Effects of ethanol on drug metabolite pharmacokinetics. Clin Pharmacokinet 10:228–247 (1985).
66. Fraser AG. Pharmacokinetic interactions between alcohol and other drugs. Clin Pharmacokinet 33:79–90 (1997).
67. Monroe ML and Doering PL. Effect of common over-the-counter medications on blood alcohol levels. Ann. Pharmacother 35:918–924 (2001).

68. Weathermon R and Crabb DW. Alcohol and medication interactions. Alc Res Health 23: 40–54 (1999).
69. Havier RG. The interaction of ethanol with drugs. Forensic Sci Rev 3:41–56 (1991).
70. Starmer GA and Bird KD. Investigating drug-alcohol interactions. Br J Clin Pharmacol 18:27S-35S (1984).
71. Kelly TH, Foltin RW, Emurian CS and Fischman MW. Performance-based testing for drugs of abuse: dose and time profiles of marijuana, amphetamine, alcohol and diazepam. J Anal Toxicol 17:264–272 (1993).
72. Irving A and Jones W. Methods for testing impairment of driving due to drugs. Eur J Clin Pharmacol 43:61–66 (1992).
73. Kelly M, Myrsten AL, Neri A and Rydberg U. Effects and after-effects of alcohol on psychological and physiological functions in man. Blutalkohol 7:422–436 (1970).
74. Parker RA. Studies should be controlled, randomized and blinded. Clin Pharmacol therap 85:461–463 (2009).
75. Boehmer J and Yong P. How well does blinding work in randomized controlled trials?: a counterpoint. Clin Pharmacol Ther 85:463–465 (2009).
76. Hróbjartsson A and Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med 256: 91–100 (2004).
77. Shapiro AK and Shapiro E. The powerful placebo. The Johns Hopkins University Press, Baltimore (1997).
78. Hrobjartsson A and Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 344:1594–1602 (2001).
79. Moskowitz H and Fiorentino D. A review of the scientific literature regarding the effects of alcohol on driving-related behavior at blood alcohol concentrations of 0.08 grams per deciliter and lower. US Department of Transportation, National Highway Traffic Safety Administration, Washington, (2000).
80. Kennedy RS, Turnage JJ, Wilkes RL and Dunlap WP. Effects of graded dosages of alcohol on nine computerized repeated-measures tests. Ergonomics 36:1195–1222 (1993).
81. Kunsman GW, Manno JE, Manno BR, Kunsman CM and Przekop MA. The use of microcomputer-based psychomotor tests for the evaluation of benzodiazepine effects on human performance: a review with emphasis on temazapine. Br J Clin Pharmacol 34:289–301 (1992).
82. Holmgren A, Holmgren P, Kugelberg FC, Jones AW and Ahlner J. Predominance of illicit drugs and poly-drug use among drug-impaired drivers in Sweden. Traffic Inj Prev 8;361–367 (2007).
83. Jones AW. Driving under the influence of drugs in Sweden with zero-concentration limits in blood for controlled substances. Traffic Inj Prev 5; 317–322 (2005).
84. Farrell LJ and Logan BK. The effects of drugs on human performance and behavior. Forensic Sci Rev 14:1–151 (2002).
85. Mezey E. Ethanol metabolism and ethanol-drug interactions. Biochem Pharmacol 25:869–874 (1976).
86. Linnoila M, Mattila MJ and Kitchell BS. Drug interactions with alcohol. Drugs 18:299–311 (1979).
87. Lieber CS. Interaction of alcohol with other drugs and nutrients: Implications for the therapy of alcoholic liver disease. Drugs 40: Suppl 3, 23–44 (1990).
88. Hoyumpa AM and Schenker S. Major drug interactions: Effect of liver disease, alcohol, and malnutrition. Ann Rev Med 33:113–149 (1982).
89. Mattila MJ. Alcohol and drug interactions. Ann Med 22:363–369 (1990).
90. Kalant H. Pharmacokinetics of ethanol: absorption, distribution, and elimination, In: Begleiter H, Kissin B eds. The Pharmacology of alcohol and alcohol dependence. Oxford University Press, Oxford & New York, 1996, pp 15–58.
91. Ramchandani VA, Bosron WF and Li T-K. Research advances in ethanol metabolism. Pathol Biol 49:676–682 (2001).

92. Widmark EMP. Principles and applications of medicolegal alcohol determination. Biomedical Publications, Davis, CA (1981).
93. Holt S. Observations on the relation between alcohol absorption and the rate of gastric emptying. Can Med Assoc J 124:267–277 (1981).
94. Winek CL, Wahba WW and Dowdell JL. Determination of absorption time of ethanol in social drinkers. Forensic Sci Int 77:169–177 (1996).
95. Jones AW, Jönsson KÅ and Neri A. Peak blood-ethanol concentration and the time of its occurrence after rapid drinking on an empty stomach. J Forensic Sci 36:376–385 (1991).
96. Berggren SM and Goldberg L. The absorption of ethyl alcohol from the gastrointestinal tract as a diffusion process. Acta Physiol Scand 1:245–270 (1940).
97. Jones AW. Biochemical and physiological research on the disposition and fate of ethanol in the body. Chapter 3 in Medicolegal Aspects of Alcohol, 5th edition, J.C. Garriott. Ed. Lawyers & Judges Publishing Co., Inc., Tucson, 2008, pp 47–156.
98. Yelland LN, Burns JP, Sims DN, Salter AB and White JM. Inter- and intra-subject variability in ethanol pharmacokinetic parameters. Effects of testing interval and dose. Forensic Sci Int. 175:65–72 (2008).
99. Lotterle J, Husslein EM, Bolt J and Wirtz PM. Tageszeitliche Unterschiede der Alkoholresorption. Blutalkohol 26:369–375 (1989).
100. Schwartz JG, Salman UA, McMahan CA and Phillips WT. Gastric emptying of beer in Mexican-Americans compared with non-Hispanic whites. Metabolism 45:1174–1178 (1996).
101. Roine RP, Gentry RT, Lim RT, Baraona E and Lieber CS. Effect of concentration of ingested ethanol on blood alcohol levels. Alcohol Clin Exp Res 15:734–738 (1991).
102. Roine RP, Gentry RT, Lim RT, Heikkonen E, Salaspuro M and Lieber CS. Comparison of blood alcohol concentration after beer and whiskey. Alcohol Clin Exp Res 17:709–711 (1993).
103. Welling PG. Effects of food on drug absorption. Ann Rev Nutr 16:383–415 (1996).
104. Welling PG. Pharmacokinetics of alcohol following single low doses to fasted and non-fasted subjects. J Clin Pharmacol 17:199–206 (1977).
105. Singh BN. Effects of food on clinical pharmacokinetics. Clin Pharmacokinet 37:213–255 (1999).
106. Sedman, A.J., Wilkinson, P.K., Sakmar, D.J., Weidler, D.J., Wagner, J.G. Food effects on absorption and metabolism of alcohol. J Stud Alcohol 37:1197–1214 (1976).
107. Pikaar NA, Wedel M and Heemus RJJ. Influence of several factors on blood alcohol concentrations after drinking alcohol. Alc Alcohol 23:289–297 (1988).
108. Cortot A, Jobin G, Ducrot F, Aymes C, Giraudeaux V and Modigliani R. Gastric emptying and gastrointestinal absorption of alcohol ingested with a meal. Dig Dis Sci 31:343–348 (1986).
109. Schultz J, Weiner H and Wetscott J. Retardation of ethanol absorption by food in the stomach. J Stud Alcohol 41:861–870 (1980).
110. Jones AW and Jönsson KÅ. Food-induced lowering of blood-ethanol profiles and increased rate of elimination immediately after a meal. J Forensic Sci 39:1084–1093 (1994).
111. Jones AW, Jönsson K-Å and Kechagias S. Effect of high-fat, high-protein and high-carbohydrate meals on the pharmacokinetics of a small dose of alcohol. Br J Clin Pharmacol 44: 521–526 (1997).
112. Ramchandani VA, Kwo PY and Li T-K. Effect of food and food composition on alcohol elimination rates in healthy men and women. J Clin Pharmacol 41:1345–1350 (2001).
113. McFarlane A, Pooley L, Welch IML, Rumsey RDE and Read NW. How does dietary lipid lower blood alcohol concentrations? Gut 27:15–18 (1986).
114. Rogers JO, Smith J, Starmer GA and Whitfield J. Differing effects of carbohydrate fat and protein on the rate of ethanol metabolism. Alc Alcohol 22:345–353 (1987).
115. O'Neill B, Williams AF and Dubowski KM. Variability in blood alcohol concentration: implications for estimating individual results. J Stud Alcohol 44:222–230 (1983).
116. Jones AW. Inter-individual variations in the disposition and metabolism of ethanol in healthy men. Alcohol 1:385–91 (1984).
117. Friel PN, Baer JS and Logan BK. Variability of ethanol absorption and breath concentrations during a large scale alcohol administration study. Alcohol Clin Exp Res 19:1055–1060 (1995).

118. Jones AW and Jönsson K-Å. Between subject and within subject variations in the pharmacokinetics of ethanol. Br J Clin Pharmacol 37:427–431 (1994).
119. Passananti GT, Wolff CA and Vesell ES. Reproducibility of individual rates of ethanol metabolism in fasting subjects. Clin Pharmacol Ther 47:389–396 (1990).
120. Jones AW and Neri A. (1985). Age-related changes in blood-alcohol parameters and subjective feelings of intoxication in healthy men. Alc Alcohol 20:45–52 (1985).
121. Hahn RG, Norberg Å and Jones AW. Over-shoot of ethanol in the blood after drinking on an empty stomach. Alc Alcohol 32:501–505 (1997).
122. Schvarcz E, Palmer M, Åman J and Berne C. Hypoglycemia increases the gastric emptying rate in healthy subjects. Diabet. Care 18:674–676 (1993).
123. Johnson RD, Horowitz M, Maddox AF, Wishart JM and Shearman DJC. Cigarette smoking and rate of gastric emptying - Effect on alcohol absorption. Br Med J 302:20–23 (1991).
124. Scott AM, Kellow JE, Shuter B, Nolan JM, Hoschl R and Jones MP. Effects of cigarette smoking on solid and liquid intragastric distribution and gastric emptying. Gastroenterology 104:410–416 (1993).
125. Klockhoff, H, Näslund I and Jones AW. Faster absorption of ethanol and higher peak concentration in women after gastric-bypass surgery. Br J Clin Pharmacol 54:587–591 (2002).
126. Bailey DN. Effect of coadministered drugs and ethanol on the binding of therapeutic drugs to human serum in-vitro. Ther Drug Monit 23:71–74 (2001).
127. Edelman IS and Leibman J. Anatomy of body water and electrolytes. Am. J. Med. 27:256–277 (1959).
128. Lucey MR, Hill E, Young JP, Demo-Dananberg L and Beresford TP. The influence of age and gender on blood ethanol concentrations in healthy humans. J. Stud. Alcohol 60:103–110 (1999).
129. Kwo PY, Ramchandani VA, O'Connor S, Amann D, Carr LG, Sandrasegaran K, Kopecky KK and Li T-K. Gender differences in alcohol metabolism: Relationship to liver volume and effect of adjusting for body mass. Gastroenterology 115:1552–1557 (1998).
130. Mumenthaler MS, Taylor JL and Yesavage JA. Ethanol pharmacokinetics in white women: Nonlinear model fitting versus zero-order elimination analysis. Alcohol. Clin. Exp. Res. 24:1353–1362 (2000).
131. Mumenthaler MS, O'Hara R, Taylor JL, Friedman L and Yesavage JA. Influence of menstrual cycle on flight simulator performance after alcohol ingestion. J. Stud. Alcohol 62:422–433 (2001).
132. Hobbes J, Boutagy J and Shenfield, GM. Interaction between ethanol and oral contraceptive steroids. Clin. Pharmacol. Therap. 38:157–163 (1987).
133. Marshall AW, Kingstone D, Boss M and Morgan MY. Ethanol elimination in males and females: Relationship to menstrual cycle and body composition. Hepatology 5:701–706. (1983).
134. Jones AW, Hahn RG and Stalberg H. Distribution of ethanol and water between plasma and whole blood: inter- and intra-individual variations after administration of ethanol by intravenous infusion. Scand. J. Clin. Invest. 50:775–780 (1990).
135. Iffland R, West A, Bilzer N and Schuff A. Zur Zuverlässigkeit der Blutalkoholbestimmung. Das Verteilungsverhältnis des Wassers zwischen Serum und Vollblut. Rechtsmedizin 9: 123–129 (1999).
136. Winek CL and Carlagna M. Comparison of plasma, serum and whole blood ethanol concentrations. J. Anal. Toxicol. 6:267–268 (1987).
137. Jones AW and Larsson H. Distribution of diazepam and nordiazepam between plasma and whole-blood and the influence of hematocrit. Ther Drug Monitor 26:380–385 (2004).
138. Wang MQ, Nicholson ME, Jones CS, Fitzhugh EC and Westerfield CR. Acute alcohol intoxication, body composition, and pharmacokinetics. Pharm. Biochem. Behav. 43:641–643 (1992).
139. McLean AJ and LeCouleur DG. Aging biology and geriatiric clinical pharmacology. Pharmocol. Rev. 56:163–184 (2004).
140. Endres HG and Gruner O. Comparison of D2O and ethanol dilutions in total body water measurements in humans. Clin. Investig. 72:830–837 (1994).

141. Jones AW, Hahn RG and Stalberg HP. Pharmacokinetics of ethanol in plasma and whole blood: Estimation of total body water by the dilution principle. Eur. J. Clin. Pharmacol. 42:445–448 (1992).
142. Chiou WL. The phenomenon and rationale of marked dependence of drug concentration on blood sampling site; implications in pharmacokinetics, pharmacodynamics, toxicology and therapeutics. Clin Pharmacokinet 17:175–199 (1989).
143. Martin E, Moll M and Schmid P. The pharmacokinetics of alcohol in human breath, venous and arterial blood after oral ingestion. Eur J Clin Pharmacol 26:619–626 (1984).
144. Jones AW, Norberg Å and Hahn RG. Concentration-time profiles of ethanol in arterial and venous blood and end-expired breath during and after intravenous infusion. J. Forensic Sci. 42:1088–1094 (1997).
145. Jones AW, Lindberg L and Olsson S-G. Magnitude and time-course of arterial-venous differences in blood-ethanol concentrations in healthy men. Clin Pharmacokinet 43:1157–1166 (2004).
146. Mather LE. Anatomical-physiological approaches in pharmacokinetics and pharmacodynamics. Clin. Pharmacokinet. 40:707–722 (2001).
147. Meibohm B, Beierle I and Derendorf H. How important are gender differences in pharmacokinetics? Clin. Pharmacokinet. 21:329–342 (2002).
148. Cheymol G. Effects of obesity on pharmacokinetics: Implications for drug therapy. Clin. Pharmacokinet 39:215–31 (2000).
149. Jones AW. Body mass index and blood-alcohol calculations. J Anal Toxicol 31:177–178 (2007).
150. Baraona E, Abittan CS, Dohmen K, Moretti M, Pozzato G, Chayes ZW, Schaefer C and Lieber CS. Gender differences in pharmacokinetics of alcohol. Alcohol Clin. Exp. Res. 25:502–507 (2001).
151. Baraona E, Gentry RT and Lieber CS. Bioavailability of alcohol: Role of gastric metabolism and its interaction with other drugs. Dig Dis 12:351–367 (1994).
152. Julkunen RJK, Dipadova C and Lieber CS. First pass metabolism of ethanol - A gastrointestinal barrier against the systemic toxicity of ethanol. Life Sci 37:567–573 (1985).
153. Frezza M, Dipadova C, Pozzato G, Terpin M, Baraona E and Lieber CS. High blood alcohol levels in women - The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med 322:95–99 (1990).
154. Wagner JG. Lack of first-pass metabolism of ethanol at blood concentrations in the social drinking range. Life Sci 39:407–414 (1986).
155. Levitt MD. The case against first-pass metabolism of ethanol in the stomach. J Lab Clin Med 123:28–31 (1994).
156. Levitt MD and Levitt DG. The critical role of the rate of ethanol absorption in the interpretation of studies purporting to demonstrate gastric metabolism of ethanol. J Pharmacol Exp Ther 269:297–304 (1994).
157. Levitt MD and Levitt DG. Appropriate use and misuse of blood concentration measurements to quantitate first-pass metabolism. J Lab Clin Med 136:275–280 (2000).
158. Jones AW. Excretion of alcohol in urine and diuresis in healthy men in relation to their age, the dose administered and the time after drinking. Forensic Sci Int 45:217–224 (1990).
159. Swift R. Direct measurement of alcohol and its metabolites. Addiction 98 Suppl 2:73–80 (2003).
160. Buono MJ. Sweat ethanol concentrations are highly correlated with co-existing blood values in humans. Exp Physiol 84:401–404 (1999).
161. Marques PR and McKnight AS. Field and laboratory alcohol detection with 2 types of transdermal devices. Alcohol Clin Exp Res 33:1–9 (2009).
162. Droenmer P, Schmitt G, Aderjan R and Zimmer H. A kinetic model describing the pharmacokinetics of ethyl glucuronide in humans. Forensic Sci. Int 126:24–29 (2002).
163. Seidl S, Wurst FM and Alt A. Ethyl glucuronide: a biological marker for recent alcohol consumption. Addic. Biol. 6:205–212 (2001).
164. Hoiseth G, Bernard JP and Karinen R. et al. A pharmacokinetic study of ethyl glucuronide in blood and urine: Applications to forensic toxicology. Forensic Sci Int 172:119–24 (2007).

165. Ehring T, Bosron WJ and Li T-K. Alcohol and aldehyde dehydrogenase. Alc. Alcohol. 25:105–116 (1990).
166. Lieber CS. Cytochrome P-4502E1: Its physiological and pathological role. Physiol Rev 77:517–544 (1997).
167. Suokas A, Forsander O and Lindros K. Distribution and utilization of alcohol-derived acetate in the rat. J Stud Alcohol 45:381–385 (1984).
168. Holford NGH. Clinical Pharmacokinetics of ethanol. Clin. Pharmacokinet. 13:273–292 (1987).
169. Wedel M, Pieters JE, Pikaar NA and Ockhuizen T. Application of a three-compartment model to a study of the effects of sex, alcohol dose and concentration, exercise and food consumption on the pharmacokinetics of ethanol in healthy volunteers. Alc Alcohol 26:329–336 (1991).
170. Norberg Å, Jones A W, Hahn RG and Gabrielsson J. Role of variability in explaining ethanol pharmacokinetics. Clin Pharmacokinet 42:1–31 (2002).
171. Lundquist F and Wolthers H. The kinetics of alcohol elimination in man. Acta Pharmacol Toxicol 14:265–289 (1958).
172. Wilkinson PK, Sedman AJ, Sakmar E, Kay DR and Wagner JG. Pharmacokinetics of ethanol after oral administration in the fasting state. J Pharmacokinet Biopharm 5:207–224 (1977).
173. Wagner JG Wilkinson PK and Games DA. Parameters of Vmax and km for elimination of alcohol in young male subjects following low doses of alcohol. Alc Alcohol 24:555–564 (1989).
174. Wilkinson PK. Pharmacokinetics of ethanol – A review. Alcohol Clin Exp Res 4:6–21 (1980).
175. Jones AW. Ultra-rapid rate of ethanol elimination from blood in drunken drivers with extremely high blood-alcohol concentration. Int J Legal Med 122:129–134 (2008).
176. Simic M and Tasic M. The relationship between alcohol elimination rate and increasing blood alcohol concentration – calculated from two consecutive blood specimens. Forensic Sci Int 172:28–32 (2007).
177. Li TK, Yin SJ, Crabb DW, O'Connor S and Ramchandani VA. Genetic and environmental influences on alcohol metabolism in humans. Alcohol Clin Exp Res 25:138–144 (2001).
178. Sladek NE. Human aldehyde dehydrogenases: potential pathological, pharmacological, and toxicological impact. J Biochem Mol Toxicol 17:7–23 (2003).
179. Pettersson G. Liver alcohol dehydrogenase. CRC Critical Rev. Biochem. 21:349–389 (1987).
180. Bonnichsen RK and Wassen A. Crystaline alcohol dehydrogenase from horse liver. Arch Biochem Biophys 18:361–363 (1948).
181. Bonnichsen RK and Theorell H. An enzymatic method for the micro-determination of ethanol. Scand J Clin lab Invest 3:58–62 (1951).
182. Peng GS, Yin SJ. Effect of the allelic variants of aldehyde dehydroogenase ALDH2*2 and alcohol dehydrogenase ADH1B*2 on blood acetaldehyde concentrations. Human Genomics 3:121–127 (2009).
183. Testa B and Kramer SD. The biochemistry of drug metabolism--an introduction: Part 2. Redox reactions and their enzymes. Chem Biodivers 4:257–405 (2007).
184. Eng MY, Luczak SE and Wall TL. ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review. Alcohol Res Health 30:22–27 (2007).
185. Jörnvall H and Höög JO. Nomenclature of alcohol dehydrogenase. Alc. Alcohol 30:153–161 (1995).
186. Wagner JG. Relationship between first-order and Michaelis-Menten kinetics. J Pharm Sci 78:521–522 (1989).
187. Pizon AF, Becker CE and Bikin D. The clinical significance of variations in ethanol toxicokinetics. J Med Tox 3:63–72 (2007).
188. Ostrovsky YM. Endogenous ethanol-its metabolic, behavioral and biomedical significance. Alcohol 3:239–247 (1986).
189. Logan BK and Jones AW. Endogenous ethanol "autobrewery syndrome" as a drunk driving defense challenge. Med Sci Law 40:206–215 (2000).

190. Dudley R. Fermenting fruit and the historical ecology of ethanol ingestion: is alcoholism in modern humans an evolutionary hangover? Addiction 97:381–388 (2002).
191. Zakhari S. Overview: how is alcohol metabolized by the body? Alcohol Res Health 29:245–254, (2006).
192. Theorell H and Bonnischsen RK. Studies on liver alcohol dehydrogenase 1 Equilibria and initial reaction velocities. Acta Chem Scand 5:1105–1126 (1951).
193. Theorell H and Yonetani T. Liver alcohol dehydrogenase-DPN-pyrazole complex – A model of a ternary intermediate in the enzyme reaction. Biochem Z 338:537–553 (1963).
194. Li TK and Theorell H. Human liver alcohol dehydrogenase inhibition by pyrazole and pyrazole analogs. Acta Chem Scand 23:892–902 (1969).
195. Blomstrand R, Ostling-Wintzell H, Lof A, McMartin K, Tolf BR and Hedstrom KG. Pyrazoles as inhibitors of alcohol oxidation and as important tools in alcohol research: an approach to therapy against methanol poisoning. Proc Natl Acad Sci 76:3499–3503 (1979).
196. Galliot M, Astier A, VuBien D and Garnier R et al. Treatment of ethylene glycol poisoning with intravenous 4-methyl pyrazole. N Engl J Med 319:97–100 (1988).
197. Jacobsen D and McMartin KE. Antidotes for methanol and ethylene glycol poisoning. J Toxicol Clin Tox 35:127–143 (1997).
198. Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Eng J Med 360: 2216–2223 (2009).
199. Jacobsen D and McMartin KE. Methanol and ethylene glycol poisonings mechanism of toxicity clinical course diagnosis and treatment. Med Toxicol 1:309–334 (1986).
200. Eder AF, McGrath CM, Dowdy YG, Tomaszewski JE and Rosenberg FM et al. Ethylene Glycol poisoning: toxicokinetics and analytical factors affecting laboratory diagnosis. Clin Chem 44:168–177 (1998).
201. Sarkola T and Eriksson CJP. Effect of 4-methyl pyrazole on endogenous plasma ethanol and methanol levels in humans. Alcohol Clin Exp Res 25:513–516 (2001).
202. Karlson-Stibler C and Persson H. Ethylene glycol poisoning: Experiences from an epidemic in Sweden. J Toxicol Clin Tox 30:565–574 (1992).
203. Mani JC, Pietruszko R and Theorell H. Methanol activity of alcohol dehydrogenase from human liver, horse liver and yeast. Arch Biochem Biophys 140:52–59 (1970).
204. Röe O. The metabolism and toxicity of methanol. Pharmacol Rev 7:399–412 (1955).
205. Majchrowicz E and Mendelson JH. Blood methanol concentrations during experimental induced ethanol intoxications in alcoholics. J Pharmacol Exp Ther 179:293–300 (1971).
206. Jones AW, Skaggerberg S, Yonekura A and Sato A. Metabolic interaction between endogenous methanol and endogenous ethanol studied in human volunteers by analysis of breath. Pharmacol Toxicol 65:48–53 (1990).
207. Jones AW and Sternebring B. Kinetics of ethanol and methanol in alcoholics during detoxication. Alc Alcohol 27:641–647 (1992).
208. Haffner H-T, Banger M, Graw M, Besserer K and Brink T. The kinetics of methanol elimination in alcoholics and the influence of ethanol. Forensic Sci Int 89:129–136 (1997).
209. Kaplan HL, Forney RB, Hughes FW and Jain NC. Chloral hydrate and alcohol metabolism in human subjects. J Forensic Sci 12:295–304 (1967).
210. Sellers EM, Lang M, Koch-Weser J, LeBlanc E and Kalant H. Interaction of chloral hydrate and ethanol in man. 1. Metabolism. Clin Pharmacol Ther13:37–49 (1972).
211. Heller PF, Goldberger BA and Caplan YH. Chloral hydrate overdose: trichloroethanol detection by gas chromatography-mass spectrometry. Forensic Sci Int 52:231–234 (1992).
212. Graham SR, Day RO, Lee R and Fulde GW. Overdose with choral hydrate. A pharmacological and therapeutic review. Med J Aust 149:686–8 (1988).
213. Inciardi JA. The changing life of Mickey Finn: some notes on chloral hydrate down through the ages. J Pop Cul 11:591–6 (1977).
214. Baum CR. A century of Mickey Finn – but who was he? J Toxicol Clin Toxicol 38:683 (2000).
215. Zvosec DL, Smith SW, McCutcheon JR, Spillane J, Hall BJ and Peacock EA. Adverse events, including death, associated with the use of 1,4-butanediol. N Engl J Med 344:87–94 (2002).

216. Jones C. Suspicious death related to gamma-hydroxybutyrate (GHB) toxicity. J Clin Forensic Med 8:74–76 (2001).
217. Caldicott DG, Chow FY and Burns BJ et al. Fatalities associated with the use of gamma-hydroxybutyrate and its analogues in Australasia. Med J Aust 181:310–313 (2004).
218. Wojtowicz JM, Yarema MC and Wax PM. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. CJEM 10:69–74 (2008).
219. Lora-Tamayo C, Tena T, Rodriguez A, Sancho JR and Molina E. Intoxication due to 1,4-butanediol. Forensic Sci int 133:256–259 (2003).
220. Nicholson KL and Balster RL. GHB: a new and novel drug of abuse. Drug Alc Dep 63:1–22 (2001).
221. Thai D, Dyer JE, Jacob P and Haller CA. Clincial pharmacology of 1,4-butanediol and gamma-hydroxybutyrate after oral 1,4-butanediol administration to healthy volunteers. Clin Pharmacol Therap 81:178–184 (2007).
222. Thai D, Dyer JE, Benowitz NL and Haller CA. Gamma-hydroxybutyrate and ethanol effects and interactions in humans. J Clin Pharmacol 26:524–529 (2006).
223. Lora-Tamayo C, Tena T and Rodriguez A, et al. Intoxication due to 1,4-butanediol. Forensic Sci int 133:256–259 (2003).
224. Wartburg JP and Bühler R. Biology of disease – alcoholism and aldehydism: new biomedical concepts. Lab Invest 50:5–15 (1984).
225. Myers RD. Tetrahydroisoquinolines and alcoholism: where are we today? Alcohol Clin Exp Res 20:498–500 (1996).
226. Crabb DW, Edenberg HJ, Bosron WH and Li T-K. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. J Clin Invest 83:314–316 (1989).
227. Eriksson CJP. The role of acetaldehyde in the actions of alcohol (update 2000). Alcohol Clin Exp Res 25:15S-32S (2001).
228. Mizoi Y, Tatsuno T, Adachi J, Kogame M, Fukunaga T and Fujiwara S et al. Alcohol sensitivity related to polymorphism of alcohol metabolizing enzymes in Japanese. Pharm Biochem Behav 18, Suppl 1:127–133 (1983).
229. Harada S, Agarwal DP, Normura F and Higuchi S. Metabolic and ethnic determinants of alcohol drinking habits and vulnerability to alcohol-related disorders. Alcohol Clin Exp Res 25:71S-75S (2001).
230. Bosron WF and Li T-K. Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases and their relationship to alcohol metabolism and alcoholism. Hepatology 6: 502–510 (1986).
231. Goedde HW, Agarwal DP, Harada S. Pharmacogenetics of alcohol sensitivity. Pharmacol Biochem Behav 18 Suppl. 1 161–166 (1983).
232. Hendershot CS, Collins SE, George WH and Wall TL et al. Associations of ALDH2 and ADH1B genotypes with alcohol-related phenotypes in Asian young adults. Alcohol Clin Exp Res 33:1–9 (2009).
233. Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehdrogenase and aldehyde dehydrogenase variants. Alcohol Res Health 30:5–13 (2007)
234. Yoshida A. Genetic polymorphisms of alcohol metabolizing enzymes related to alcohol sensitivity and alcoholic disease. Alc Alcohol 29:693–696 (1994).
235. McBride WJ, Li T-K, Deitrich RA, Zimatkin S, Smith BR and Rodd-Henricks ZA. Involvement of acetaldehyde in alcohol addiction. Alcohol Clin Exp Res 26:114–119 (2002).
236. Quertemont E and Didone V. Role of acetaldehyde in mediating the pharmacological and behavioral effects of alcohol. Alcohol Res Health 29:258–265 (2006).
237. Lindros KO. Human blood acetaldehyde levels. With improved methods a clearer picture emerges. Alcohol Clin Exp Res 7:70–75 (1983).
238. Moore S, Montane-Jaime LK, Carr LG and Ehlers CL. Variations in alcohol-metabolizing enzymes in people of East Indian and African descent from Trinidad and Tobago. Alcohol Res Health 30:28–30 (2007).

239. Wall TL, Carr LG and Ehlers CL. Protective association of genetic variation in alcohol dehydrogenase with alcohol dependence in Native Americans mission Indians. Am J Psychiatry 160:41–46 (2003).
240. Scott DM and Taylor RE. Health-related effects of genetic variations of alcohol-metabolizing enzymes in African Americans. Alcohol Res Health 30:18–21 (2007).
241. Ehlers CL. Variations in ADH and ALDH in Southwest California Indians. Alcohol Res Health 30:14–17 (2007).
242. Hald J and Jacobsen E. A drug sensitizing the organism to ethyl alcohol. Lancet ii:1001–1004 (1948).
243. Krafh H. From disulfiram to antabuse: the invention of a drug. Bull Hist Chem 33:82–88 (2008).
244. Peachey JE and Sellers EM. The disulfiram and calcium carbimide acetaldehyde mediated ethanol reaction. Pharmacol Ther 15:89–97 (1981).
245. Lindberg P, Bergman R and Wickberg B. On the disulfiram-like effect of coprin the pharmacologically active principle of Coprinus atramentarius. Acta Pharmacol Toxicol 42:292–297 (1978).
246. Jones AW, Neiman J and Hillbom M. Concentration-time profiles of ethanol and acetaldehyde in human volunteers treated with the alcohol-sensitizing drug, calcium carbimide. Br J Clin Pharmacol 25:213–221 (1988).
247. Lindros KO, Stowell A, Pikkarainen P and Salaspuro M. The disulfiram (antabuse) alcohol reaction in male alcoholics: Its efficient management by 4-methyl pyrazole. Alcohol Clin Exp Res 5:528–530 (1981).
248. Heath MJ, Pachar JV, Perez-Martinez and Toseland PA. An exceptional case of lethal disulfiram alcohol reaction. Forensic Sci Int 56:45–50 (1992).
249. Yamamoto H, Tangegashima A, Hosoe H and Fukunaga T. Fatal acute alcohol intoxication in an ALDH2 heterozygote: a case report. Forensic Sci Int 112:201–207 (2000).
250. Jerntorp P, Ohlin H, Sundkvist G, and Almer LO. Effects of chlorpropamide and alcohol on aldehyde dehydrogenase activity and blood acetaldehyde concentration. Diabetes Res 3:369–372 (1986).
251. Jerntorp P. The chlorpropamide alcohol flush test in diabetes mellitus: methods for objective evaluation. Scand. J Clin Lab Invest 43:249–254 (1984).
252. Groop L, Eriksson CJP, Boll-Wåhlin E and Melander A. Chlorpropamide-alcohol flush: significance of body weight, sex, and serum chlorpropamide level. Eur J Clin Pharmacol 26:723–725 (1984).
253. Chen Z, Zhang J and Stamler JS. Identification of the enzymatic mechanism of nitroglycerine bioactivation. Proc Nat Acad Sci (USA) 99:8306–11 (2002).
254. Williams CS and Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? Ann Pharmacother 34:255–257 (2000).
255. Cina SJ, Russell RA and Conradi SE. Sudden death due to metronidazole - ethanol interaction. Am J Forensic Med Pathol 17:343–346 (1996).
256. Visapää J-P, Tillonen JS, Kalhovaara PS and Salaspuro MP. Lack of disulfiram-like reaction with metronidazole and ethanol. Ann Pharmacother 36:971–974 (2002).
257. Gonzalez FJ. Role of cytochromes P450 in chemical toxicity and oxidative stress: studies with CYP2E1. Mutat Res 569:101–10 (2005).
258. Lieber CS. Microsomal ethanol-oxidizing system (MEOS): The first 30 years (1958–1998) – a review. Alcohol Clin Exp Res 23:991–1007 (1999).
259. Bertilsson L, Dahl M-L, Dalen P and Al-Shurbaji A. Molecular genetics of CYP2D6: Clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol 53:111–122 (2001).
260. Cho AK, Narimatsu S and Kumagai Y. Metabolism of drugs of abuse by cytochromes P450. Addict Biol 4:283–301 (1999).
261. Teschke R and Gellert J. Hepatic microsomal ethanol-oxidizing system (MEOS): Metabolic aspects and clinical implications. Alcohol Clin Exp Res 10:20S–32S (1986).

262. Landrum-Michalets E. Update: Clinically significant cytochrome P-450 drug interactions. Pharmacotherapy 18:84–112 (1998).
263. Klotz U and Ammon E. Clinical and toxicological consequences of the inductive potential of ethanol. Eur. J. Clin. Pharmacol. 54:7–12 (1998).
264. Barry M and Feely J. Enzyme induction and inhibition. Pharmacol Ther 48:71–94 (1990).
265. Lin JH and Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. Clin. Pharmacokinet. 35:361–390 (1998).
266. Pelkonen, O and Sotaniemi E. Drug metabolism in alcoholics. Pharmacol Ther 16:261–268 (1982).
267. Nakajima T. Cytochrome P450 isoforms and the metabolism of volatile hydrocarbons of low relative molecular mass. J. Occup. Health 99:83–101 (1997).
268. Murray M and Reidy GF. Selectivity in the inhibition of mammalian cytochromes P-450 by chemical agents. Pharmacol. Rev. 42:85–101 (1990).
269. Keiding S, Christensen NJ and Damgaard SE et al. Ethanol metabolism in heavy drinkers after massive and moderate alcohol intake. Biochem. Pharmacol. 32:3097–3102 (1983)
270. Oneta CM, Lieber AS, Li J, Rüttimann S, Schmid B, Lattmann J, Rosman AS and Seitz HK. Dynamics of cytochrome P4502E1 activity in man: induction by ethanol and disappearance during withdrawal phase. J. Hepatol. 36:47–52 (2002).
271. Park BK, Pirmohamed M and Kitteringham NR. The role of cytochrome P450 enzymes in hepatic and extrahepatic human drug toxicity. Pharmacol Ther 58:385–424 (1995).
272. Park BK, Kitteringham NR, Pirmohamed M and Tucker GT. Relevance of induction of human drug-metabolizing enzymes: pharmacological and toxicological implications. Br. J. Clin. Pharmacol. 41:477–91 (1996).
273. Ramdhan DH, Kamijima M, Yamada N, Ito Y, Yanagiba Y and Nakamura D, et al. Molecular mechanism of trichloroethylene-induced hepatotoxicity mediated by CYP2E1. Toxicol Appl Pharmacol 231:300–7 (2008).
274. Park DV, Ioannides C and Lewis DFV. The role of the cytochrome P450 in the detoxication and activation of drugs and other chemicals. Can. J. Physiol. Pharmacol. 69:537–549 (1991).
275. Salmela KS, Kessova IG, Tsyrlov IB and Lieber CS. Respective roles of human cytochrome P4502E1 1A2 and 3A4 in the hepatic microsomal oxidizing system. Alcohol. Clin. Exp. Res. 22:2125–2132 (1998).
276. Tanaka E, Terada M and Misawa S. Cytochrome P450 2E1: its clinical and toxicological role. J Clin Pharm Therap 25:165–175 (2000).
277. Makin AJ and Williams R. Acetaminophen-induced hepatotoxicity: Predisposing factors and treatments. Adv Intern Med. 42:3433–483 (1997).
278. Slattery JT, Nelson SD and Thummel KE. The complex interaction between ethanol and acetaminophen. Clin Pharmacol Ther 60:241–246 (1996).
279. Prescott LF. Paracetamol, alcohol and the liver. Br. J. Clin. Pharmacol. 49:291–301 (2000).
280. Lee SS, Buters JT, Pineau T, Fernandez-Salguero P and Gonzalez FJ. Role of CYP2E1 in the hepatotoxicity of acetaminophen. J Biol Chem 271:12063–12067 (1996).
281. Schmidt LE and Dalhoff K. Concomitant overdosing of other drugs in patients with paracetamol poisoning. Br J Clin Pharmacol 53:535–541 (2002).
282. Riordan SM and Williams R. Alcohol exposure and paracetamol-induced hepatotoxicity. Addict Biol 7:191–206 (2002).
283. Thomas SHL. Paracetamol (acetaminophen) poisoning. Pharmacol Ther 60:91–120 (1993).
284. Vale JA and Proundfoot AT. Paracetamol (acetaminophen) poisoning. Lancet 346:547–552 (1995).
285. Zimmerman HJ and Maddrey WC. Acetaminophen (paracetamol) hepatoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 22:767–773 (1995).
286. Seeff LB, Cuccherini BA, Zimmerman HJ, Adler E and Benjamin SB. Acetaminophen hepatotoxicity in alcoholics. Ann Intern Med 104:399–404 (1986).
287. Rumack BH. Acetaminophen hepatotoxicity: The first 35 years. Clin Toxicol 40:3–20 (2002).

288. Makin AJ, Wendon J and Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–1993). Gastroenterology 109:1907–1916 (1995).
289. Jones AL. Mechanism of action and value of N-acetylcysteine in the treatment of early and late acetaminophen poisoning: A critical review. J Toxicol Clin Toxicol 36:277–285 (1998).
290. Whitcomb DC and Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. JAMA 272:1845–1850 (1994).
291. Thummel KE, Slattery JT, Ro H, Chien JY, Nelson SD, Lown KE and Watkins PB. Ethanol and production of the hepatoxic metabolite of acetaminophen in healthy adults. Clin Pharmacol Ther 67:591–599 (2000).
292. Janes J and Routledge PA. Recent developments in the management of paracetamol (acetaminophen) poisoning. Drug Safety 7:170–177 (1992).
293. Jones AL. Recent advances in the management of poisoning. Ther Drug Monit 24:150–155 (2002).
294. Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med 359:285–92 (2008).
295. Pond SM and Tozer TN. First-pass elimination; Basic concepts and clinical consequences. Clin Pharmacokinet 9:1–25 (1984).
296. Conney AH. Drug metabolism and therapeutics. N Engl J Med 280:653–660 (1969).
297. Lin JH, Chiba M and Baillie TA. Is the role of the small intestine in first-pass metabolism overemphasized? Pharmacol Rev 51:135–157 (1999).
298. DiPadova C, Roine R, Frezza M, Gentry RT, Baraona E and Lieber CS. Effects of ranitidine on blood alcohol levels after ethanol ingestion. Comparison with other H2-receptor antagonists. JAMA 267:83–86 (1992).
299. Hempel JD and Pietruszko R. Human stomach alcohol dehydrogenase: isoenzyme composition and catalytic properties. Alcohol Clin Exp Res 3:95–98 (1979).
300. Baraona E, Yokoyama A, Ishii H, Hernandez-Munoz R and Takagi T et al. lack of alcohol dehydrogenase isoenzyme activity in the stomach of Japanese subjects. Life Sci 49:1929–1934 (1991).
301. Caballeria J, Frezza M, Hernandez–Munoz R, Dipadova C, Korsten MA, Baraona E and Lieber CS. Gastric origin of the first-pass metabolism of ethanol in humans: Effect of gastrectomy. Gastroenterology 97:1205–1209 (1989).
302. Gentry RT, Baraona E and Lieber CS. Gastric first pass metabolism of alcohol. J Lab Clin Med 123:21–26 (1994).
303. Lieber CS. Hepatic, metabolic and nutritional disorders of alcoholism: from pathogenesis to therapy. Crit Rev Clin Lab Sci 37:551–584 (2000).
304. Julkunen RJK, Tannenbaum L, Baraona E and Lieber CS. First-pass metabolism of ethanol: An important determinant of blood levels after alcohol consumption. Alcohol 2:437–441 (1985).
305. Roine R, Gentry RT, Hernandez-Munoz R, Baraona E and Lieber CS. Aspirin increases blood alcohol concentrations in humans after ingestion of ethanol. JAMA 264:2406-2408 (1990).
306. DiPadova C, Worner TM, Julkunen RJK and Lieber CS. Effects of fasting and chronic alcohol consumption on the first-pass metabolism of ethanol. Gastroenterology 92:1169–1173 (1987).
307. Lim RT, Gentry RT, Ito D, Yokoyarna H, Baraona E and Lieber CS. First-pass metabolism of ethanol is predominantly gastric. Alcohol Clin Exp Res 17:1337–1344 (1993).
308. Lieber CS. Gastritis in the alcoholic, relationship to gastric alcohol metabolism and Helicobacter pylori. Addict Biol 3:423–434 (1998).
309. Gupta AM, Baraona E and Lieber CS. Significant increase of blood alcohol by cimetidine after repetitive drinking of small alcohol doses. Alcohol Clin Exp Res 19:1093–1087 (1995).
310. Levitt MD. Do histamine-2 receptor antagonists influence the metabolism of ethanol. Ann Intern Med 118:564–565 (1993).
311. Arora S, Baraona E and Lieber CS. Alcohol levels are increased in social drinkers receiving ranitidine. Am J Gastroenterol 95:208–213 (2000).

312. Oneta CM, Simanowski UA, Martinez M and Allali-Hassani A et al. First pass metabolism of ethanol is strikingly influenced by the speed of gastric emptying. Gut 43:612–619 (1998).
313. Horowitz M, Maddox A and Bochner M, et al. Relationship between gastric emptying of solid and caloric liquid meals and alcohol absorption. Am J Physiol 257:G291–G298 (1989).
314. Mattila MJ and Venho VMK. Drug absorption from abnormal gastrointestinal tract. Prog Pharmacol 2:63–86 (1979).
315. Madsen JL. Effects of gender, age, and body mass index on gastrointestinal transit times. Dig Dis Sci 37:1548–1553 (1992).
316. Ammon E, Schäfer C, Hoffmann U and Klotz U. Disposition and first pass metabolism of ethanol in humans: Is it gastric or hepatic and does it depend on gender? Clin Pharmacol Ther 59:503–513 (1996).
317. Petring OU and Flachs H. Intersubject and intrasubject variability of gastric emptying in healthy volunteers measured by scintigraphy and paracetamol absorption. Br J Clin Pharmacol 29:703–708 (1990).
318. Lartigue S, Bizais Y, Desvarannes SB, Murat A, Pouliquen B and Galmiche JP. Inter- and intrasubject variability of solid and liquid gastric emptying parameters - a scintigraphic study in healthy subjects and diabetic patients. Dig Dis Sci 39:109–115 (1994).
319. Elashoff JD, Reedy TJ and Meyer JH. Analysis of gastric emptying data. Gastroenterology 83:1306–1312 (1982).
320. Goo RH, Moore JG, Greenberg E and Alazraki NP. Circadian variations in gastric emptying of meals in humans. Gastroenterology 93:515–518 (1987).
321. Hunt JN and Stubbs DF. The volume and energy content of meals as determinants of gastric emptying. J Physiol 245:209–225 (1975).
322. Rinetti M, Ugolotti G, Calbiani B, Colombi-Zinelli L, Cisternino M and Papa N. Anti-inflammatory drugs and gastric emptying. A comparison between acetylsalicylic acid and carprofen. Arzneimittelforschung 32:1561–1563 (1982).
323. Pfeiffer A, Högl B and Kaess H. Effect of ethanol and commonly ingested alcoholic beverages on gastric emptying and gastrointestinal transit. Clin Investig 70:487–491 (1992).
324. Mascord D, Smith J, Starmer G and Whitfield J. Effect of increasing the alcohol metabolism rate on plasma acetate concentration. Alc Alcohol 27:25–28 (1992).
325. O'Conner S, Morzorati S, Christian J and Li TK. Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol and alcohol elimination rate. Alcohol Clin Exp Res 22:202–210 (1998).
326. Ramchandani VA, O'Connor S, Meumark Y, Zimmermann US, Morzorati SL and de Witt, H. The alcohol clamp: applications, challenges, and new directions – an RSA 2004 symposium summary. Alcohol Clin Exp Res 30:155–164 (2006).
327. Svensson CK, Edwards DJ, Mauriello PM, Barde SH and Foster AC et al. Effect of food on hepatic blood flow. Implications in the "food effect" phenomenon. Clin Pharmacol Ther 34:316–323 (1983).
328. Palmer RH, Frank WO, Nambi P, Wetherington JD and Fox MJ. Effects of various concomitant medications on gastric alcohol dehydrogenase and the first-pass metabolism of ethanol. Am J Gastroenterol. 86:1749–1755 (1991).
329. Melander O, Liden A and Melander A. Pharmacokinetic interactions of alcohol and acetylsalicylic acid. Eur J Clin Pharmacol 48:151–153 (1995).
330. Gentry RT, Baraona E, Amir I, Roine R, Chayes ZW, Sharma R and Lieber CS. Mechanism of the aspirin-induced rise in blood alcohol levels. Life Sci 65:2505–2512 (1999).
331. Locher KB, Mallach HJ, and Moosmayer A. Pharmacokinetishe Wechselwirkungen zwischen Alkohol und Acetylsalicylsäure. Blutalkohol 28:273–278 (1991).
332. Kechagias S, Jönsson KÅ, Norlander B, Carlsson B and Jones AW. Low-dose aspirin decreases blood alcohol concentrations by delaying gastric emptying. Eur J Clin Pharmacol 53:241–246 (1997).
333. Heading RC, Nimmo J, Prescott LF and Tothill P. The dependence of paracetamol absorption on the rate of gastric emptying. Br J Pharmacol 47:415–421 (1973).

334. Barron SE, Perry JR and Ferslew KE. The effect of ibuprofen on ethanol concentration and elimination rate. J Forensic Sci 37:432–435 (1992).
335. Minocha A, Barth JT, Herold DA, Gideon DA and Spyker DA. Modulation of ethanol-induced central nervous system depression by ibuprofen. Clin Pharmacol Ther 39:123–127 (1986).
336. Greiff JMC and Rowbotham D. Pharmacokinetic drug interactions with gastrointestinal motility modifying agents. Clin Pharmacokinet 27:447–461 (1994).
337. Madsen JL. Effects of cisapride on gastrointestinal transit in healthy humans. Dig Dis Sci 35:1500–1504 (1990).
338. McCallum RW, Prakash C, Campoli-Richards DM and Goa KL. Cisapride. A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic use as a prokinetic agent in gastrointestinal motility disorders. Drugs 36:652–681 (1988)
339. Dziekan G, Contesse J, Werth B, Schwarzer G and Reinhart WH. Cisapride increases peak plasma and saliva ethanol levels under fasting conditions. J. Intern Med 242:479–482 (1997).
340. Kechagias S, Jönsson KÅ and Jones AW. Impact of gastric emptying on the pharmacokinetics of ethanol as influenced by cisapride. Br J Clin Pharmacol 48:728–732 (1999).
341. Deponti F, Giaroni C, Cosentino M, Lecchini S and Frigo G. Calcium-channel blockers and gastrointestinal motility - basic and clinical aspects. Pharmacol Ther 60:121–148 (1993).
342. Bauer LA, Schumock G, Horn J and Opheim K. Verapamil inhibits ethanol elimination and prolongs the perception of intoxication. Clin Pharmacol Ther 52:6–10 (1992)
343. Perez-Reyes M, White WR and Hicks RE. Interaction between ethanol and calcium channel blockers in humans. Alcohol Clin Exp Res 16:769–775 (1992).
344. Edelbroek MAL, Horowitz M, Wishart JM and Akkermans LMA. Effects of erythromycin on gastric emptying, alcohol absorption and small intestinal transit in normal subjects. J Nucl Med 34:582–588 (1993).
345. Peeters T, Matthijs G, Depoortere I, Cachet T, Hoogmartens J and Vantrappen G. Erythromycin is a motilin receptor agonist. Am J Physiol 257:G470–G474 (1989).
346. Urbain JL, Vantrappen G, Janssens J, Van Cutsem E, Peeters T and De Roo M. Intravenous erythromycin dramatically accelerates gastric emptying in gastroparesis diabeticorum and normals and abolishes the emptying discrimination between solids and liquids. J Nucl Med 31:1490–1493 (1990).
347. Smith SR and Kendall MJ. Ranitidine and cimetidine: A comparison of their potential to cause clinically important drug interactions. Clin Pharmacokinet 15: 44–56 (1988).
348. Hernandez-Munoz R, Caballeria J, Baraona E, Uppal R, Greenstein R and Lieber CS. Human gastric alcohol dehydrogenase - Its inhibition by H2-receptor antagonists, and its effect on the bioavailability of ethanol. Alcohol Clin Exp Res 14:946–950 (1990).
349. Amir I, Anwar N, Baraona E and Lieber CS. Ranitidine increases the bioavailability of imbibed alcohol by accelerating gastric emptying. Life Sci 58:511–518 (1996).
350. Bye A, Lacey LF, Gupta S and Powell JR. Effect of ranitidine hydrochloride (150 mg twice daily) on the pharmacokinetics of increasing doses of ethanol (0.15, 0.3, 0.6 g kg-1). Br J Clin Pharmacol 41:129–133 (1996).
351. Toon S, Khan AZ, Holt BI, Mullins FG, Langley SJ and Rowland MM. Absence of effect of ranitidine on blood alcohol concentrations when taken morning, midday, or evening with or without food. Clin Pharmacol Ther 55:385–391 (1994).
352. Raufman JP, Notarfrancesco V, Raffaniello RD and Straus EW. Histamine-2 receptor antagonists do not alter serum ethanol levels in fed, non-alcoholic men. Ann Intern Med 118:488–494 (1993).
353. Tanaka E and Nakamura, K. Effects of H-2 receptor antagonists on ethanol metabolism in Japanese volunteers. Br J Clin Pharmacol 26: 96–99 (1988).
354. Somogyi, A and Muirhead, M. Pharmacokinetic interactions of cimetidine. Clin. Pharmacokinet. 12:321–366 (1987).
355. Caballeria J, Baraona E, Rodamilans M and Lieber CS. Effects of cimetidine on gastric alcohol dehydrogenase activity and blood ethanol levels. Gastroenterology 96:388–392 (1989).

356. Dauncey H, Chesher GB and Palmer RH. Cimetidine and ranitidine: Lack of effect on the pharmacokinetics of an acute ethanol dose. J Clin Gastroenterol 17:189–194 (1993).
357. Fraser AG, Hudson M, Sawyerr AM, Smith M, Rosalki SB and Pounder RE. Ranitidine, cimetidine, famotidine have no effect on post-prandial absorption of ethanol 0.8 g/kg taken after an evening meal. Aliment Pharmacol Ther 6:693–700 (1992).
358. Fraser AG, Prewett EJ, Hudson M, Sawyerr AM, Rosalki SB and Pounder RE. The effect of ranitidine, cimetidine or famotidine on low-dose post-prandial alcohol absorption. Aliment Pharmacol Ther 5:263–272 (1991).
359. Clemmesen JO, Ott P and Sestoft l. The effect of cimetidine on ethanol concentrations in fasting women and men after two different doses of alcohol. Scand J Gasterenterol 32: 217–220 (1997).
360. Casini A, Pizzigallo AM, Mari F, Bertol E and Surrenti C. Prolonged bedtime treatment with H2-receptor antagonists (ranitidine and famotidine) dose not affect blood alcohol levels after ethanol ingestion in male patients with duodenal ulcer. Am J Gastroenterol 89:745–749 (1994).
361. Sharma R, Gentry RT, Lim RT and Lieber CS. First-pass metabolism of ethanol: Absence of diurnal variation and its inhibition by cimetidine after evening meal. Dig Dis Sci 40: 2091–2097 (1995).
362. Seitz HK, Bösche J, Czygan P, Veith S, Simon B and Kommerell B. Increased blood ethanol levels following cimetidine but not ranitidine. Lancet ii, 700 (1983).
363. Seitz HK, Veith S, Czygan P, Bösche J, Simon B, Gugler R and Kommerell B. In-vivo interactions between H2-receptor antagonists and ethanol metabolism in man and in rats. Hepatology 4:1231–1233 (1984).
364. Feely J and Wood AJJ. Effects of cimetidine on the elimination and actions of ethanol. JAMA 247: 2819–2821 (1982).
365. Webster LK, Jones BD and Smallwood RA. Influence of cimetidine and ranitidine on ethanol pharmacokinetics. Austr NZ J Med 15: 359–360 (1985).
366. Dobrilla G., de Pretis G and Piazzi L., et al. Is ethanol metabolism affected by oral administration of cimetidine and ranitidine at therapeutic doses?. Hepatogastroenterology 31:35–37 (1984).
367. Jönsson K-Å, Jones AW, Boström KL and Andersson T. Lack of effect of omeprazole, cimetidine and ranitidine on the pharmacokinetics of ethanol in fasting male volunteers. Eur J Clin Pharmacol 42:209–212 (1992).
368. Fraser AG. Is there an interaction between H2-antagonists and alcohol? Drug Metabol Drug Interact 14:123–145 (1998).
369. Crabbe DW. First-pass metabolism of ethanol; Gastric or hepatic: Mountain or molehill. Gasterenterology 25:1292–1294 (1997).
370. Zakhari S and Li T-K. Determinants of alcohol use and abuse. Impact of quantity and frequency patterns on liver disease. Hepatology 46:2032–2039 (2007).
371. Lieber CS. The metabolism of alcohol. Sci Am 234:25–34 (1976).
372. Lieber CS. Alcohol and the liver – metabolism of alcohol and its role in hepatic and extrahepatic diseases. Mount Sin J med 67:84–94 (2000).
373. Hawkins RD and Kalant H. The metabolism of ethanol and its metabolic effects. Pharmacol Rev 24:67–157 (1972).
374. Gable RS. Comparison of acute lethal toxicity of commonly abused psychoactive substances. Addiction 99:686–696 (2004).
375. Nutt D, King LA, Saulsbury W and Blakemore C. Development of a rational scale to assess the harm of drugs of potential abuse. Lancet 369:1047–53 (2007).
376. Antkowiak B. How do general anaesthetic work? Naturwissenschaften 88:201–213 (2001).
377. Urban BW and Bleckween M. Concepts and correlations relevant to general anaesthesia. Br J Anesth 89:3–16 (2002).
378. Campagna JA, Miller KW and Forman SA. Mechnaism of action of inhaled anesthetics. N Eng J Med 348:2110–2124 (2003).

379. Little HJ. Mechanisms that may underlie the behavioural effects of ethanol. Prog Neurbiol 36:171–194 (1991).
380. Lüddens H, Pritchett DB, Köhler M and Killisch I et al. Cerebellar GABAA receptor selective for a behavioural alcohol antagonist. Nature 346:648–651 (1990).
381. Gilpin NW and Koob GF. Neurobiology of alcohol dependence. Alc Res Health 31:185–195 (2008)
382. Lovinger DM. Alcohols and neurotransmitter gated ion channels: past, present and future. Namyn-Schmiedeberg's Arch Pharmacol 356:267–282 (1997).
383. Claoo P, Bhave SV and Hoffman PL. How adaptation of the brain to alcohol leads to dependence. A pharmacological perspective. Alc Res Health 31:310–339 147 (2008).
384. Bormann J. The ABC of GABA receptors. Trends Pharmacol Sci 21:16–19 (2000).
385. Pritchett DB, Sontheimer H, Shivers BD and Ymer S et al. Importance of a novel GABAA receptor subunit for benzodiazepine pharmacology. Nature 338:582–585 (1989).
386. Meheta AK and Ticku MK. An update on GABAA receptors. Brain Res Bull 29:196–217 (1999).
387. Rudolph U, Crestani F and Möhler H. GABAA receptor subtypes: dissecting their pharmacological functions. Trends Pharmacol Sci 22:188–194 (2001).
388. Nagy J. Alcohol related changes in regulation of NMDA receptor functions. Curr Neuropharmacol 6:39–54 (2008).
389. Vengeliene V, Bilbao A, Molander A and Spanagel R. Neuropharmacology of alcohol addiction. Br J Pharmacol 154:299–315 (2008).
390. Tupala E and Tühonen J. Dopamine and alcoholism. Neurobiological basis of ethanol abuse. Prog Neuro-psychopharmacol Biol Psych 28:1221–1247 (2004).
391. Hobbs WR, Rall TW and Verdoorn TA. Hypnotics and sedatives; ethanol. Chapter 17 in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th edition, McGraw-Hill, New York, 361–396 (1996).
392. Byatt C and Volans G. ABC of poisoning: sedative and hypnotic drugs. Br Med J 289: 1214–1217 (1984).
393. Gary NE and Tresznewsky O. Barbiturates and a potpourri of other sedative, hypnotics, and tranquilizers. Heart & Lung 12:122–127 (1983).
394. Johnson HRM. At what blood levels does alcohol kill? Med Sci Law 25:127–130 (1985).
395. Odesanmi WO. The fatal blood alcohol level in acute poisoning. Med Sci Law 23:25–30 (1983).
396. Kalant H. Research on tolerance: What can we learn from history. Alcohol Clin Exp Res 22:67–76 (1998).
397. Ekman G, Frankenhaeuser M, Goldberg L and Bjerver K et al. Effects of alcohol intake on subjective and objective variables over a five-hour period. Psychopharmacologia 4:28–38 (1963).
398. Mellanby E. Alcohol: Its absorption into and disappearance from the blood under different conditions. Special report Series No. 31, London, National Safety Council, (1919).
399. Cruz MT, Bajo M, Schweitizer P and Roberto M. Shared mechanisms of alcohol and drug tolerance. Alc Res Health 31:137–147 (2008).
400. Pietrzykowski AZ and Treistman SN. The metabolic basis of tolerance. Alc Res Health 31:298–309 (2008).
401. Alha A. Blood alcohol and clinical inebriation in Finnish men – A medico-legal study. Ann Acad Sci Fenn Series A. V. Medica-Anthropologica 26:1–92 (1951).
402. Jones AW and Holmgren P. Comparison of blood-ethanol concentration in deaths attributed to acute alcohol poisoning and chronic alcoholism. J Forensic Sci. 48:874–9 (2003).
403. Koski A, Ojanperä I and Vuori E. Alcohol and benzodiazepines in fatal poisonings. Alcohol Clin Exp Res 26:956–959 (2002).
404. Becker HC. Alcohol dependence, withdrawal, and relapse. Alc Res Health 31:348–361 (2008).
405. Jones AW. The drunkest drinking driver in Sweden; blood alcohol concentration 0.545% w/v. J Stud Alcohol 60:400–406 (1999).

406. Urso T, Gavaler JS and Van Thiel DH. Blood ethanol levels in sober alcohol users seen in an emergency room. Life Sci. 28:1053–1056 (1985).
407. Jones AW. Alcohol; post-mortem. Encyclopedia of Forensic Sciences, Academic Press Inc., London 2000, pp 112–126.
408. Correy JEL. Possible sources of ethanol ante- and post-mortem. Its relationship to the biochemistry and microbiology of decomposition. J Appl Bacteriol 44:1–56 (1978).
409. Kalant H and Le AD. Effects of ethanol on thermoregulation. Pharmacol Ther 23:313–364 (1984).
410. Ward ME and Cowley AR. Hypothermia: A natural cause of death. Am. J. Forensic Med. Pathol 20:383–386 (1999).
411. Gallaher MM, Fleming DW, Berger LR and Sewell CM. Pedestrian and hypothermia deaths among native Americans in New Mexico. JAMA 267:1345–2348 (1992).
412. Kortelainen ML. Drugs and alcohol in hyporthermia and hypethermia related deaths. A retrospective study. J Forensic Sci 32:1704–12 (1987).
413. Larach MG. Accidential hypothermia. Lancet 345:493–498 (1995).
414. Lundevall J, Olaisen B, Olving JH and Clausen OPE et al. Blodkonsentrasjoner ved akutte forgiftningsdodsfall. Tidsskr. Nor. Laegeforen 103:679–685 (1983).
415. Padosch SA, Schmidt PH, Kröner LU and Madea B. Death due to positional asphyxia under severe alcoholisation: pathophysiologic and forensic considerations. Forensic Sci Int 149:67–73 (2005).
416. De Donno A, De Fazio A, Greco MG, Introna F and Maglietta RAG. Death in head-down position in a heavily intoxicated obese man. Leg Med 10:204–309 (2008).
417. Glatter K and Karch SB. Positional asphyxia: inadequate oxygen or inadequate theory? Forensic Sci int 141:201–202 (2004).
418. Byard RW, Wick R and Gilbert JD. Conditions and circumstances predisposing to death from positional asphyxia in adults. J Forensic Leg Med 15:415–419 (2008).
419. Thomsen JL, Theilade P, Felby S and Nielsen E. Alcoholic ketoacidosis as a cause of death in forensic cases. Forensic Sci Int 75:163–171 (1995).
420. Thomsen JL. Various mechanisms of death and their possible association with alcoholism. Forensic Sci Int 79:199–204 (1996).
421. Pounder DJ, Stevenson RJ and Taylor KK. Alcoholic ketoacidosis at autopsy. J Forensic Sci 43:812–816 (1998).
422. Brinkmann B, Fechner G, Karger B and DuChesne A. Ketoacidosis and lactic acidosis – frequent causes of death in chronic alcoholics? Int J Legal Med 111:115–119 (1998).
423. Felby S, Nielsen E and Thomsen JL. The post-mortem distribution of ketone bodies between blood, vitreous humor, spinal fluid and urine. Forensic Sci Med Pathol 4:100–107 (2008).
424. Lahti RA and Vuori E. Fatal alcohol poisoning: medico-legal practices and mortality statistics. Forensic Sci Int 126:203–209 (2002).
425. Höjer J, Baehrendtz S and Gustafsson L. Benzodiazepine poisoning: experience of 702 admissions to an intensive care unit during a 14-year period. J Intern Med 226:117–122 (1989).
426. Buckley NA, Dawson AH, Whyte IM and O'Connell DL. Relative toxicity of benzodiazepines in overdose. Br Med J 310:219–221 (1995).
427. Serfaty M and Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. Br J Psychiatry 163:383–93 (1993).
428. Drummer OH and Ranson DL. Sudden death and benzodiazepines. Am J Forensic Med Pathol 7:336–342 (1996).
429. Tanaka E. Toxicological interactions between alcohol and benzodiazepines. J Toxicol Clin Toxicol 40:69–75 (2002).
430. Caplan YH, Ottinger WE and Crooke CR. Therapeutic and toxic drug concentrations in post mortem. A six year study in the state of Maryland. J Anal Toxicol 7:225–230 (1983).
431. Jonasson B, Jonasson U and Saldeen T. The manner of death among fatalities where dextropropoxyphene caused or contributed to death. Forensic Sci Int 96:181–187 (1998).

432. Jonasson U, Jonasson B, Holmgren P and Saldeen T. The prevalence of dextropropoxyphene in autopsy blood samples. Forensic Sci Int 96:135–142 (1998).
433. Sturner WQ and Garriott JC. Deaths involving propoxyphene: A study of 41 cases over a two-year period. JAMA 223:1125–1130 (1973).
434. Buckley BM and Vale JA. Dextropropoxyphene poisoning: problems with interpretation of analytical data. Hum Toxiciol 3:95–101 (1984).
435. Young RJ. Dextropropoxyphene overdosage: pharmacological considerations and clinical management. Drugs 26:70–79 (1983).
436. Finkle BS, Caplan YH, Garriott JC, Montforte JR, Shaw RF and Sonsalla PK. Propoxyphene in postmortem toxicology 1976–1978. J Forensic Sci 26:739–57 (1981).
437. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds. Hum. Toxicol Supp. 115S–134S (1984).
438. Tallman JF, Paul SM, Skolnick P and Gallager DW. Receptors for the age of anxiety: Pharmacology of the benzodiazepines. Science 207:274–281 1980.
439. Carmen Del Rio M, Prada C and Alvarez FJ. Do Spanish patients drink alcohol while undergoing treatment with benzodiazepines? Alcohol 26:31–34 (2002).
440. Drummer OK, Syrjanen ML and Cordner SM. Deaths involving the benzodiazepine flunitrazepam. Am. J Forensic Med Pathol 14:238–243 (1993).
441. Druid H, Holmgreen P and Ahlner J. Flunitrazepam: an evaluation of use, abuse and toxicity. Forensic Sci Int 122: 136–141 (2001).
442. Fisher E, and Von Mering J. Ueber eine neue Klasse von Schlafmittlen. Ther. d. Gegenw 44:97–101 (1903).
443. Adams E. The barbiturates. Sci Am 198:60–64 (1958).
444. Gillespie RD. On the alleged dangers of the barbiturates. Lancet (Feb 17): 337–345 (1934).
445. Koniaris LG, Zimmers TA, Lubarsky DA and Sheldon JP. Inadequate anaesthesia in lethal injection for execution. Lancet 365:1412–4 (2005).
446. Stead AH and Moffatt AC. Quantification of the interaction between barbiturates and alcohol at different concentrations. Hum Toxicol 2:5–14 (1983).
447. Stead AH, Allan AR, Ardrey RE and Bal TS, et al. Drug misuse – the barbiturate problem. J Forensic Sci Soc 21:41–53 (1981).
448. Teige D and Fleischer E. Blodkonsentrasjoner ved akutte forgiftningsdodsfall. Tidsskr nor Laegeforen 103:679–685 (1983).
449. George CFP. Pyrazolopyrimidines. Lancet 358:1623–1626 (2001).
450. Baenninger A, Costa e Silva JA, Hindmarch I, Moeller HJ and Rickels K. Good chemistry – The life and legacy of valium inventor Leo Sternbach. McGraw-Hill, New York, (2004).
451. Woods JH and Wingler G. Abuse liability of flunitrazepam. J Clin Psychopharmacol 17:1S–57S (1997).
452. Laurijssens BE and Greenblatt DJ. Pharmacokinetic-pharmacodynamic relationships for benzodiazepines. Clin Pharmacokinet. 30:52–76 (1996).
453. Steentoft A and Worm K. Cases of fatal triazolam poisoning. J Forensic Sci Soc 33:45–48 (1993).
454. Sunter JP, Bal TS and Cowan WK. Three cases of fatal triazolam poisoning. Br Med J 297:719 (1998).
455. Steentoft A, Teige B, Ceder G and Vuori E et al. Fatal poisoning in drug addicts in the Nordic countries. Forensic Sci Int 123:63–69 (2001).
456. Finkle BS, McCloskey KL and Goodman LS. Diazepam and drug-associated deaths. JAMA 242:429–434 (1979).
457. Homgren P and Jones AW. Coexistence and concentrations of ethanol and diazepam in postmortem blood samples: Risk for enhanced toxicity? J Forensic Sci 48:1416–1421 (2003).
458. Mandelli M, Tognono G and Gerattini S. Clinical pharmacokinetics of diazepam. Clin. Pharmacokinet. 3:72–91 (1978).
459. Greenblatt DJ, Harmatz JS, Friedman H, Locnisker A and Shader RI. A large sample study of diazepam pharmacokinetics. Ther Drug Monit 11:652–657 (1989).

460. Greenblatt DJ, Laughren TP, Allen, MD, Harmatz JS and Shader RI. Plasma diazepam and desmethyldiazepam concentrations during long term diazepam therapy. Br J Clin Pharmacol 1:35–40 (1981).
461. Joynt BP. Triazolam blood concentrations in forensic cases in Canada. J Anal Toxicol 17:171–177 (1993).
462. Edwards JG. Medicolegal aspects of benzodiazepine dependence: Duties and responsibilities of doctors. Med J Aust 156:733–737 (1992).
463. Laisi U, Linnoila M, Seppälä T, Himberg I-J and Mattila MJ. Pharmacokinetic and pharmacodynamic interactions of diazepam with different alcoholic beverages. Eur J Clin Pharmacol 16:263–270 (1979).
464. Costa E and Guidotti A. Benzodiazepines on trial: a research strategy for their rehabilitation. Trends Pharmacol Sci 17:192–200 (1996).
465. Garretty DJ, Wolff K, Hay AWM and Raistrick D. Benzodiazepine misuse by drug addicts. Ann Clin Biochem 34:68–73 (1997).
466. Woods JH, Katz JL and Winger G. Abuse liability of benzodiazepines. Pharmacol Rev 39:251–419 (1987).
467. Woods JH, Katz JL and Winger G. Benzodiazepines: use, abuse and consequences. Pharmacol Rev 44:151–347 (1992).
468. Gruchalla RS. Clinical assessment of drug-induced disease. Lancet 356:1505–1511 (2000).
469. Möhler H, Fritschy JM and Rudolph U. A new benzodiazepine pharmacology. J Pharmacol Exp Ther 300:2–9 (2002).
470. Liebreich O. Das Chloralhydrat. Ein neues hypnoticum und anaestheticum und dessen anwendung in der Medicin. Otto Müller's Verlag, Berlin, (1869).
471. Jonasson B and Saldeen T. Citalopram in fatal poisoning cases. Forensic Sci Int 126:1–6 (2002).
472. Worm K, Dragsholt C, Simonsen K and Kringsholm B. Citalopram concentrations in samples from autopsies and living persons. Int J Legal Med 111:188–190 (1998).
473. Bailey DN and Shaw RF. Interpretation of blood and tissue concentrations in fatal self-poisoning overdoses involving amitriptyline: An update 1978–1979. J Anal Toxicol 4:232–236 (1980).
474. Tournier M, Grolleau A, Cougnard A, Verdoux H and Molimard M. The prognostic impact of psychotropic drugs in intentional drug overdose. Pharmacopsychiatry 42:51–56 (2009).
475. Pennings EJM, Leccese AP and de Wolff FA. Effects of concurrent use of alcohol and cocaine. Addiction 97:773–779 (2002).
476. Farre M, de la Torre R, Gonzalez ML, Teran MT, Roset PN, Menoyo E and Cami J. Cocaine and alcohol interactions in humans: Neuroendocrine effects and cocaethylene metabolism. J Pharmacol Exp Ther 283:164–176 (1997).
477. Hearn WL, Rose S, Wagner J, Ciarleglio A and Mash DC. Cocaethylene is more potent than cocaine in mediating lethality. Pharmacol Biochem Behav 39:531–533 (1991).
478. McCance EF, Price LH, Kosten TR and Jatlow P. Cocaethylene: pharmacology, physiology and behavioral effects in humans. J Pharmacol Exp Ther 274:215–223 (1995).
479. Andrews P. Cocaethylene toxicity. J Addict Diseases 16:75–84 (1997).
480. Bailey DN. Serial plasma concentrations of cocoethylene, cocaine, and ethanol in trauma victims. J Anal Toxicol 17:79–83 (1993).
481. Bailey DN. Comprehensive review of cocaethylene and cocaine concentrations in patients. Am J Clin Pathol 106:701–704 (1996).
482. Jatlow P. Cocaethylene. Pharmacologic activity and clinical significance. Ther Drug Monit 15:533–536 (1993).
483. Jatlow P, McChance EF, Bradberry CW, Elsworth JD, Taylor JR and Roth RH. Alcohol plus cocaine: The whole is more than the sum of its parts. Ther Drug Monit 18:460–464 (1996).
484. Schuckit MA. Alcohol-use disorder. Lancet 373:492–499 (2009).
485. Dawson DA. Methodological issues in measuring alcohol use. Alcohol Res Health 27:18–29 (2003).

486. Ewing, J. A. Screening for alcoholism using CAGE. Cut down, Annoyed, Guilty, Eye opener. JAMA 280:1904–1905 (1998).
487. Hannuksela ML, Liisanantti MK, Nissinen AE and Savolainen MJ. Biochemical markers of alcoholism. Clin Chem Lab Med 45:953–961 (2007).
488. Jones AW. Biomarkers of acute and chronic alcohol consumption. Chapter 4 in Medicolegal Aspects of Alcohol, 5th edition, J.C. Garriott. Ed. Lawyers & Judges Publishing Co., Inc., Tucson, 2008, pp 157–203.
489. Saitz R. Unhealthy alcohol use. N Eng J Med 352:596–607 (2005).
490. Garbutt JC, West SL, Carey TS, Lohr KN and Crews FT. Pharmacological treatment of alcohol dependence: A review of the evidence. JAMA 281:1318–1325 (1999).
491. Kreek MJ, LaForge KS and Butelman E. Pharmacotherapy of addictions. Nature Rev Drug Disc 1:710–726 (2002).
492. Johnson BA. Update on neuropharmacological treatments for alcoholism: scientific basis and clinical findings. Biochem Pharmacol 75:34–56 (2008).
493. Leggio L, Kenna GA and Swift RM. New developments for the pharmacological treatment of alcohol withdrawal syndrome. A focus on non-benzodiazepine GABAergic medications. Prog Neuropsychopharmacol Biol Psychiatry 32:1106–1117 (2008).
494. Johnson BA, Swift RM, Addolorato G, Ciraulo DA and Myrick H. Safety and efficacy of GABAergic medications for treating alcoholism. Alcohol Clin Exp Res 29:248–254 (2005).
495. Johnsen J, Stowell A, Stensrud T, Ripel A and Morland J. A double-blind placebo controlled study of healthy volunteers given a subcutaneous disulfiram implantation. Pharmacol Toxicol 66:227–230 (1990).
496. Swift RM. Medications and alcohol craving. Alc Res Health 23:207–213 (1999).
497. Attard A, Ranjith G and Taylor D. Delirium and its treatment. CNS Dtugs 22:631–644 (2008).
498. Hughes JR. Alcohol withdrawal seizures. Epilepsy Behav 15:92–97 (2009).
499. Carter LP, Pardi D, Gorsline J and Griffiths RR. Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem): differences in characteristics and misuse. Drug Alcohol Depend 104:1–10 (2009).
500. Wedin GP, Hornfeldt CS and Ylitalo LM. The clinical development of gamma-hydroxy butyrate (GHB). Curr Drug Saf 1:99–106 (2006).
501. Ferrara SD, Zotti S, Tedeschi L, Frison G, Castagna F, Gallimberti L, Gessa Gl and Palatini P. Pharmacokinetics of gamma-hydroxybutyrate in alcohol dependent patients after single and repeated oral doses. Br J Clin Pharmacol 34:231–235 (1992).
502. Carai MAM, Colombo G, Reali R and Serra S et al. Central effects of 1,4 butanediol are mediated by GABAB receptors via its conversion into g-hydroxybutyric acid. Eur J Pharmacol 441:157–163 (2002).
503. Caputo F, Vignoli T, Maremmani I, Bernardi M and Zoli G. Gamma hydroxybutyric acid (GHB) for the treatment of alcohol dependence: a review. Int J Environ Res Public Health. 6:1917–1929 (2009).
504. Caputo F, Addolorato G, Stoppo M, Francini S, Vignoli T and Lorenzini F, et al. Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: an open randomised comparative study. Eur Neuropsychopharmacol 17:781–9 (2007).
505. Swift RM. Effect of naltrexone on human alcohol consumption. J Clin Psychiatry 56 (supp. 7) 24–29 (1995).
506. Krystal JH, Cramer JA, Krol WF, Kirk GF and Rosenheck RA. Naltrexone in the treatment of alcohol dependence. N Engl J Med 345:1734–39 (2001).
507. Swift RM. Opioid antagonists and alcoholism treatment. CNS Spectr 5:49–57 (2000).
508. Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med 359:715–21 (2008).
509. Ray LA, Hutchison KE, MacKillop J, Miranda R Jr., Audette A, Swift R and Monti PM. Effects of naltrexone during the descending limb of the blood alcohol curve. Am J Addict 17:257–264 (2008).

510. Baros AM, Latham PK and Anton RF. Naltrexone and cognitive behavioral therapy for the treatment of alcohol dependence: do sex differences exist? Alcohol Clin Exp Res 32:771–776 (2008).
511. Tidey JW, Monti PM, Rohsenow DJ, Gwaltney CJ, Miranda R, Jr and McGeary JE, et al. Moderators of naltrexone's effects on drinking, urge, and alcohol effects in non-treatment-seeking heavy drinkers in the natural environment. Alcohol Clin Exp Res 32:58–66 (2008).
512. Mann K, Kiefer F, Spanagel R and Littleton J. Acamprosate: recent findings and future research directions. Alcohol Clin Exp Res 32:1105–1110 (2008).
513. Boothby LA and Doering PL. Acamprosate for the treatment of alcohol dependence. Clin Ther 27:695–714 (2005).
514. Wilde MI and Wagstaff AJ. Acamprosate – A review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. Drugs 53:1038–1053 (1997).
515. Swift RM, Davidson D, Whelihan W and Kuznetsov O. Ondansetron alters human alcohol intoxication. Biol Psychiatry 40:514–21 (1996).
516. Swift RM. Topiramate for the treatment of alcohol dependence: initiating abstinence. Lancet 361:1666–1667 (2003).
517. Florez G, Garcia-Portilla P, Alvarez S, Saiz PA, Nogueiras L and Bobes J. Using topiramate or naltrexone for the treatment of alcohol-dependent patients. Alcohol Clin Exp Res 32:1251–1259 (2008).
518. Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L and Beyers K, et al. Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. Arch Intern Med 168:1188–1199 (2008).
519. Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L and Beyers K, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 298:1641–1651 (2007).
520. Miranda R, Jr., MacKillop J, Monti PM, Rohsenow DJ, Tidey J and Gwaltney C, et al. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcohol Clin Exp Res 32:489–497 (2008).
521. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L and Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 370:1915–1922 (2007).
522. Agabio R, Marras P, Addolorato G, Carpiniello B and Gessa GL. Baclofen suppresses alcohol intake and craving for alcohol in a schizophrenic alcohol-dependent patient: a case report. J Clin Psychopharmacol 27:319–320 (2007).
523. Hutchison KE, Ray L, Sandman E, Rutter MC, Peters A, Davidson D and Swift R. The effect of olanzapine on craving and alcohol consumption. Neuropsycho-pharmacology 31:1310–1317 (2006).
524. Hutchison KE, Swift R, Rohsenow DJ, Monti PM, Davidson D and Almeida A. Olanzapine reduces urge to drink after drinking cues and a priming dose of alcohol. Psychopharmacology (Berl) 155:27–34 (2001).
525. Garbutt JC. The state of pharmacotherapy for the treatment of dependence. J Subst Abuse Treat 36:S15-S23 (2009).
526. Linnoila M and Mattila MJ. How to antagonize ethanol-induced inebriation. Pharmacol Ther 15:99–109 (1981).
527. Schneble H. Ernüchterungsmittel – nüchtern betrachtet. Blutalkohol 25:18–65 (1988).
528. Carni J and Farre M. Drug addiction. N Eng J Med 349:975–986 (2003).
529. Jones AW. Forensic science aspects of ethanol metabolism. Forensic Sci Prog 31:229–238 (1991).
530. Wiese JG, Shlipak MG and Browner WS. The alcohol hangover. Ann Intern Med 132:897–902 (2000).
531. Prat G, Adan A and Sanchez-Turet M. Alcohol hangover. A critical review of explanatory factors. Hum Psychopharmacol Clin Exp 24:259–267 (2009).

532. Stephens R, Ling J, Heffernan TM, Heather N and Jones K. A review of the literature on the cognitive effects of alcohol hangover. Alcohol Alcohol 43:163–170 (2008).
533. Ylikahri RH, Leino T, Huttunen MO, Poso AR, Eriksson CJ and Nikkila EA. Effects of fructose and glucose on ethanol-induced metabolic changes and on the intensity of alcohol intoxication and hangover. Eur J Clin Invest 6:93–102 (1976).
534. Rowland J, Rohsenow DJ, Allensworth-David D and Greece J et al. The incidence and severity of hangover the morning after moderate alcohol consumption. Addiction 103:758–765 (2008).
535. Pittler MH, Verster JC and Ernst E. Interventions for preventing or treating alcohol hangover: systematic review of randomized controlled trials. BMJ 331:1515–1518 (2005).
536. Goldberg L, Jones AW and Neri A. Effect of a sugar mixture on blood ethanol profiles and on ethanol metabolism in man. Blutalkohol 16:431–438 (1988).
537. Soterakis J and Iber FL. Increased rate of alcohol removal from blood with oral fructose and sucrose. Am J Clin Nut 28:254–257 (1975).
538. Clark ER, Hughes IE and Letley E. The effect of oral administration of various sugars on blood ethanol concentration in man. J Pharm Pharmacol 25:309–323 (1973).
539. Mascord D, Smith J, Starmer GA and Whitfield JB. The effect of fructose on alcohol metabolism and on the lactate/pyruvate ratio in man. Alc Alcohol 26:53–59 (1991).
540. Crow KE, Newland KM and Batt RD. The fructose effect. NZ Med J 93:232–234 (1981).
541. Bode C. The metabolism of alcohol: Physiological and pathological aspects. J Roy Coll Phys 12:122–135 (1978).
542. Cohen RD. Effect of fructose on blood alcohol level. Lancet ii:1086 (1972).
543. Lister R and Nutt DJ. Is RO 15–4513 a specific alcohol antagonist?. Trends Neur Sci 10: 223–225 (1987).
544. Allan AN and Harris RA. A new alcohol antagonist: Phaclofen. Life Sci 45:1771–1779 (1989).
545. Polacsek P. Interaction of alcohol and other drugs an annotated bibliography. Addiction Research Foundation, Toronto pp 1–535 (1970).
546. Li J, Mills T and Erato R. Intravenous saline has no effect on blood ethanol clearance. J Emerg Med 17:1–5 (1999).
547. Hyvärinen J, M. Laakso, H. Sippel and Roine R. et al. Alcohol detoxification accelerated by oxygenated drinking water. Life Sci 22:553–560 (1978).
548. Ylikahri R and Leino T. Metabolic interactions of xylitol and ethanol in healthy males. Metabolism 28:25–29 (1979).
549. Alkana RL, Parker ES, Cohen HB, Birch H and Nobel EP. Interaction of sted-eze, niketh-amide, pipradrol, or ammonium chloride with ethanol in human males. Alcohol Clin Exp Res 4:84–92 (1980).
550. Kelly M, Myrsten AL and Goldberg L. Intravenous vitamins in acute alcoholic intoxication: effects on physiological and psychological functions. Br J Addict 66:19–30 (1971).
551. Chen MF, Boyce Worth H and Hsu JM. Effect of ascorbic acid on alcohol clearance. J Am Coll Nutrit 9:185–189 (1990).
552. Susick RL and Zannoni VG. Effect of ascorbic acid on the consequences of acute alcohol consumption in humans. Clin Pharmacol Ther 41:502–509 (1987).
553. Linnoila M, Mattila MJ, Karhunen P, Nuotto E and Seppäla T. Failure of TRH and ORG 2766 hexapeptide to counteract alcoholic inebriation in man. Eur J Clin Pharmacol 21:27–32 (1981).
554. Kraemer R, Mallach HJ, Raff G and Schulz H. Influence of mobiletten on the effect of alcohol drinking in man. Int J Clin Pharmacol 15:301–309 (1977).
555. Mallach HJ, Raff G and Kraemer R. On the influence of mobiletten on the effect of alcohol in the human. Int J Clin Pharmacol 15:576–580 (1977).
556. Miller LG. Herbal medicines: selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med 158:2200–2211 (1998).
557. Azcona O, Barbanol MJ, Torrent J and Jane F. Evaluation of the central effects of alcohol and caffeine interaction. Br J Clin Pharmacol 40:393–400 (1993).

558. Liguori A and Robinson JH. Caffeine antagonism of alcohol-induced driving impairment. Drug Alc Depend 63:123–129 (2001)
559. Shoaf SE and Linnoila M. Interaction of ethanol and smoking on the pharmacokinetics and pharmacodynamics of psychotropic medications. Psychopharm Bull 27:577–594 (1991).
560. Mendelson J, Jones RT, Upton R and Jacob P. Methamphetamine and ethanol interactions in humans. Clin Pharmacol Ther 57:559–568 (1995).
561. Mattila MJ, Kuitunen T and Pletan Y. Lack of pharmacodynamic and pharmacokinetic interactions of the antihistamine ebastine with ethanol in healthy subjects. Eur J Clin Pharmacol 43:179–184 (1992).
562. Lader M, Melhuish A, Frcka G, Fredricson Overo K and Christensen V. The effects of citalopram in single and repeated doses and with alcohol on physiological and psychological measures in healthy subjects. Eur J Clin Pharmacol 31:183–190 (1986).
563. Van Harten J, Stevens LA, Raghoebar M and Holland RL et al. Fluvoxamine does not interact with alcohol or potentiate alcohol-related impairment of cognitive function. Clin Pharmacol Ther 52:427–436 (1992).
564. Naranjo CA, Sullivan JT, Kadlec KE, Woodley-Remus DV, Kennedy G and Sellers EM. Differential effects of viqualine on alcohol intake and other consummatory behaviors. Clin Pharmacol Ther 46:301–309 (1989).
565. Anton R, Paladino JA, Morton A and Thomas RW. Effect of acute alcohol consumption on lithium kinetics. Clin Pharmacol Ther 38:52–55 (1985).
566. Dole VP, Fishman J, Goldfrank L, Khanna J and McGivern RF. Arousal of ethanol-intoxicated comatose patients with naloxone. Alcohol Clin Exp Res 6:275–279 (1982).
567. Bodd E., Beylich M, Christophersen A and Morland J. Oral administration of codeine in the presence of ethanol: A pharmacokinetic study in man. Pharmacol Toxicol 61:297–300 (1987).
568. Donnelly B, Balkon J, Lasher C and DePaul Lynch V et al. Evaluation of the methadone-alcohol interaction. 1. Alterations of plasma concentration kinetics. J Anal Toxicol 7:246–248 (1983).
569. Griffin JP, D'Arcy PF and Speirs CJ. A manual of adverse drug interactions. 4th edition, Wright, London 1988.
570. Buajordet I, Ebbesen J, Erikssen J, Brors O, Hilberg T. Fatal adverse drug events. The paradox of drug treatment. J Intern Med 250:327–341 (2001).
571. Ebbesen J, Buajordet I, , Erikssen J, Brors O, Hilberg T et al. Drug-related deaths in a department of internal medicine. Arch Intern Med 161:2317–2323 (2001).
572. Bjornaas MA, Jacobsen D, Haldorsen T and Ekeberg O. Mortality and cases of death after hospital treated self-poisoning in Oslo, A 20-year follow up. Clin Toxicol 47:116–123 (2009).
573. Hovda KE, Bjornaas MA, Skog K, Opdahl A. et al. Acute poisonings treated in hospitals in Oslo: A one-year prospective study (I): Pattern of poisoning. Clin Toxicol 46:35–41 (2008).
574. Heyerdahl F, Bjornaas MA, Hovda KE, Skog K, et al. Acute poisonings treated in hospitals in Oslo: A one-year prospective study (II): Clinical outcome. Clin Toxicol 46:42–49 (2008).
575. Jönsson A, Holmgren P and Ahlner J. (2004) Fatal intoxications in a Swedish forensic autopsy material during 1992–2002. Forensic Sci Int 143:53–9 (2004).
576. Wester K, Jönsson AK, Spigset O, Druid H, and Hägg S. Incidence of fatal adverse drug reactions a population based study Br J Clin Pharmacol 65:573–579 (2008).
577. Lazarou J, Poimeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. JAMA 279:1200–1205 (1998).
578. Room R, Babor T, Rehm J. Alcohol and public health. Lancet 365:519–530 (2005).
579. Avorn J. Dangerous deception - hiding the evidence of adverse drug effects. N Engl J Med 355:2169–2171 (2006).
580. Phillips DP, Jarvinen JR and Phillips RR. A spike in fatal medication errors at the beginning of each month. Pharmacotherapy 25:1–9 (2005).
581. Phillips DP, Christenfeld N and Ryan NM. An increase in the number of deaths in the United States in the first week of the month. N Eng J Med 341:93–98 (1999).

582. Ulrich RG. Idiosyncratic toxicity: A convergence of risk factors. Annu Rev Med 58:17–34 (2007).
583. Bugelski PJ. Genetic aspects of immue-mediated adverse drug effects. Nat Rev Drug Disc 4:59–69 (2005).
584. Knowles SR, Uetrecht J and Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndrome. Lancet 356:1587–1591 (2000).
585. Logan BK and Distefano S. Ethanol content of various foods and soft drinks and their potential for interference with a breath-alcohol test. J Anal Toxicol 22:181–183 (1998).
586. Baum CR, Shannon MW and Woolf A. Breath and blood ethanol following use of a cough-cold preparation. J Tox Clin Tox 35:643–644 (1997).
587. Mallon L, Broman J-E and Hetta J. Is usage of hypnotics associated with mortality. Sleep Med 10:279–286 (2009).
588. Schmidt G. Detection and estimation of barbituric acid derivatives. Methods of Forensic Science edited by F Lundquist, vol 1, Interscience Publishers pp 373–496, (1962).
589. Druid H and Holmgren P. A compilation of fatal and control concentrations of drugs in post-mortem femoral blood. J Forensic Sci 42:79–87 (1997).
590. Jones AW, Holmgren A and Kugelberg F. Concentrations of scheduled prescription drugs in blood of impaired drivers. Considerations for interpreting the results. Ther Drug Monit 29:248–260, (2007).
591. Katz DA, Murray B, Bhathema A, Schelijo L. Defining drug disposition determinants: a pharmacogenetic pharmacokinetic strategy. Nat rev Drud disc 7:293–305 (2008).
592. Pelkonen O, Kapitulnik J, Gundert-Remy U, Boobis AR, Stockis A. Local kinetics and dynamics of xenobiotics. Clin Rev Toxicol 38:697–720 (2008).
593. Nestler EJ. Genes and addiction. Nature Med 26:277–281 (2000).
594. Mayfield RD, Harris RA, Schuckit MA. Genetic factors influencing alcohol dependence. Br J Pharmacol 154:275–287 (2008).
595. Koob GF, Lloyd GK, Mason NJ. Development of pharmacotherapies for drug addiction: a Rosetta Stone approach. Nat rev Drug Disc 8:500–515 (2009).
596. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J 5:6–13 (2005).
597. Ingelman-Sundberg M and Rodriguez-Antona C. Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy. Philos Trans R Soc Lond B Biol Sci 360:1563–1570 (2005).
598. Ingelman-Sundberg M, Sim SC, Gomez A and Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther 116:496–526 (2007).
599. Nebert DW and Russell DW Clinical importance of the cytochromes P450. Lancet 360: 1155–1162 (2002).
600. Guengerich FP. Cytochrome P450s and other enzymes in drug metabolism and toxicity. The AAPS journal 8:E101-E111 (2006).
601. Kirchheiner J and Seeringer A. Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. Biochim Biophys Acta 1770:489–494 (2007).
602. Ingelman-Sundberg M. Genetic variability in susceptibility and response to toxicants. Toxicol Lett 120: 259–268 (2001).
603. Pirmohamed M and Park BK. Genetic susceptibility to adverse drug reactions. Trends Pharmacol Sci 22:298–305 (2001).
604. Nebert DW. Drug-metabolizing enzymes, polymorphisms and interindividual response to environmental toxicants. Clin Chem Lab Med 38:857–861 (2000).
605. Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet 359:1667–1671 (2000).
606. Ingelman-Sundberg M. Pharmacogenetics: an opportunity for a safer and more efficient pharmacotherpy. J Intern Med 250:186–200 (2001).
607. Evans WE, and McLeod HL. Pharmacogenomics-drug disposition, drug targets, and side effects. N Engl J Med 348:538–549 (2003).

608. Shurin SB, and Nabel EG. Pharmacogenomics--ready for prime time? N Engl J Med 358:1061–1063 (2008).
609. Nakamura Y. Pharmacogenomics and drug toxicity. N Engl J Med 359:856–858 (2008).
610. Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. Clin Pharmacol Therap 84:417–423 (2008).
611. Chen ML. Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 45:957–964 (2006).
612. Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet 336:1667–1671 (2000).
613. Li T-K. Pharmacogenetics of responses to alcohol and genes that influence alcohol drinking. J Studies Alc 61:5–12 (2000).
614. Kalow W. Pharmacogenetics in biological perspective. Pharmacol Rev 49:369–379 (1997).
615. Li T-K, Yin SJ, Crabb DW, O'Connor S and Ramchandani VA. Genetic and environmental influences on alcohol metabolism in humans. Alcohol Clin Exp Res 25:136–144 (2001).
616. Vesell ES, Page JG and Passananti GT. Genetic and environmental factors affecting ethanol metabolism in man. Clin Pharmacol Ther 12:192–201 (1971).
617. Kim BH, Yi S, Kim J, Lim KS et al. Influence of alcohol on the hemodynamic effects and pharmacokientic properties of mirodenafil: A single-dose, randomized-sequence, open-label, crossover study in healthy male volunteers in Korea. Clin Therap 31:1234–1243 (2009).

Chapter 14
Nicotine and Tobacco

Edward J. Cone, Reginald V. Fant, and Jack E. Henningfield

Abstract Roughly one-quarter of adults in the United States smoke tobacco products. Further, millions of smokers use nicotine replacement therapies (NRTs) as aids to quit smoking. NRTs are available in several forms including oral forms (gum, lozenge), transdermal patch, nasal spray, and vapor inhaler. Because of the high prevalence of smoking and use of NRTs, it is important that clinicians be aware of potential drug interactions that may occur. Nicotine and tobacco constituents may influence metabolic rates by induction or inhibition of enzyme systems. Nicotine is mainly metabolized in the liver to cotinine by the enzyme CYP2A6. Cigarette smoke contains literally thousands of compounds, among which polycyclic aromatic hydrocarbons (PAHs) are primarily responsible for its enzyme-inducing characteristics. PAHs have been shown to induce primarily three cytochrome P450 enzymes (e.g., CYP1A1, CYP1A2, and CYP2E1) as well as glucuronosyltransferases. Nicotine has been shown to interact with numerous drugs including alcohol, antidepressants, antihistamines, antipsychotics, barbiturates, benzodiazepines, caffeine, carbon tetrachloride, cimetidine, cocaine, nitrates, opioids, and phencyclidine. Tobacco has been shown to interact with alcohol, analgesics/antipyretics, anticoagulants, antidepressants, antipsychotics, benzodiazepines, caffeine, carbamazepine, cardiovascular drugs, insulin, opioids, steroid hormones, tacrine, and theophylline. The only drug class contraindicated for smokers are combined oral contraceptives. Specifically, because of cardiovascular risk in smokers, combined oral contraceptives are considered contraindicated in heavy smokers who are older than 35 years. In addition, people who smoke, or people who stop smoking, may require dosage adjustments when using some medications including acetaminophen, caffeine, imipramine,

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oxazepam, pentazocine, propranolol, theophylline, insulin, adrenergic antagonists, and adrenergic agonists. This chapter will discuss the underlying evidence regarding these potential drug interactions.

Keywords Nicotine • Tobacco • Acetaminophen • Caffeine • Imipramine • Oxazepam • Pentazocine • Propranolol • Theophylline • Insulin • Adrenergic antagonist • Adrenergic agonist

Introduction

Forms of Nicotine Replacement Therapy and Prevalence of Use

Forms of Nicotine Replacement Therapy

The first nicotine replacement therapy (NRT) made available to consumers was transmucosally delivered nicotine polacrilex ("nicotine gum"). The 2-mg containing formulation of nicotine gum was first marketed in the United States in 1984 as a prescription medication. The 4-mg form was marketed in 1992 to enable heavier smoking patients the replacement levels that they required for successful smoking cessation. In 1996, both the 2- and 4-mg forms were marketed as over-the-counter (OTC) medications in the United States, which has made the products much more widely available to consumers. In 1999, a mint-flavored gum was marketed in the United States in an effort to increase compliance with useful instructions among patients who found the original ("peppery") flavor to be unpalatable. About 50% of the nicotine in gum is absorbed, most via the buccal mucosa and a small portion through the stomach due to swallowed saliva [1]. Thus, when nicotine gum is chewed on a fixed schedule of 10 pieces per day, a smoker receives about 10 mg or 20 mg of nicotine per day using the 2-mg or 4-mg gum formulations, respectively. The average systemic intake of nicotine from cigarettes is about 30 mg/day [2]. Thus, most gum chewers do not match daily the nicotine levels achieved through the smoking of a cigarette. Furthermore, because of the relatively slow absorption of nicotine from gum compared to smoke inhalation, individual doses do not produce the extremely high arterial levels of nicotine produced by smoke inhalation [3].

In the United States, prescription-only marketing of four transdermal-delivery ("nicotine patch") systems began in late 1991 and 1992. In 1996, two brands of nicotine patches were marketed as OTC medications to increase availability to consumers. The transdermal patch delivers nicotine throughout the day. Compliance is based on whether or not the patient places the patch on the body in the morning, rather than on the patients actively using a product throughout the day, as is the case with the gum. As shown in Fig. 14.1, the nicotine patch delivers nicotine more slowly to the bloodstream than the gum does, although nicotine plasma concentrations can get higher during the day with patch use than with gum use, especially if

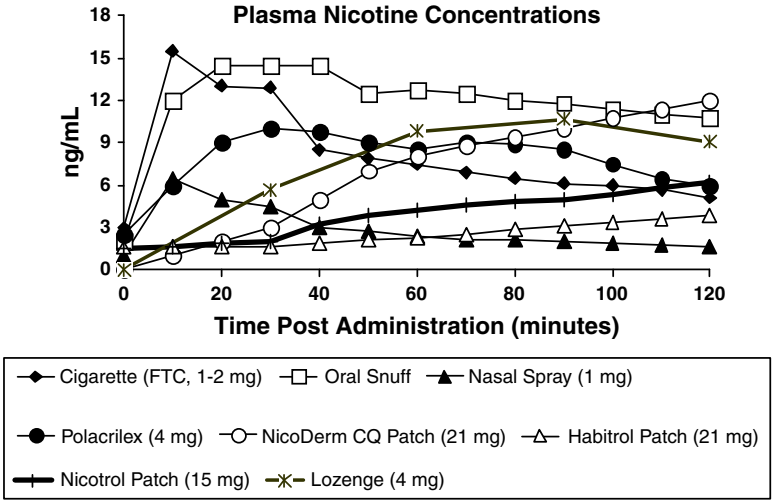

Fig. 14.1 Venous plasma nicotine concentrations in nanograms of nicotine per milliliter of blood as a function of time for various nicotine delivery systems (adapted from references [182–184])

the patient uses fewer pieces of gum than recommended. The highest dose of all patch brands deliver an average of 0.9 mg nicotine per hour although, as shown in Fig. 14.1, the within-day kinetics varies considerably across the brands. The maximum plasma concentrations range from 13 to 23 ng/mL and the time taken to reach maximum plasma concentration ranges from 4 to 9 h [4].

Nicotine nasal spray was first marketed in the United States as a prescription smoking cessation medication in 1997. The nasal spray was designed to deliver doses of nicotine to the smoker more rapidly than was possible with use of the gum or patch. The device currently available to consumers is a multi-dose bottle with a pump mechanism fitted to a nozzle that delivers 0.5 mg of nicotine per 50-uL spray. Each dose consists of two sprays, one to each nostril. As shown in Fig. 14.1, nicotine nasal spray is absorbed into the blood rapidly relative to gum and patch. Although the rate of plasma nicotine absorption with the spray approaches that of cigarettes and oral snuff, the magnitude of the increase in plasma nicotine concentrations is lower. According to labeling, the dose of nasal spray should be individualized for each patient based on the patient's level of nicotine dependence and the occurrence of adverse effects resulting from nicotine excess. Patients should be started with one or two doses per hour, which may be increased up to the maximum of 40 doses per day. One dose of nasal spray per hour (1-mg nicotine) for 10 h produces average plasma concentrations of 8 ng/mL. The nasal spray is the only nicotine replacement product documented to provide rapid enough delivery to produce an arterial blood level spike. Although not achieving the tenfold arterial to venous ratio sometimes produced by cigarettes [5], it can produce a twofold arterial bolus [6].

The nicotine vapor inhaler, which consists of a mouthpiece and a plastic cartridge containing nicotine, was first marketed in the United States in 1998 as a prescription

smoking cessation medication. The vapor inhaler was designed to satisfy behavioral aspects of smoking, namely, the hand-to-mouth ritual, while delivering nicotine to combat physiological withdrawal symptoms produced by tobacco withdrawal. Each inhaler cartridge contains 10 mg nicotine, of which 4 mg can be delivered, and 2 mg can be absorbed by inhaling approximately 80 times per inhaler [7]. Because, extraction of nicotine from the mouthpiece is influenced by ambient air temperature and the difficulty of many people in taking 80 inhalations per hour that would be required to provide 2 mg doses, typical absorption levels are probably substantially lower than 2 mg per hour [8]. The majority of nicotine is delivered into the oral cavity (36%) and in the esophagus and stomach (36%) [9]. Very little nicotine is delivered to the lung (4%). Because absorption is primarily through the oral mucosa, the rate of absorption is similar to that of nicotine gum. Patients may self-titrate with the inhaler to the level of nicotine they require. However, as with nicotine gum, success is largely dependent on the number of doses taken per day. In clinical trials, most smokers who successfully abstained from smoking used between 6 and 16 cartridges per day.

A nicotine lozenge was approved for marketing in the United States in 2002 as an over-the-counter product. Each lozenge contains 2 or 4 mg nicotine. As shown in Fig. 14.1, nicotine is absorbed at a relatively slow rate, comparable to nicotine polacrilex. A slightly higher peak plasma concentration is reached relative to the gum; however, a longer period of time is taken to reach the peak.

Prevalence of Use of Nicotine Replacement Therapy

According to the Centers for Disease Control, in 1998, there were about 8.5 million pharmacologically assisted quit attempts [10] by smokers. The nicotine patch accounted for 49% of pharmacologically assisted quit attempts and nicotine gum accounted for 28%. Twenty-one percent of pharmaceutically assisted cessation attempts were made using bupropion (Zyban). The nicotine inhaler and nasal spray accounted for less than 3%.

Forms of Tobacco and Prevalence of Use

Forms of Tobacco

Tobacco is available in a variety of forms for human consumption. The most common form today is the cigarette. Although cigarettes come in many forms, there are specific definitions for their composition. According to section 26 U.S.C. 5702(b) of the BATF, a cigarette is defined as follows: (a) any roll of tobacco wrapped in paper or in any substance not containing tobacco, and (b) any roll of tobacco wrapped in any substance containing tobacco, which, because of its appearance, the type of tobacco used in the filter, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette. The FDA further clarified the definition of a

cigarette for purposes of regulation in section 897.3 of 21 CRF Part 801 as follows: any product (including components, accessories, or parts) which contains or delivers nicotine, and is intended to be burned under ordinary conditions of use [11]. Cigarette tobacco is flue-cured, i.e., it is rapidly dried over smokeless heat, resulting in an acidic smoke when the product is burned [12]. Because of the acidity of the smoke, there is little resulting nicotine absorption via the oral mucosa. However, pulmonary absorption of nicotine from the inhaled smoke is rapid and almost complete.

Cigars, in contrast, consist of tobacco that is air-cured, then wrapped in tobacco leaf or reconstituted paper made of tobacco plant material. The resulting smoke of air-cured tobacco is much more basic than flue-cured tobacco [12]. Nicotine from this smoke is readily absorbed through the oral mucosa, as well as the lung. Nicotine can also be absorbed directly from the tobacco if the cigar is held in the mouth. Unlike cigarettes, which are fairly consistent in their tobacco weight and size, cigars vary greatly. Henningfield et al. [13] studied a variety of cigar types and found that the weight of the cigars ranged from 0.77 to 22 g, lengths ranged from 68 to 214 mm, and diameter ranged from 8 to 21 mm. In addition, the total nicotine content of these cigars ranged from 10.1 to 444 mg, and the pH values of the tobacco ranged from 6.2 to 8.2.

The tobacco from pipes can be air-cured, fire-cured, sun-cured, or flue-cured, depending on the quality of the tobacco [12]. The tobacco is not wrapped for smoking. Because of these differences in curing methods, the resulting smoke can vary widely in its pH, in turn resulting in wide variability of nicotine absorption through the oral mucosa.

Chewing tobacco and oral snuff are made from air-cured tobacco, resulting in a tobacco that has a basic pH, which is ideal for buccal absorption. However, there is wide variability between products on the nicotine concentration of the tobacco as well as the pH of the tobacco in solution, resulting in large differences in rate of nicotine absorption and peak plasma levels [14].

Prevalence of Use

The 2007 National Survey on Drug Use and Health [15], conducted by the Substance Abuse and Mental Health Services Administration, is the most recent source of national data on rates of tobacco use. The latest survey estimated that in 2007, 70.9 million Americans aged 12 and older (28.6%) reported current use of a tobacco product. An estimated 60.1 million (24.2%) smoked cigarettes, 13.3 million (5.4%) smoked cigars, 8.1 million (3.2%) used smokeless tobacco, and 2 million (0.8%) smoked tobacco in pipes. The majority of current cigarette adult smokers smoke at least a pack of cigarettes on a daily basis. Among the 60.1 million current cigarette smokers aged 12 or older in 2007, 36.8 million (61.3%) used cigarettes daily. The percentage of daily cigarette smokers increased with age, with 26.3% among past month cigarette users aged 12–17, 49.3% among those aged 18–25, and 66.3% among those aged 26 or older. In addition, over half (50.9%) of daily smokers aged 12 or older reported smoking 16 or more cigarettes per day; this is approximately

one pack or more. The percentage of daily smokers who used a pack of cigarettes or more per day was steadily higher with age from 18.5% among those aged 12–17 to 33.1% among those aged 18–25 to 55.0% among those aged 26 or older.

In 2007, males were more likely than females to report past month use of any tobacco product. In 2007, 35.2% of males aged 12 and older were current users of any tobacco product compared to 22.4% of females. Males were 15 times more likely than their female counterparts to report current use of smokeless tobacco (6.3% of males aged 12 and older compared with 0.4% of females). As seen for smokeless tobacco, males were more likely than females to report past month cigar use. Specifically, males were five times more likely than females to report the past month use of cigars (9.1% compared to 1.8%).

Passive smoking also delivers nicotine to nonsmokers. Passive smoking is exposure to tobacco smoke that occurs when a nonsmoker is exposed to the sidestream smoke of a cigarette. Drug interactions may occur in nonsmokers, particularly infants and children, exposed to tobacco smoke in the home. The proportion of infants exposed to tobacco smoke varies across the United States. In 2000, the percentage of homes with at least one smoker ranged from 21% in Colorado to 39.2% in West Virginia [16]. Smoking in the workplace also varies widely. The proportion of indoor workplaces with no-smoking policies ranged from 61.4% in Mississippi to 83.9% in Montana.

Components of Nicotine Replacement Therapy and Tobacco

NRTs essentially contain nicotine and ingredients required for the specific formulations to operate as intended, e.g., stabilizing ingredients, buffering compounds, and flavors. Nicotine is generally the only compound in these products of interest in determining drug interactions.

In contrast to NRTs, ingredients included in cigarette tobacco may be any combination from a list of approximately 600 provided at the Philip Morris web site (http://www.philipmorrisusa.com). Brown & Williamson, according to their website (see http://www.bw.com/index_sub2.cfm?Page=/SHC/Index.cfm%3FID%3D4%26Sect%3D4), in 2000, used 299 ingredients in the manufacture of their tobacco products. These include: ammonium compounds that have been shown to enhance the delivery of nicotine, glycerol to which nicotine binds for effective lung delivery, and flavorings such as chocolate and cinnamon. Although the website states that these ingredients "…are either a food, a beverage, an approved food additive, an approved tobacco product additive, or affirmed to be acceptable for addition to foods by an Expert Body such as the U.S. Food & Drug Administration (FDA), the Flavor and Extract Manufacturers Association (FEMA) or the Council of Europe (COE)," none of them have been specifically approved by any regulatory as safe for use in conditions in which they are subjected to pyrolysis and combustion since that process can radically alter their chemistry and toxicity. In addition, the process of generating cigarette smoke produces more than 4,000 compounds together with those

contained in tobacco [17, 18]. Thus, identifying all of the potential drug interactions with individual compounds in tobacco smoke is not possible. Nonetheless, several major influences on drug disposition and several important interactions have been documented as discussed further on in this review.

Nicotine and Tobacco Pharmacology

Two medical disorders are now widely recognized elements of what is more generally referred to as "tobacco addiction" or "tobacco dependence". The first is nicotine dependence, which is characterized by the maladaptive and persistent use of tobacco products. The second is nicotine withdrawal, which is characterized by a constellation of symptoms that accompany abstinence from tobacco use [19]. These withdrawal symptoms include: dysphoric or depressed mood, insomnia, irritability, frustration, or anger, anxiety, difficulty in concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Tobacco craving is also common and can be persistent. These signs and symptoms make it difficult if not impossible for the vast majority of cigarette smokers to sustain abstinence for more than a few days [17].

Tobacco dependence and withdrawal are associated with a number of changes in the structure and function of the nervous and endocrine system, which lead the individual to feel "normal" and perform optimally while receiving daily doses of nicotine, and to feel dysfunctional when abstinent. Many of these symptomatic feelings correspond to objectively measurable changes in EEG, regional cerebral glucose metabolism, and performance on cognitive test batteries [20, 21]. These changes in the structure and function of the body, and the fact that the tobacco industry engineered its products to ensure that their use could cause such effects, led the Food and Drug Administration to conclude that nicotine in cigarettes and smokeless tobacco is a drug and that these products are drug delivery systems [22].

Even though most nicotine clears the body within 1–2 days of abstinence (its half-life is about 2 h), the mental dysfunction and other signs of withdrawal can persist for weeks and powerful cravings can resurge for months and years. Individuals vary widely in the severity and course of these symptoms. In part, the persistence of these symptoms can be attributed to changes in the body from which it may take many months to fully recover. However, the addictive process is more than altered physiology, but rather is related to psychological and behavioral factors as well.

Nicotine and Tobacco Toxicity

The toxicity of nicotine is generally related to its pharmacological activity at the high dosages delivered by cigarettes, though rarely achieve by nicotine replacement medications. For example, nicotine delivered by cigarettes can produce striking levels of heart rate acceleration and sympathetic hormone release which can be mimicked by

rapid intravenous infusions but rarely by nicotine medication use [6, 23]. Similarly, cigarette smoking readily produces plasma nicotine levels associated with increased fetal risk during pregnancy, but nicotine medications do not reliably produce such levels [24]. Nicotine has well-documented effects on cardiovascular physiology [23]. It increases blood pressure and force of contraction of the heart. Nicotine poisoning, as has occurred after exposure to nicotine containing insecticides, can produce cardiovascular collapse and death. Rapid delivery of high doses of nicotine, as in cigarette smoking, produces more intense cardiovascular effects than does more gradual dosing with products such as nicotine gum or transdermal nicotine patches [25].

Nicotine has also been shown to be potentially harmful to the gastrointestinal mucosa because it increases acid and pepsin secretions, gastric motility, and gastric reflux of bile salts [26]. Nausea and vomiting are the most common symptoms of acute nicotine poisoning in man. In animals, vomiting and diarrhea have also been observed. Such responses are caused by both the central and peripheral actions of nicotine.

Single-Dose Nicotine Toxicity

In experimental animals, the dose of nicotine that is lethal to 50% of animals (LD_{50}) varies widely, depending on the route of administration and the species tested. Intravenous LD_{50} doses of nicotine in mice range between 0.3 and 1.8 mg/kg body weight. The intraperitoneal LD_{50} values for nicotine bitartrate in mice and rats have been found to be 13 and 83 mg/kg body weight, respectively, while the values for five inbred hamster strains varied between 125 and 320 mg/kg body weight. The lethal oral dose of nicotine in adult humans has been estimated to be 40–60 mg [27, 28].

Lethal doses of nicotine cause peripheral curare-like paralysis of the respiratory muscles [29]. Extremely high doses of nicotine can cause transient stimulation followed by depression and paralysis of the central nervous system. Such doses also affect peripheral autonomic nervous system ganglia and nerve endings on skeletal muscles. Death usually occurs within a short period and is most often due to paralysis of respiratory muscles. Excessive doses of nicotine may also produce tremors followed by convulsions.

Smoking and Cardiovascular Disease Risk

Smoking has firmly been linked to increased risks of cardiovascular diseases including coronary heart disease, arteriosclerotic vascular disease, and stroke [30]. There are a number of mechanisms by which smoking may increase the risk of cardiovascular disease [31]. Nicotine and carbon monoxide acutely affect myocardial performance and cause tachycardia, hypertension, and vasoconstriction. Components of cigarette smoke injure the walls of blood vessels by destroying endothelial cells. Smoking produces metabolic and biochemical changes including elevations in plasma, free fatty acids, and vasopressin. Smoking causes an inhibition of cyclooxygenase, which decreases levels of prostacyclin and increase

levels of thromboxane A2. Chronic smoking leads to arteriosclerosis by increasing serum cholesterol and reducing high-density lipoprotein. In addition, smokers have increased platelet adhesiveness and aggregability that may lead to increased risk of thrombosis.

Many toxins are believed to contribute to smoking-related cardiovascular disease, including carbon monoxide, polycyclic aromatic hydrocarbons, glycoproteins, and nicotine. Some but not all of the characteristics of tobacco-related disease seem to be nicotine-related. Nicotine increases CNS sympathetic outflow, adrenal release of catecholamines, and local release of catecholamines from vascular nerve endings [26]. The net result is heart rate acceleration, increased myocardial contractility, constriction of some blood vessels, and a small increase in blood pressure. Nicotine can precipitate or aggravate acute coronary ischemic events by increasing myocardial work, and therefore nutrient demand, while reducing nutrient supply through coronary vasoconstriction. Catecholamine release may also precipitate or aggravate ischemia-induced arrhythmias, leading to sudden arrhythmic death. Other possible adverse effects of nicotine include injury to endothelial cells, induction of atherogenic lipid profile, and promotion of thrombosis [17].

Smoking and Cancer Risk

Several forms of cancer have been shown to be associated with smoking including cancers of the lung, lip and oral cavity, esophagus, pancreas, larynx, uterine cervix, bladder, and kidney [30]. Cigarette smoke is known to contain more than 4,000 compounds including over 40 carcinogens that include polyaromatic hydrocarbons, heterocyclic hydrocarbons, N-nitrosamines, aromatic amines, aldehydes, volatile carcinogens, inorganic compounds, and radioactive elements [30]. Carcinogenesis can be divided into two phases: initiation, in which DNA is damaged by the bonding of the carcinogen, and promotion, in which initiated cells become malignant. Compounds found in the particulate matter of cigarette smoke ("tar") have been shown to be major tumor initiators in laboratory animals [30]. There are data suggesting that nicotine could theoretically play some role as a cancer promoter [32–36]; however, the majority of the effects of tobacco on cancer appear related to non-nicotine components of tobacco smoke and the risk of nicotine-related cancer, if any, is small or insignificant in smokers who are exposed to a high concentration of many carcinogens [32].

Smoking and Pulmonary Disease Risk

Pulmonary problems associated with tobacco smoking include chronic obstructive pulmonary disease (COPD), asthma, pneumonia, influenza, bronchitis, and emphysema [30]. Several mechanisms have been identified by which smoking may contribute to the development of these pulmonary problems [37, 38]. These include smoking-induced alterations of central and peripheral airways, alveoli

and capillaries, and immune function. Changes in the central airways include loss of cilia, mucus gland hyperplasia, increased number of goblet cells, and histological changes. These histological changes include regression of normal pseudostratified ciliated epithelium to squamous metaplasia, carcinoma in situ, and eventually invasive bronchogenic permeability. Changes in peripheral airways include inflammation and atrophy of the airways, goblet cell metaplasia, mucus plugging, smooth muscle hypertrophy, and peribronchiolar fibrosis. Changes in alveoli and capillaries include destruction of peribronchiolar alveoli, reduction in the number of small arteries, bronchoalveolar lavage fluid abnormalities, elevated levels of IgA and IgG, and increased percentages of activated macrophages. Regarding immune function, smoking produces higher peripheral leukocyte cell counts, elevations in peripheral eosinophils, increased levels of serum IgE, lower allergy skin test reactivity, and reduced immune response to inhaled antigens. None of these effects appear to be related to nicotine delivery, but rather to other constituents of tobacco smoke.

Summary of Toxicity

The foregoing discussion of the health effects of nicotine and tobacco suggests that most of the adverse health effects of tobacco are related to non-nicotine components of tobacco smoke, rather than from the delivery of nicotine per se. Further, the vast majority of smokers who use nicotine replacement medications obtain lower doses of nicotine than when they were smoking. Thus, to the extent that diseases demonstrate a dose–response to nicotine, persons on NRT have lower risk of these diseases.

Mechanisms of Interactions with Nicotine and Tobacco

Pharmacokinetic Mechanisms

Pharmacokinetic interactions of nicotine and tobacco with other drugs can take place through direct drug–drug interactions or via indirect mechanisms. Kinetic alterations can result from changes in absorption, distribution, metabolism, and elimination. Changes in absorption can occur through delayed gastric emptying. Changes in distribution can occur through displacement of drug binding to plasma protein by nicotine or tobacco constituents. When a highly protein-bound drug is displaced from binding, a sharp increase in free drug concentration may occur, leading to changes in distribution and possible toxic effects. Drug metabolic alterations can occur through multiple mechanisms. Most drugs are metabolized by oxidation, reduction, hydrolysis, and conjugation reactions. The resultant metabolite(s) usually is less active than the parent compound, but occasionally metabolism

results in conversion of drug to a species with increased pharmacological activity and increased potential for toxicity. Metabolism also generally results in production of molecules that are more amenable to excretion. Changes in the level or activity of metabolic processes can substantially increase or reduce drug and tissue levels leading to either enhanced or diminished effects or even toxic effects. Enzyme inhibition is the most commonly encountered form of drug–drug interaction, and perhaps is the most common mechanism responsible for development of toxic drug levels. Enzyme induction generally lowers effective drug levels and reduces therapeutic effects. Changes in elimination rate could potentially be produced by an alteration in excretory processes.

Nicotine and tobacco constituents may influence metabolic rates by induction or inhibition of enzyme systems. Nicotine is mainly metabolized in the liver via multiple pathways. Inhibition of one or more of these pathways could lead to increased nicotine plasma levels. For example, 70–80% of nicotine is metabolized to cotinine by the enzyme CYP2A6. Sellers et al. [39] showed that inhibition of the CYP2A6 enzyme with the selective inhibitor, methoxsalen, significantly increased plasma levels of oral nicotine. In addition, studies have shown that individuals carrying defective CYP2A6 alleles are under-represented in the tobacco-dependent population, and that smokers with deficient nicotine metabolism smoked fewer cigarettes [40, 41]. It was postulated that individuals with genetically deficient CYP2A6 nicotine metabolism are at lower risk to become smokers and that CYP2A6 inhibitors could play an important role in smoking cessation therapy.

Nicotine also has been reported to induce its own metabolism, but smokers have been shown to have a lower clearance of nicotine compared to nonsmokers [42]. Cigarette smoke contains literally thousands of compounds, among which polycyclic aromatic hydrocarbons (PAHs) are primarily responsible for its enzyme-inducing characteristics. PAHs have been shown to induce primarily three cytochrome P450 enzymes (e.g., CYP1A1, CYP1A2, and CYP2E1) as well as glucuronosyltransferases [43]. CYP1A2 and CYP2E1 are primarily associated with the liver but have been found in lung and other tissues and in the placenta of mothers who smoke. CYP1A1 levels are low in hepatic microsomes, but are found in lung, intestine, skin, lymphocytes, and placenta.

Pharmacodynamic Mechanisms

Pharmacodynamic interactions can occur through receptor site competition, by alteration of receptors, and through additive or opposing pharmacological effects. Nicotine is the major alkaloid in tobacco and exerts prominent effects including catecholamine release, peripheral and coronary vasoconstriction, decreased skin temperature, tachycardia, and elevated blood pressure [44]. Acute tolerance develops rapidly. Depending upon the drug, interactions may occur by additive, synergistic, or opposing effects.

Nicotine Interactions

Interactions

Alcohol

In animals, Soderpalm et al. [45] reported that subchronic intermittent pretreatment with nicotine enhanced the dopamine activating and reinforcing properties of ethanol in rats. Another study in dogs showed that nicotine administration after alcohol produced significant increases in cardiovascular measures, but when alcohol was administered after nicotine, all excitatory effects were attenuated [46].

Ethanol administration also has effects on nicotine metabolism. When administered acutely to laboratory animals, ethanol retards rates of nicotine metabolism, whereas chronic ethanol pretreatment generally accelerates metabolic rates of nicotine [47]. Administration of nicotine was shown to lower peak blood alcohol concentrations in neonatal rats [48], as well as adult rats [49]. This may be because nicotine delays gastric emptying, and the longer the alcohol is retained in the stomach, the more likely that the alcohol would be metabolized by gastric alcohol dehydrogenase before its absorption into the bloodstream by the small intestine (the major site of alcohol absorption).

In humans, nicotine (spray, 20 μg/kg) administered together with alcohol to abstinent smokers generally produced additive subjective effects ("head rush" and dizziness) and cardiovascular effects, although nicotine tended to attenuate fatigue and intoxication [50]. Some differences were noted between men and women in subjective responses from combined administration. For men, nicotine combined with alcohol attenuated measures of dizzy, relaxed and tension, whereas effects were enhanced in women. In a study of female smokers and nonsmokers who chewed nicotine gum (2 mg), memory and motor function were facilitated by nicotine, and the debilitating effects of alcohol were antagonized [51].

Nicotine administration may increase alcohol consumption. In one study [52], occasional smokers smoked four nicotine-containing or four de-nicotinized cigarettes at 30-min intervals. Throughout the session, subjects could earn units of their preferred alcoholic beverage and glasses of water using a progressive-ratio task. The results indicated that nicotine increased alcohol self-administration in a significant proportion of participants without affecting water consumption.

Alcohol may potentiate the rewarding effects of nicotine. In a study of smokers who regularly consumed alcoholic beverages [53], ethanol potentiated some of the subjective rewarding effects of nicotine, including smoking satisfaction, stimulant as well as calming effects, and relief of craving for cigarettes. During the ad lib smoking period, the nicotine antagonist mecamylamine decreased satisfaction associated with the nicotine-containing cigarettes; mecamylamine also induced smoking but only in the placebo ethanol condition.

Antidepressants

Nicotine enhances the acute locomotor effects of bupropion, which may reflect alterations in common dopaminergic processes [54]. When rats were preexposed to nicotine or saline and then tested with bupropion in locomotor chambers, the acute stimulant effect of bupropion was potentiated by nicotine preexposure. When rats received nicotine repeatedly paired with the locomotor chambers or home cages, an additive effect was observed between acute bupropion and nicotine-conditioned hyperactivity in the chamber-paired group.

Nicotine appears to enhance the antidepressant effects of fluoxetine [55]. Using the forced swim test model, nicotine induced a significant reduction of the time in immobility during the (antidepressant effect). Fluoxetine failed to induce any effect after acute administration but did induce a significant decrease of immobility after subchronic administration. The combination of both drugs induced a larger effect than that observed after a single administration, but only after subchronic treatment.

Nicotine also appears to potentiate the antidepressant effects of imipramine and citalopram [56]. Using the tail-suspension test model, nicotine given before the measurement exerted no effect on immobility. Citalopram alone produced a slight decrease in immobility; however, coadministration of nicotine to citalopram-treated mice resulted in a robust decrease in immobility. Imipramine alone did not affect immobility, but given in combination with nicotine, a decrease in immobility was observed.

Antihistamines

In rats, nicotine in combination with tripelennamine produced supra-additive toxicity [57]. The interaction of nicotine with diphenhydramine was more complicated; supra-additive toxicity was observed at some doses, but antagonism occurred at other doses.

Antipsychotics

Nicotine has been widely shown to stimulate the release of dopamine. Given the disturbances of dopamine systems in schizophrenics, it has been speculated that schizophrenics may smoke as a form of self-medication, or to alleviate the side effects of antipsychotics. In rats, nicotine has been shown to potentiate the catalepsy produced by haloperidol [58, 59]. Neither cotinine nor nornicotine, the principal pharmacologically active metabolites of nicotine, produced potentiation. Although the mechanism remains unclear, it was suggested that nicotine's effect is related to striatal D2 receptor mechanisms. Nicotine attenuated the impairment in working memory performance caused by clozapine [60] and olanzapine [61]. Haloperidol and risperidone significantly attenuated the working memory improvement induced by nicotine [60]. Nicotine attenuated the decrement in attentional performance produced

by haloperidol [62]. Nicotine also attenuated the cognitive impairment produced by clozapine and risperidone [63].

In humans, the interactions of haloperidol and nicotine (patch, 7 & 14 mg/day) on cognitive performance in a group of schizophrenics were studied by Levin et al. [64]. Nicotine administration was found to produce a dose-related reversal of impairments in memory and complex reaction times induced by haloperidol. In addition, nicotine gum [65, 66] and transdermal nicotine patch [67] are reported to ameliorate symptoms of Tourette's syndrome in haloperidol-treated adolescents. [59]

Barbiturates

Nicotine potentiated sodium pentobarbital sleep time in a dose-dependent manner in mice [68]. At the highest tested dose of nicotine (5 mg/kg), an increase of 52% in sleep time was observed. Atropine reduced sleep time, but did not change the nicotine effect. Pretreatment with mecamylamine, a nicotine receptor antagonist, normalized sleep time.

Phenobarbital is a model-inducing agent for numerous drug metabolizing enzyme systems. Phenobarbital pretreatment of laboratory animals has been shown to induce the metabolism of nicotine and its metabolites, primarily through increased expression of CYP enzymes [47]. Phenobarbital induces not only the metabolism of nicotine, but also its metabolite, cotinine. Nicotine also has effects on phenobarbital disposition. A study in rats showed that acute pretreatment of rats with nicotine significantly reduced phenobarbital concentrations in serum, brain, and CSF at the onset of the righting reflex, but acute or chronic pretreatment with nicotine had no effect on the elimination kinetics of phenobarbital [69].

Benzodiazepines

The combination of nicotine and diazepam in rats responding to a fixed-interval schedule of liquid food reinforcement produced rate-increasing effects of nicotine at low diazepam doses [70]. At higher diazepam doses, the interaction between nicotine and diazepam was complex and was determined by the doses of drug and the aspect of behavior studied.

Nicotine may affect the development of tolerance to some effects of benzodiazepines [71]. In the social interaction test of anxiety, microinjections of midazolam into the dorsal hippocampus or dorsal raphé nucleus significantly increased the time spent in active social interaction, without changing locomotor activity, thus indicating specific anxiolytic effects. However, tolerance developed to these effects in rats that had been pretreated for 6 days with nicotine.

Caffeine

Nicotine and caffeine are among the most widely self-administered licit substances. Anecdotal evidence suggests that a pharmacological interaction may occur between

these substances [72]. Tanda and Goldberg [73] reviewed the pharmacologic effects of combining caffeine and nicotine. They indicated that the rewarding and subjective properties of nicotine can be changed by chronic caffeine exposure and concluded that caffeine exposure may be an important environmental factor in shaping and maintaining tobacco smoking. In particular, chronic exposure to caffeine in drinking water potentiated nicotine self-administration.

In dogs, the caffeine and nicotine combination produced significant synergistic excitatory effects [74]. In rats, nicotine decreased the anxiogenic effects of caffeine [75] in the elevated plus maze model of anxiety. In rats, caffeine potentiates the discriminative-stimulus effects of nicotine [76], suggesting that caffeine consumption may be a contributing factor in the onset, maintenance of, and relapse to tobacco dependence.

In humans, acute administration of nicotine (gum, 2 mg) combined with caffeine (250 mg) has been shown to facilitate memory and motor function of female smokers and nonsmokers [51]. In addition, a study in ten healthy volunteers (five men and five women) showed that nicotine (gum, 4 mg) combined with intravenous caffeine (250 mg) produced additive effects on cardiovascular parameters [77].

In contrast to the animal research, in humans, caffeine does not appear to affect the discriminative stimulus properties of nicotine in humans [78]. In a study of smokers initially trained to discriminate 20 μg/kg nicotine by nasal spray from placebo, pretreatment with caffeine did not alter nicotine discrimination and self-administration. Caffeine and nicotine influenced some subjective and cardiovascular responses, but there were no interaction effects except for diastolic blood pressure.

The appetite-suppressant effect of nicotine is enhanced by caffeine [79]. Chewing gums with nicotine and caffeine were administered to healthy young men of normal weight. Different combinations of 0, 1 or 2 mg of nicotine and 0, 50 or 100 mg of caffeine were administered during a 2-h period. Hunger and prospective food consumption were negatively associated with the increasing doses of nicotine, whereas satiety and fullness were positively associated with the increasing doses of nicotine. Caffeine appeared to amplify the effects of nicotine on hunger and fullness.

Carbon Tetrachloride

The effects of nicotine on the liver were studied both in the presence and absence of carbon tetrachloride, a known hepatotoxic solvent [80]. Nicotine alone, when given to rats at a concentration of 54 μmol/L, produced slight hepatotoxic effects, but when co-administered with carbon tetrachloride, the result was significant confluent necrosis compared to the control group and to the group receiving only carbon tetrachloride. Treatment with a higher dose of nicotine, 108 μmol/L, alone also showed significant pathological changes. These levels of nicotine were indicated to be comparable to those found in chronic smokers. It was also reported that pregnant rats were more resistant to the hepatotoxicity produced by nicotine and carbon tetrachloride suggesting that pregnancy somehow protects animals from the hepatotoxicity of nicotine and carbon tetrachloride.

Cimetidine

Cimetidine produces a variety of drug–drug interactions by inhibition of oxidative metabolism. In humans, cimetidine has been shown to increase plasma area-under-the-curve (AUC) of nicotine and half-life by 48% and 45%, respectively [81]. A similar effect by cimetidine has also been demonstrated in stumptailed macaques [82].

Cocaine

In rats, chronic nicotine differentially alters cocaine-induced locomotor activity in adolescent vs. adult male and female rats [83]. During a 7-day nicotine pretreatment period, nicotine increased locomotor activity in all groups compared to vehicle controls. Following the pretreatment period, male periadolescent rats pretreated with nicotine were more markedly sensitized to the locomotor-activating effects of cocaine than male adult rats, while female rats pretreated with nicotine were not sensitized to cocaine. In contrast, male and female periadolescent rats, but not adult rats, had increased amounts of repetitive beam breaks induced by cocaine after nicotine pretreatment. The authors concluded that these results suggest that nicotine use during adolescence carries a greater risk than during adulthood and that male adolescents may be particularly vulnerable to the risk of cocaine abuse after nicotine use.

In humans, nicotine treatment (two transdermal patches containing 22 mg) produced enhanced cue-induced cocaine craving and anxiety in patients with a history of crack cocaine abuse [84]. In contrast, nicotine treatment (transdermal patch containing 14 mg) of seven male tobacco smokers who used cocaine occasionally attenuated cocaine-induced increases of “high” and “stimulated,” but did not alter cocaine’s cardiovascular effects or plasma concentrations of cocaine and its metabolites [85].

Nitrites

The presence of nitrosamines in tobacco has been conclusively established. Additional amounts of nitrosamines could be formed endogenously by interaction between nicotine and sodium nitrite. Carmella et al. [86] identified N′-nitrosonornicotine (NNN), a known carcinogen, in the urine of rats treated with nicotine and sodium nitrite. The authors hypothesized that NNN formation could have occurred by direct reaction of nicotine with sodium nitrite in the acidic evirons of the stomach, or by nitrosation of nornicotine produced metabolically from nicotine. Interestingly, Du et al. [87] found that penetration of NNN across porcine oral mucosa was significantly increased in the presence of nicotine and ethanol. The authors suggested that the synergy between tobacco and alcohol in the etiology of oral cancer could be explained by the permeabilizing effects of alcohol on the penetration of tobacco-specific carcinogens across the oral mucosa.

Opioids

In mice, chronic nicotine has been shown to modify the effects of morphine on extracellular striatal dopamine and ventral tegmental GABA [88]. In nicotine-pretreated mice, morphine-induced dopamine release in the caudate putamen and nucleus accumbens was significantly augmented, as measured by microdialysis. Chronic nicotine treatment alone did not change basal extracellular concentrations of dopamine and its metabolites in the caudate putamen and nucleus accumbens, nor did it affect the rate of dopamine synthesis. In nicotine-treated mice, morphine increased GABA levels in the presence of nipecotic acid. There were no alterations in $GABA_B$-receptor function after chronic nicotine treatment alone.

Chronic nicotine treatment modifies the reinforcing effects of morphine in mice [89]. Specifically, nicotine-treated mice developed conditioned place preference after being conditioned twice with morphine, whereas in control mice a higher dose of morphine was required. Repeated nicotine administration also appears to attenuate the development of morphine tolerance and dependence in mice [90]. The authors found that the inhibitory effect of nicotine on the morphine tolerance and dependence was mediated by central nicotinic receptors and there was a cross-dependence between nicotine and morphine.

In self-administration studies with methadone-maintained patients, nicotine administration (gum, 2 and 4 mg) produced a significant increase in methadone consumption as compared to when subjects were nicotine-abstinence [91]. It was suggested that nicotine enhanced methadone consumption either by potentiating the reinforcing effects of methadone or by serving as a conditioned or discriminative stimulus.

Phencyclidine

In mice, nicotine blocked phencyclidine-induced behavioral toxicity (circular movements, side-to-side head movements, and hyperactivity) at high doses (12.3 and 30.8 μmol/kg), but at low doses (1.5 μmol/kg) significantly potentiated phencyclidine-induced convulsions [92]. In rats treated chronically with saline or nicotine (1 mg/kg twice daily for 11 days), there were no significant differences in the disposition of phencyclidine [93]. These results suggested that the interactions of phencyclidine and nicotine occurred through central nicotinic and muscarinic acetylcholine receptors.

Tobacco Interactions

Alcohol

It is well known that heavy drinkers tend to be heavy smokers and that consumption of alcohol is correlated with cigarette smoking. It has also been suggested that tobacco smoking could serve to attenuate the sedating effects of alcohol consumption [94].

Both drugs appear to operate through common neurologic systems. Behavioral reinforcement by either nicotine or ethanol is associated with the release of dopamine from mesolimbic dopaminergic terminals located in the nucleus accumbens [95]. Accordingly, it has been hypothesized that tobacco may decrease the risk of drinking for abstinent alcoholics. However, the role of smoking in the alcohol relapse process is controversial. If alcohol craving involves depletion of dopamine or endogenous opiates, the stimulatory effects of smoking on these systems may decrease craving. On the other hand, tobacco use may stimulate common neurological mechanisms, thereby increasing craving. It seems doubtful at this point that any favorable effects of smoking on alcohol recovery would outweigh the long-term harmful effects produced by smoking [95].

Analgesic/Antipyretics

The inductive effect of smoking on the metabolism of phenacetin was first reported by Pantuck et al. [96]. Oral doses of 900 mg of phenacetin resulted in significantly lower plasma phenacetin concentrations in smokers compared to nonsmokers. Peak phenacetin plasma levels of phenacetin at 2 h were 2.24 μg/mL in nonsmokers and 0.48 μg/mL in smokers. Recovery of *N*-acetyl-*p*-aminophenol (APAP) in urine indicated that similar drug absorption had occurred in both groups leading to the presumption that smoking had induced increased metabolism during the "first pass" through the liver [97]. Subsequent studies in animals exposed to cigarette smoke confirmed this assumption [98]. The effects of smoking on the disposition of acetaminophen have not been as consistent [99]. Miller [100] concluded that because of the large therapeutic index of acetaminophen, it is not likely that an increase in its metabolism would be clinically important.

The metabolism of nonsteroidal anti-inflammatory drugs (NSAIDs) may be affected by smoking. For example, Garg and Ravi [101] administered a single oral dose of 6 mg/kg of phenylbutazone to seven cigarette smokers and to seven nonsmokers. Plasma phenylbutazone half-life was shortened significantly in the cigarette smokers as compared to the nonsmoker control group. Phenylbutazone was cleared from the blood significantly faster in the smoking group than in the nonsmoking group. This difference in metabolism was attributed to liver enzyme induction. However, there are no studies reporting similar effects with other NSAIDs including aspirin, ibuprofen, naproxen, and indomethacin. Further, there are no data indicating a decreased analgesic efficacy of higher dose requirements of these medications among smokers compared to nonsmokers.

There is an indication that smokers may be more susceptible to the anti-aggregatory effects of aspirin. Aspirin has been recommended as an adjuvant therapy in the prevention of cardiovascular event. Smoking causes atherosclerosis, and smokers have increased thromboxane (TXA2) formation [30]. The effect of smoking on TXA2 appears to be related to a non-nicotine component of tobacco smoke. In a study comparing the effects of smoking compared to nicotine patch, Benowitz et al. [102] found that smoking produced significantly greater increases in TXA2 metabolite excretion than with nicotine patch treatment, despite comparable levels of nicotine.

Weber et al. [103] investigated the effects of aspirin (100 mg every second day for 14 days) on platelet function in nine healthy nonsmokers and in nine healthy habitual smokers. There was a significantly stronger inhibition of collagen- and ADP-induced platelet aggregation by aspirin in smokers as compared to nonsmokers. This difference occurred in the presence of an almost complete inhibition of thromboxane A2 (TXA2) synthesis in both groups. The platelet capacity to generate TXA2 in vitro was significantly reduced in smokers, urinary excretion of TXA2, however, was significantly increased. Thus, the better susceptibility of smokers to anti-aggregatory effects of aspirin is very likely to be related to a chronic smoking-induced alteration of platelet TXA2 system.

Anticoagulants

Heparin pharmacokinetics has been shown to be altered in smokers compared to nonsmokers. Smoking induced a significant decrease in heparin's elimination half-life (0.97 ± 0.28 h in nonsmokers and 0.62 ± 0.16 h in smokers), faster clearance rate, and a modest increase in dosage requirements [104]. Consequently, smokers may require higher heparin doses relative to nonsmokers for anticoagulant therapy. This may also be the case with smokeless tobacco use, as a case study was reported in which a smokeless tobacco user was unsuccessfully treated with warfarin [105]. The authors suggested that a pharmacokinetic interaction with tobacco was the cause.

Smoking has modest effects on the pharmacokinetics of warfarin. In a study of nine cigarette smokers who ingested an average of 0.032 mg/kg of warfarin for 2 weeks while smoking and for two additional weeks following a month of abstinence, clearance was decreased by 13% during smoking abstinence [106]. A concomitant 13% increase in warfarin concentration occurred, but there was no accompanying effect on prothrombin time. It was concluded that despite the apparent pharmacokinetic interaction between smoking and warfarin, the net effect on warfarin pharmacodynamics was negligible.

Antidepressants

There is clear evidence that smoking in patients with depression is higher than in the general population. Indications are that induction of CYP isoenzymes by smoking generally lower plasma levels of the parent antidepressant, but may or may not affect active metabolite levels. Desai et al. [107] recently reviewed the evidence of smoking on psychotropic medications. Serum levels of amitriptyline, nortriptyline, imipramine, clomipramine, fluvoxamine, and trazodone were found to be lower in smokers compared to nonsmokers; however, differences were not always significant. Amfebutamone (bupropion) levels do not appear to be affected by smoking. Dosage adjustments for smokers receiving amitriptyline, nortriptyline and bupropion were not suggested, but there may be a need for higher dosages of fluvoxamine and trazodone for optimal therapy.

Antipsychotics

Smoking prevalence in schizophrenia is generally highest among neuropsychiatric disorders (approximately 80%) and smoking withdrawal results in worsening of schizophrenic symptoms [108]. Tobacco use may represent an attempt to self-medicate, relieve drug-induced adverse events, and improve cognitive deficits. The reduction in drug-induced adverse events may be caused by PAH enzyme induction with resultant reduced blood concentrations of medication [109]. In a review by Desai et al. [107], it was reported that the frequency of drowsiness induced by chlorpromazine was lowest in heavy smokers (3%) compared to light smokers (11%) and nonsmokers (16%). Pantuck et al. [110] evaluated the disposition of a single 75 mg oral dose of chlorpromazine in healthy men smokers and nonsmokers. Greater sleepiness was noted in nonsmokers compared to smokers.

Chlorpromazine peak levels and AUC were 24% and 36% lower, respectively, in smokers compared to nonsmokers. However the differences were not significant, probably because of the small number of subjects in the study. There was no correlation between plasma drug concentrations and either the degree of sleepiness or the degree of orthostatic hypotension in the subjects. Chetty et al. [111] reported higher clearance rate of chlorpromazine in smokers with chronic schizophrenia (175 L/h) compared to nonsmokers (127 L/h). It was suggested that a higher dosage may be necessary in patients who are smokers. Interestingly, cannabis smokers demonstrated even higher clearance rates (191 L/h) than tobacco smokers.

Clearance rates of tiotixene and fluphenazine have been reported to be significantly higher and resulting plasma levels lower for smokers compared to nonsmokers [107]. Plasma levels of haloperidol and metabolite were significantly lower in smokers in some studies [112, 113], but results in other studies were inconclusive [107, 114]. No significant differences in pharmacokinetic parameters were found for patients receiving a single dose of trifluoroperazine.

Haring et al. [115] and Seppala et al. [116] reported significantly lower mean plasma clozapine concentrations in smokers compared to nonsmokers. Haseqawa et al. [117] also found lower plasma levels of clozapine in schizophrenic patients who were smokers, but the differences were not significant. If enzyme induction by smoking is the cause for lower clozapine plasma levels, it is reasonable to expect that smoking cessation could result in increased drug levels and incidence of adverse side effects. Meyer [118] reported a mean increase in clozapine levels of 71.9% upon smoking cessation in 11 patients who were on stable clozapine doses. Oyewumi [119] describes a case in which emergence of clozapine side effects (urinary hesitancy, constipation, and erectile and ejaculatory dysfunction) occurred in a male patient who stopped smoking. The patient had been successfully maintained on clozapine for 4 years prior to his decision to stop smoking. Skogh et al. [120] describes a 35-year-old man who had been successfully treated with clozapine at a daily dose of 700–725 mg for more than 7 consecutive years. Two weeks after cessation of smoking, he suddenly developed tonic–clonic seizures followed by stupor and coma. When he recovered, clozapine therapy was reinstituted successfully at 425 mg daily.

Plasma levels of zotepine have been generally found to be lower in smokers compared with nonsmokers. In contrast, the C_{max} of olanzapine was slightly greater in smokers, but clearance rates for smokers were significantly higher (23% increase). Cigarette smoking has been shown in several studies to induce the metabolism of the cytochrome P450 1A2 (CYP1A2) substrates clozapine and olanzapine. A daily consumption of 7–12 cigarettes appears sufficient for maximum induction of clozapine and olanzapine metabolism [121]. The authors recommend a 50% lower starting dose of both drugs in nonsmokers seems rational to avoid side effects.

Benzodiazepines

No significant differences in the pharmacokinetic parameters of smokers versus nonsmokers were found in a study of a single dose of 0.5 mg of triazolam [122]. Similar findings were made in studies of 0.5 mg of triazolam and 0.8 mg alprazolam in healthy Japanese men, but the mean elimination half-life of alprazolam was significantly shorter in smokers than in nonsmokers [123]. However, another study of alprazolam showed that cigarette smoking caused a 100% increase in the clearance of alprazolam compared with nonsmokers [124]. The minimal differences in plasma levels found in these studies suggest that dosage adjustments would not be needed for smokers versus nonsmokers. Intravenous administration of 2 mg of lorazepam resulted in significantly shorter half-lives in smokers compared with nonsmokers, but other pharmacokinetic parameters were unchanged [125].

The incidence of drowsiness in patients receiving diazepam and chlordiazepoxide has been noted to be highest in nonsmokers, intermediate in light smokers, and lowest in heavy smokers [126]. Whether the interaction between cigarette smoking and benzodiazepines is related to altered pharmacokinetics or altered end-organ response is not known. The results of pharmacokinetic studies of diazepam and desmethyldiazepam in smokers compared to nonsmokers have not been conclusive. In one study, cigarette smoking produced significantly lower clearance rates in elderly men compared to young men [127]. In a study of desmethyldiazepam, the half-life was significantly shorter and C_{max} was lower in smokers than in nonsmokers. In contrast, other researchers have found no effect of smoking on the pharmacokinetics of diazepam or desmethyldiazepam [125, 128, 129]. Chlordiazepoxide kinetics have also been shown to be unaffected by smoking [130]. However, in a study of oxazepam in relation to age, sex and cigarette smoking, the mean clearance of oxazepam in smokers was shown to be significantly higher in smokers than in nonsmokers, suggesting that smoking is a more important determinant of oxazepam clearance than age or sex [131].

Caffeine

The metabolism of caffeine in humans results in production of at least 17 urinary metabolites. Considerable effort has been focused on the use of caffeine as a substrate probe for CYP1A and other xenobiotic metabolizing enzymes [132]. Caffeine clearance

is increased by cigarette smoking [133], presumably through induction of CYP1A enzymes by polycyclic aromatic hydrocarbons. An increase in metabolism results in a shorter half-life for caffeine during smoking. Consequently, it would be reasonable to expect that smoking cessation would result in an increase in caffeine levels thereby increasing risk for caffeine toxicity. Brown et al. [134] reported that abstinence from smoking for 4 days resulted in a 46% increase in the 24-h AUC blood caffeine levels for subjects while consuming six cups of coffee per day. Oliveto et al. [135] also found abstinence increased caffeine levels; however, the effect was not statistically significant. Benowitz et al. [136] also reported that plasma caffeine concentrations increased during abstinence after people gave up smoking and remained increased for at least 6 months. The increase in plasma caffeine levels was substantial, averaging more than 250%, whereas levels were unchanged in subjects who continued to smoke. Thus, it appears that when a person stops smoking, metabolism of caffeine slows, clearance slows, half-life lengthens, and plasma caffeine increases.

Carbamazepine

Carbamazepine is metabolized mainly not only by CYP3A4, but also by CYP1A2. Chronic dosing produces enzyme induction and an increase in its metabolism. Studies of the effects of smoking, however, have shown no influence on postinduction carbamazepine clearance [137].

Cardiovascular Drugs

The effectiveness of β-blockers in control of blood pressure, heart rate, and prevention of end-organ damage is reduced in smokers compared with nonsmokers [138, 139]. However, another study found no difference in benefit derived from β-blockers between smokers and nonsmokers [140]. The basis of this interaction may be pharmacodynamic since nicotine causes catecholamine release and increases blood pressure and heart rate.

Hitzenberger et al. [141] found no effect of smoking on propranolol or pindolol; however, Walle et al. [142] reported that cigarette smoking increased the oral clearance of propranolol in male subjects by 77%. The kinetic and metabolic effects induced by smoking were characterized by a large induction of side-chain oxidation of propranolol without an effect on aromatic ring oxidation. Smoking also induced an increase in the glucuronidation of propranolol. The results suggest that side-chain oxidation and glucuronidation of propranolol are mediated by isoenzymes inducible by aromatic hydrocarbons found in cigarette smoke, whereas the rate of aromatic ring oxidation was not changed by smoking.

Increased clearance of some antiarrhythmics has also been reported. Higher metabolic clearance rates and lower trough concentrations for flecainide was observed for smokers compared to nonsmokers resulting in the need for higher doses of flecainide for arrhythmia control [143]. Oral clearance of lidocaine [144] and mexiletine [145] has been reported to be increased in smokers. Although the mechanism is unknown,

enhanced hepatic metabolism from smoking is likely responsible for the increased clearance of antiarrhythmics.

Furosemide is a potent diuretic. Lambert et al. [146] found that tobacco smoking in normal subjects affects the diuretic response to furosemide without modifying kinetics. Five nonsmokers and five smokers were given a single intravenous injection of 40 mg furosemide. Cumulative 8-h urinary excretion of sodium was identical for smokers and nonsmokers. However, diuresis was smaller by 800 mL (20%) in smokers than in nonsmokers. Furosemide increased endogenous creatinine clearance from 117 to 196 mL/min in nonsmokers and from 136 to 180 mL/min in smokers. The increase in free water clearance caused by furosemide was smaller in the smoking group than in the nonsmoking group. Protein binding and distribution of furosemide were not affected by tobacco smoking. Furosemide clearance was slightly higher in smokers than in nonsmokers, which was primarily the result of a slight increase in extrarenal furosemide clearance. Although the foregoing suggests that higher doses of furosemide might be required in smokers to compensate for the diminished effects on diuresis, Vapaatalo et al. [147] report that tolerance develops to nicotine's effects on furosemide. This development of tolerance suggests that chronic smokers would not require different doses of furosemide, but that a dosage adjustment may be required among patients using furosemide who begin smoking while on the medication.

Insulin

Nicotine increases central nervous system sympathetic overflow, adrenal release of catecholamines, and local release of catecholamines from vascular nerve endings [23]. This results in constriction of some blood vessels, including cutaneous blood vessels. Because of decreased blood flow through cutaneous blood vessels, the rate of absorption of insulin after subcutaneous injection is reduced [148]. Klemp et al. [149] demonstrated that insulin absorption is decreased by 113% during cigarette smoking, and showed a 30% decrease in the 30 min after smoking [149]. For this reason, smokers may require more insulin compared with nonsmokers. For example, Madsbad et al. [150] found smokers had on the average a 15–20% higher insulin requirement compared with nonsmokers. Further, as suggested by NRT product labeling (e.g., Nicorette), a dose adjustment may be required upon smoking cessation. It should be noted that there does not seem to be a difference in glycemic control between smokers and nonsmokers. For example, Mathiesen et al. [151] found no significant difference between smokers and nonsmokers in glycemic control as judged from the level of stable hemoglobin A1c [151].

Opioids

There appears to be an interaction between some component of tobacco smoke and dextropropoxyphene. For example, 10% of nonsmokers did not have an analgesic effect from dextropropoxyphene treatment compared to 20% of heavy smokers [152, 153]. The effect of smoking status on the analgesic effects of dextropropoxyphene

may be related to lower pain tolerance among smokers. It has been shown that, at least among Caucasians, smokers have less pain tolerance than nonsmokers [154]. This may indicate that smokers may require higher doses of dextropropoxyphene to obtain effective analgesia.

Vaughan et al. [155] studied the metabolism of pentazocine among 70 male and female smokers and nonsmokers. They found an overall threefold intersubject variation in elimination. The cumulative urinary excretion of pentazocine was normally distributed in both smokers and nonsmokers. Smokers metabolize 40% more pentazocine than nonsmokers. It was concluded that induction is principally responsible for the observed subject variability. Consistent with the lower plasma concentrations of pentazocine caused by the increased metabolism of the drug by smokers, Keeri-Szanto et al. [156] found that smokers required larger doses of pentazocine to achieve an analgesic effect.

Cigarette smoking has no clinically important influence on codeine absorption or disposition. Hull et al. [157] found no significant difference between smokers and nonsmokers in either codeine or morphine AUCs or oral bioavailability, after oral administration of codeine [158]. Similarly, Rogers et al. [159] found no differences between smokers and nonsmokers with respect to maximum plasma concentration (C_{max}) of codeine, time to attain this concentration (t_{max}), codeine plasma half-life ($t_{1/2}$), or AUCs for codeine or morphine. There was a faster, but clinically unimportant, mean apparent plasma clearance in smokers (52.8 mL/min/70 kg) than in nonsmokers (45.0 mL/min/70 kg) after intramuscular injection only. Mean oral codeine bioavailability in smokers and in nonsmokers did not differ. Cigarette smoking slightly but significantly induced the glucuronidation of codeine as shown by a decreased metabolic ratio for glucuronidation in the smokers, while O- and N-demethylations were not significantly changed as indicated by the similar metabolic ratios in smokers and in nonsmokers. Increased codeine dose requirements may be required because of the differences in pain tolerance between smokers and nonsmokers.

Long-term administration of tobacco for 28 days to rats resulted in the increase in N-demethylation of meperidine by 2.5-fold and morphine by twofold [160]. In humans, however, the mean total clearance rates of meperidine in smokers and nonsmokers have not been found to be different [161].

In self-administration studies with methadone-maintained patients, cigarette smoking produced a significant increase in methadone consumption as compared to when subjects were nicotine-abstinence [91].

Steroid Hormones

Cigarette smoking provides a protective effect in women against endometrial cancer, but may lead to earlier natural menopause and increased risk of osteoporosis [162, 163]. This anti-estrogenic effect appears to be explained by increased hepatic metabolism of estradiol to 2-hydroxy-estrogens, metabolites that are devoid of peripheral estrogenic activity. Michnovicz et al. [164] found an approximate 50% increase in 2-hydroxylation of estradiol in premenopausal women who smoked at

least 15 cigarettes per day. Increased metabolism via the 2-hydroxylation pathway would lead to decreased bioavailability at estrogen target tissues.

Pharmacokinetic interactions between smoking and oral contraceptives appear to be minimal. Crawford et al. [165] examined the effects of smoking on ethinyl estradiol and levonorgestrel in 311 women and concluded that smoking did not significantly affect plasma concentrations. Kanarkowski et al. [166] evaluated the pharmacokinetics of single and multiple doses of ethinyl estradiol and levonorgestrel in smoking and nonsmoking women and found a joint effect of chronic oral contraceptive use and smoking. There was a tendency toward lower ethinyl estradiol clearances after acute oral contraceptive use in smokers, but the effect was not significant. There was a significant smoking-oral contraceptive effect noted, but this effect was only based on three subjects. Importantly, Vessey et al. [167] observed no increase in failure rates of oral contraceptives in a study of nonsmokers, ex-smokers, and smoking women. Miller [168] concluded that based on available evidence, it would be premature to adjust estrogen dosages based on cigarette consumption.

The cardiovascular effects of combined oral contraceptives include venous thromboembolism (e.g., deep leg vein thrombosis and pulmonary embolism), ischemic stroke, and myocardial infarction [169, 170]. Stroke and myocardial infarction are arterial events. Smoking seems primarily to increase the risk of these arterial events [169]. Because of the increased risk of these events in smokers, combined oral contraceptives are considered contraindicated in heavy smokers (≥15 cigarettes/day) who are older than 35 years [171].

Tacrine

Smoking significantly induces the metabolism of tacrine. Welty et al. [172] reported consistently lower plasma levels of tacrine and its hydroxy-metabolites. The AUC for tacrine was approximately tenfold higher in nonsmokers. The AUCs for 1-hydroxy-tacrine and 2-hydroxytacrine were approximately threefold higher in nonsmokers. The mean tacrine elimination half-life was 2.1 h in smokers and 3.2 h in nonsmokers. It was suggested that the increased clearance in smokers was due to induction of CYP1A2 enzyme. Consequently, smokers may require higher doses of tacrine than nonsmokers [173].

Theophylline

Theophylline is commonly prescribed to smokers with chronic pulmonary disease. Concentrations of 10–20 μg/mL are needed to produce effective bronchodilation, but higher levels increasingly produce unacceptable adverse reactions. Higher levels may produce severe toxicities including cardiac arrhythmias and seizure. Consequently, serum theophylline monitoring is essential for careful patient-management. Cigarette smoking is known to induce the metabolism of theophylline resulting in increased theophylline clearance and a shorter half-life [174–176]. Hunt et al. [175] has suggested that young patients who require theophylline and smoke

would probably need daily dosages about twice those needed by nonsmokers. Abstinence from smoking would be expected to return an individual to basal levels of theophylline metabolism. Lee et al. [177] showed that the effects of brief abstinence (1 week) from smoking resulted in a 37.6% decrease in theophylline clearance and a 35.8% increase in half-life, whereas nicotine gum (4 mg) had no effect. The lack of effect by nicotine indicated that accelerated metabolism of theophylline is related to the effects of polycyclic aromatic hydrocarbons or other constituents in tobacco smoke. It was suggested that theophylline-treated patients be carefully monitored during periods of abstinence or smoking cessation and that doses of theophylline be reduced by one-fourth to one-third to avoid development of theophylline toxicity.

Passive exposure to tobacco smoke may engender many of the same effects as active smoking. Mayo [178] investigated the effects of passive tobacco smoking on the metabolism of theophylline in a pediatric population. Total body clearance of theophylline was significantly elevated in children exposed to environmental tobacco smoke (1.36 mL/min compared to 0.90 mL/min), and steady-state plasma serum levels were significantly lower in those exposed compared to the children without any environmental exposure to tobacco smoke.

Oral Tobacco Use and Interactions

Drug interactions with oral tobacco have not been well studied. However, because plasma nicotine levels reach levels as high as those seen during use of smoked tobacco, one could predict similar nicotine interactions as those discussed during smoking, as discussed above. Whether or not there are non-nicotine components of oral tobacco that interact with other drugs has not been studied.

There is an indication that nicotine and alcohol interact to increase the permeability of the tobacco-specific carcinogen, nitrosonornicotine (NNN) across the oral mucosa [87]. Concentrations of ethanol of 25% and above significantly increased the permeability of the porcine oral mucosa to NNN and the presence of 0.2% nicotine significantly increased the permeability of oral mucosa to NNN. Combined use of nicotine and ethanol significantly increased the penetration of NNN across oral mucosa over that of ethanol alone until the concentration of ethanol reached 50%. This suggests that the interaction of nicotine and alcohol could increase the risk of oral cancer. In addition, because nicotine alone increased the permeability of NNN, permeability of other oral-mucosa-delivered medications may increase among users of smokeless tobacco.

Contraindications

The only contraindications listed for nicotine replacement therapies are hypersensitivity or allergy to nicotine, or to components of the specific formulations (e.g., menthol in the vapor inhaler or adhesives in the patch). There are no contraindications based upon use of other medications.

The only drug class contraindicated for smokers are the combined oral contraceptives. Specifically, because of cardiovascular risk in smokers, combined oral contraceptives are considered contraindicated in heavy smokers (≥15 cigarettes/day) who are older than 35 years [171]. As discussed below, people who smoke, or people who stop smoking, may require dosage adjustments when using some medications.

Precautions for Use

Labeling for all nicotine replacement medications instruct patients to stop tobacco use completely when using nicotine replacement therapy. This is due to the fact that concomitant use of NRT and smoking might produce nicotine levels higher than smoking or NRT use alone. All NRT products urge patients to discontinue use if there is a clinically significant cardiovascular or other effects attributable to nicotine. They also note, as discussed in the next section, that concomitant medications may require a dose adjustment during cessation. This is not an effect of the nicotine replacement medication, per se, but rather an effect of reduced exposure to nicotine compared to smoking levels during a cessation attempt.

Because tobacco is not regulated by the Food and Drug Administration, there are no specific precautions for use. However, smoking is known to cause a number of cancers and heart disease, cause adverse effects on fetal development, and cause physical dependence and addiction.

Frequent or Serious Reactions

Given that approximately 25% of the U.S. adult population smokes cigarettes and that these persons are substantially more likely than nonsmokers to having co-morbid cardiovascular and psychiatric disorders [179, 180], there is a substantial potential that persons undergoing smoking cessation will be receiving medications for which there will be potential alterations in dosing required to avoid toxicity and/or sustain therapeutic effects. Conversely, except during adolescence when nearly all tobacco use begins [181], there is only a small risk that an adult who is receiving a medication will take up smoking and virtually no risk that nicotine medications will be used. A caveat is that with the increasing occurrence of cigar smoking among persons of all ages, this form of tobacco intake should be routinely considered for its potential interactive effects with medications. As suggested by the incredible diversity of cigar dosing potential and patterns of use, relative to cigarette smoking, it would be important to carefully question persons about the size of their cigars and frequency of use in order to provide some basis for beginning to estimate the probability of an interaction of concern. Monitoring of therapeutic effects and potential adverse interactions of the sort that would be consistent with those predicted in studies currently reviewed (e.g., potentially increased phenylephrine effects when cigars are smoked) would then be indicated.

Table 14.1 Drugs that may require dosage adjustments when smokers quit smoking

Drug	Possible mechanism
Drugs that may require a dose decrease upon cessation	
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase of subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation
Drugs that may require an increase in dose at cessation of smoking	
Adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Table 14.2 Drugs that often require higher doses in smokers compared to nonsmokers

Drug	Possible mechanism
Insulin	Lower subcutaneous insulin absorption during smoking
Propoxyphene	Unknown
Propranolol	Increased oral clearance
Theophylline	Enzyme induction increases clearance and reduced half-life in smokers
Clozapine	Enzyme induction

Approximately 17 million persons attempt smoking cessation each year and even though less than 10% of these persons achieve lasting cessation success, the numbers of people who will need potential modification of their dosing regimens for other drugs is considerable. Furthermore, because of the increasing rates of attempted smoking cessation, interactions as summarized in this review could become even more commonplace than they currently are. It is clear that, although there is a scientific base for predicting many commonplace types of potential interactions, much more research is needed to provide more practically useful guidance to health care professionals regarding their use of therapeutic drugs in tobacco users, nicotine medication users, and those seeking abstinence from tobacco.

As shown in Table 14.1, some medications may require a dose adjustment during smoking cessation. Table 14.1, from nicotine gum labeling, lists several drugs that may require a dose alteration upon smoking cessation, with or without use of NRT.

There are five medications identified that interact with tobacco use to the extent that higher dosages of these medications may be required for tobacco users compared to patients who do not use tobacco. In addition, theophylline clearance has been shown to be altered by passive smoking, and the possibility exists that other medications may also be affected by passive smoking. These medications and their possible mechanisms of action are summarized in Table 14.2. It should also be noted that for each of these medications, smoking cessation might require a decrease in dosage.

References

1. N.L. Benowitz. Nicotine Replacement Therapy. What Has Been Accomplished - Can We Do Better? *Drugs* **45:** 157–170 (1993).
2. N.L. Benowitz and P. Jacob, III. Daily intake of nicotine during cigarette smoking. *Clin. Pharmacol. Ther.* **35:** 499–504 (1984).
3. J.E. Henningfield. Nicotine medications for smoking cessation. *N. Engl. J. Med.* **333:** 1196–1203 (1995).
4. N.L. Benowitz. Clinical Pharmacology of Transdermal Nicotine. *European Journal of Pharm. Biopharm.* **41:** 168–174 (1995).
5. J.E. Henningfield, J.M. Stapleton, N.L. Benowitz, R.F. Grayson, and E.D. London. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug Alcohol Depend.* **33:** 23–29 (1993).
6. S.G. Gourlay and N.L. Benowitz. Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. *Clin. Pharmacol. Ther.* **62:** 453–463 (1997).
7. E. Lunell, L. Molander, and S.B. Andersson. Temperature dependency of the release and bioavailability of nicotine from a nicotine vapour inhaler; in vitro/ in vivo correlation. *European Journal of Pharmacology* **52:** 495–500 (1997).
8. K.J. Schuh, L.M. Schuh, J.E. Henningfield, and M.L. Stitzer. Nicotine nasal spray and vapor inhaler: abuse liability assessment. *Psychopharmacology (Berl)* **130:** 352–361 (1997).
9. E. Lunell, M. Bergstrom, G. Antoni, B. Langstrom, and A. Nordberg. Nicotine deposition and body distribution from a nicotine inhaler and a cigarette studied with positron emission tomography. *Clin. Pharmacol. Ther.* **59:** 593–594 (1996).
10. Use of FDA-approved pharmacologic treatments for tobacco dependence-United States, 1984-1998. *MMWR* **49:** 665–668 (2000).
11. Department of Health and Human Services and Food and Drug Administration. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents. *Federal Register* **61:** 44396–45318 (1996).
12. *Drugs and Behavior: An Introduction to Behavioral Pharmacology,*Prentice-Hall, Englewood Cliffs, New Jersey, 1986, pp. 125–127.
13. J.E. Henningfield, M. Hariharan, and L.T. Kozlowski. Nicotine content and health risks of cigars. *JAMA* **276:** 1857–1858 (1996).
14. R.V. Fant, J.E. Henningfield, R. Nelson, and W.B. Pickworth. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tobacco Control* **8:** 387–392 (1999).
15. O.o.A.S. Substance Abuse and Mental Health Services Administration. Results from the 2007 National Survey on Drug Use and Health: National Findings. NSDUH Series H-34, DHHS Publication No. SMA 84343, Rockville, MD, (2008).
16. State-specific prevalence of current cigarette smoking among adults, and policies and attitudes about secondhand smoke--United States, 2000. *MMWR* **50:** 1101–1105 (2001).
17. *The Health Benefits of Smoking Cessation; A Report of the Surgeon General, 1990,* DHHS Publication No. (CDC) 90-8416th ed., U.S. Government Printing Office, Washington, DC, 1990,
18. D. Hoffmann and I. Hoffmann. The changing cigarette, 1950-1995. *J. Toxicol. Environ. Health* **50:** 307–364 (1997).
19. *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed., American Psychiatric Association, Washington, DC, 1994,
20. S.J. Heishman, R.C. Taylor, and Henningfield J.E. Nicotine and smoking: a review of effects on human performance. *Experimental and Clinical Psychopharmacology* **2:** 345–395 (1994).
21. J.E. Henningfield, L.M. Schuh, and M.E. Jarvik. Pathophysiology of Tobacco Dependence. *Psychopharmacology: The Fourth Generation of Progress***:** 1715–1729 (1995).
22. D.A. Kessler, A.M. Witt, P.S. Barnett, M.R. Zeller, S.L. Natanblut, J.P. Wilkenfeld, C.C. Lorraine, L.J. Thompson, and W.B. Schultz. The Food and Drug Administration's regulation of tobacco products. *N. Engl. J. Med.* **335:** 988–994 (1996).

23. N.L. Benowitz. Cardiovascular Toxicity of Nicotine: Pharmacokinetic and Pharmacodynamic Considerations. *Nicotine Safety and Toxicity*, N. L. Benowitz, Ed. Oxford University Press, New York, 1998, pp 19–27.
24. C.A. Oncken, H. Hardardottir, and J. S. Smeltzer. Human Studies of Nicotine Replacement During Pregnancy. *Nicotine Safety and Toxicity*, N. L. Benowitz, Ed. Oxford University Press, New York, 1998, pp 107–116.
25. H.C. Porchet, N.L. Benowitz, L.B. Sheiner, and J.R. Copeland. Apparent tolerance to the acute effect of nicotine results in part from distribution kinetics. *J. Clin. Invest.* **80:** 1466–1471 (1987).
26. N.L. Benowitz. Toxicity of nicotine: implications with regard to nicotine replacement therapy. *Prog. Clin. Biol. Res.* **261:** 187–217 (1988).
27. L. Goldfrank, M. Minek, and A. Blum. Nicotine. *Hospital Physician* **16:** 22–35 (1980).
28. *Tobacco. Experimental and Clinical Studies. A Comprehensive Account of the World Literature.,*Williams and Wilkins, Co., Baltimore, 1961,
29. *The Health Consequences of Smoking: Nicotine Addiction; A Report of the Surgeon General, 1988,*U.S. Government Printing Office, Washington, DC, 1988,
30. *Reducing the Health Consequences of Smoking: 25 Years of Progress; A Report of the Surgeon General, 1989, Executive Summary,* DHHS Publication No. (CDC) 89-8411th ed., U.S. Government Printing Office, Washington, DC, 1989,
31. W.C. Krupski. The peripheral vascular consequences of smoking. *Ann. Vasc. Surg.* **5:** 291–304 (1991).
32. N.L. Benowitz. Summary: Risks and benefits of nicotine. *Nicotine Safety and Toxicity*, N. L. Benowitz, Ed. Oxford University Press, New York, 1998, pp 185–194.
33. P. Dasgupta, W. Rizwani, S. Pillai, R. Kinkade, M. Kovacs, S. Rastogi, S. Banerjee, M. Carless, E. Kim, D. Coppola, E. Haura, and S. Chellappan. Nicotine induces cell proliferation, invasion and epithelial-mesenchymal transition in a variety of human cancer cell lines. *Int. J. Cancer* **124:** 36–45 (2009).
34. Q. Zhang, X. Tang, Z.F. Zhang, R. Velikina, S. Shi, and A.D. Le. Nicotine induces hypoxia-inducible factor-1alpha expression in human lung cancer cells via nicotinic acetylcholine receptor-mediated signaling pathways. *Clin. Cancer Res.* **13:** 4686–4694 (2007).
35. R.D. Egleton, K.C. Brown, and P. Dasgupta. Nicotinic acetylcholine receptors in cancer: multiple roles in proliferation and inhibition of apoptosis. *Trends Pharmacol. Sci.* **29:** 151–158 (2008).
36. R. Zeidler, K. Albermann, and S. Lang. Nicotine and apoptosis. *Apoptosis.* **12:** 1927–1943 (2007).
37. C.B. Sherman. The health consequences of cigarette smoking. Pulmonary diseases. *Med. Clin. North Am.* **76:** 355–375 (1992).
38. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease; A Report of the Surgeon General, 1984,* DHHS (PHS) 84-50205th ed., U.S. Government Printing Office, Washington, DC, 1984,
39. E.M. Sellers, H.L. Kaplan, and R.F. Tyndale. Inhibition of cytochrome P450 2A6 increases nicotine's oral bioavailability and decreases smoking. *Clin. Pharmacol. Ther.* **68:** 35–43 (2000).
40. M.L. Pianezza, E.M. Sellers, and R.F. Tyndale. Nicotine metabolism defect reduces smoking. *Nature* **393:** 750– (1998).
41. R.F. Tyndale and E.M. Sellers. Variable CYP2A6-mediated nicotine metabolism alters smoking behavior and risk. *Drug Metab. Dispos.* **29:** 548–552 (2001).
42. N.L. Benowitz and P. Jacob, III. Nicotine and cotinine elimination pharmacokinetics in smokers and nonsmokers. *Clin. Pharmacol. Ther.* **53:** 316–323 (1993).
43. S. Zevin and N.L. Benowitz. Drug interactions with tobacco smoking. An update. *Clin. Pharmacokinet.* **36:** 425–438 (1999).
44. N.L. Benowitz and S.G. Gourlay. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J. Am. Coll. Cardiol.* **29:** 1422–1431 (1997).
45. B. Soderpalm, M. Ericson, P. Olausson, O. Blomqvist, and J.A. Engel. Nicotinic mechanisms involved in the dopamine activating and reinforcing properties of ethanol. *Behav. Brain Res.* **113:** 85–96 (2000).

46. M.C. Mehta, A.C. Jain, and M. Billie. Combined effects of alcohol and nicotine on cardiovascular performance in a canine model. *J. Cardiovasc. Pharmacol.* **31:** 930–936 (1998).
47. M.J. Seaton and E.S. Vesell. Variables affecting nicotine metabolism. *Pharmacol. Ther.* **60:** 461–500 (1993).
48. W.J. Chen, S.E. Parnell, and J.R. West. Nicotine decreases blood alcohol concentration in neonatal rats. *Alcohol Clin. Exp. Res.* **25:** 1072–1077 (2001).
49. S.E. Parnell, J.R. West, and W.J. Chen. Nicotine decreases blood alcohol concentrations in adult rats: a phenomenon potentially related to gastric function. *Alcohol Clin. Exp. Res.* **30:** 1408–1413 (2006).
50. K.A. Perkins, J.E. Sexton, A. DiMarco, J.E. Grobe, A. Scierka, and R.L. Stiller. Subjective and cardiovascular responses to nicotine combined with alcohol in male and female smokers. *Psychopharmacology (Berl)* **119:** 205–212 (1995).
51. J.S. Kerr, N. Sherwood, and I. Hindmarch. Separate and combined effects of the social drugs on psychomotor performance. *Psychopharmacology (Berl)* **104:** 113–119 (1991).
52. S.P. Barrett, M. Tichauer, M. Leyton, and R.O. Pihl. Nicotine increases alcohol self-administration in non-dependent male smokers. *Drug Alcohol Depend.* **81:** 197–204 (2006).
53. J.E. Rose, L.H. Brauer, F.M. Behm, M. Cramblett, K. Calkins, and D. Lawhon. Psychopharmacological interactions between nicotine and ethanol. *Nicotine. Tob. Res.* **6:** 133–144 (2004).
54. J.L. Wilkinson, M.I. Palmatier, and R.A. Bevins. Preexposure to nicotine alters the subsequent locomotor stimulant effects of bupropion in rats. *Nicotine. Tob. Res.* **8:** 141–146 (2006).
55. G. Vazquez-Palacios, H. Bonilla-Jaime, and J. Velazquez-Moctezuma. Antidepressant-like effects of the acute and chronic administration of nicotine in the rat forced swimming test and its interaction with fluoxetine. *Pharmacol. Biochem. Behav.* **78:** 165–169 (2004).
56. P. Popik, E. Kozela, and M. Krawczyk. Nicotine and nicotinic receptor antagonists potentiate the antidepressant-like effects of imipramine and citalopram. *Br. J. Pharmacol.* **139:** 1196–1202 (2003).
57. R.G. Sewell, K.P. Nanry, J. Kennedy, T.R. Stiger, and R.E. Harmon. Supra-additive toxic interaction of nicotine with antihistamines, and enhancement by the proconvulsant pentylenetetrazole. *Pharmacol. Biochem. Behav.* **22:** 469–477 (1985).
58. D.F. Emerich, A.B. Norman, and P.R. Sanberg. Nicotine potentiates the behavioral effects of haloperidol. *Psychopharmacol. Bull.* **27:** 385–390 (1991).
59. S.M. Boye and P.B. Clarke. Enhancement of haloperidol-induced catalepsy by nicotine: an investigation of possible mechanisms. *Can. J. Physiol. Pharmacol.* **78:** 882–891 (2000).
60. N. Addy and E.D. Levin. Nicotine interactions with haloperidol, clozapine and risperidone and working memory function in rats. *Neuropsychopharmacology* **27:** 534–541 (2002).
61. E.D. Levin, A. Petro, and A. Beatty. Olanzapine interactions with nicotine and mecamylamine in rats: effects on memory function. *Neurotoxicol. Teratol.* **27:** 459–464 (2005).
62. A.H. Rezvani and E.D. Levin. Nicotine-antipsychotic drug interactions and attentional performance in female rats. *Eur. J. Pharmacol.* **486:** 175–182 (2004).
63. A.H. Rezvani, D.P. Caldwell, and E.D. Levin. Chronic nicotine interactions with clozapine and risperidone and attentional function in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **30:** 190–197 (2006).
64. E.D. Levin, W. Wilson, J.E. Rose, and J. McEvoy. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. *Neuropsychopharmacology* **15:** 429–436 (1996).
65. P.R. Sanberg, H.M. Fogelson, P.Z. Manderscheid, K.W. Parker, A.B. Norman, and B.J. McConville. Nicotine gum and haloperidol in Tourette's syndrome. *Lancet* **1:** 592– (1988).
66. P.R. Sanberg, B.J. McConville, H.M. Fogelson, P.Z. Manderscheid, K.W. Parker, M.M. Blythe, W.M. Klykylo, and A.B. Norman. Nicotine potentiates the effects of haloperidol in animals and in patients with Tourette syndrome. *Biomed. Pharmacother.* **43:** 19–23 (1989).
67. A.A. Silver and P.R. Sanberg. Transdermal nicotine patch and potentiation of haloperidol in Tourette's syndrome. *Lancet* **342:** 182– (1993).
68. A.T. Modak and B.E. Alderete. Nicotine potentiates sodium pentobarbital but not ethanol induced sleep. *Subst. Alcohol Actions Misuse* **4:** 321–329 (1983).

69. M. Hisaoka and G. Levy. Kinetics of drug action in disease states XI: effect of nicotine on the pharmacodynamics and pharmacokinetics of phenobarbital and ethanol in rats. *J. Pharm. Sci.* **74:** 412–415 (1985).
70. J.M. White. Behavioral interactions between nicotine and diazepam. *Pharmacol. Biochem. Behav.* **32:** 479–482 (1989).
71. E.E. Irvine, S. Cheeta, C. Lovelock, and S.E. File. Tolerance to midazolam's anxiolytic effects after short-term nicotine treatment. *Neuropharmacology* **40:** 710–716 (2001).
72. J.A. Swanson, J.W. Lee, and J.W. Hopp. Caffeine and nicotine: a review of their joint use and possible interactive effects in tobacco withdrawal. *Addict. Behav.* **19:** 229–256 (1994).
73. G. Tanda and S.R. Goldberg. Alteration of the behavioral effects of nicotine by chronic caffeine exposure. *Pharmacol. Biochem. Behav.* **66:** 47–64 (2000).
74. A.C. Jain, M.C. Mehta, and M. Billie. Combined effects of caffeine and nicotine on cardiovascular hemodynamics in canine model. *J. Cardiovasc. Pharmacol.* **29:** 574–579 (1997).
75. H. Kayir and I.T. Uzbay. Nicotine antagonizes caffeine- but not pentylenetetrazole-induced anxiogenic effect in mice. *Psychopharmacology (Berl)* **184:** 464–469 (2006).
76. M. Gasior, M. Jaszyna, P. Munzar, J.M. Witkin, and S.R. Goldberg. Caffeine potentiates the discriminative-stimulus effects of nicotine in rats. *Psychopharmacology (Berl)* **162:** 385–395 (2002).
77. P. Smits, L. Temme, and T. Thien. The cardiovascular interaction between caffeine and nicotine in humans. *Clin. Pharmacol. Ther.* **54:** 194–204 (1993).
78. K.A. Perkins, C. Fonte, A. Stolinski, R. Blakesley-Ball, and A.S. Wilson. The influence of caffeine on nicotine's discriminative stimulus, subjective, and reinforcing effects. *Exp. Clin. Psychopharmacol.* **13:** 275–281 (2005).
79. A. Jessen, B. Buemann, S. Toubro, I.M. Skovgaard, and A. Astrup. The appetite-suppressant effect of nicotine is enhanced by caffeine. *Diabetes Obes. Metab* **7:** 327–333 (2005).
80. S.T. Yuen, A.R. Gogo, Jr., I.S. Luk, C.H. Cho, J.C. Ho, and T.T. Loh. The effect of nicotine and its interaction with carbon tetrachloride in the rat liver. *Pharmacol. Toxicol.* **77:** 225–230 (1995).
81. R. Bendayan, J.T. Sullivan, C. Shaw, R.C. Frecker, and E.M. Sellers. Effect of cimetidine and ranitidine on the hepatic and renal elimination of nicotine in humans. *Eur. J. Clin. Pharmacol.* **38:** 165–169 (1990).
82. M. Seaton, G.A. Kyerematen, M. Morgan, E.V. Jeszenka, and E.S. Vesell. Nicotine metabolism in stumptailed macaques, Macaca arctoides. *Drug Metab. Dispos.* **19:** 946–954 (1991).
83. S.L. Collins and S. Izenwasser. Chronic nicotine differentially alters cocaine-induced locomotor activity in adolescent vs. adult male and female rats. *Neuropharmacology* **46:** 349–362 (2004).
84. M.S. Reid, J.D. Mickalian, K.L. Delucchi, S.M. Hall, and S.P. Berger. An acute dose of nicotine enhances cue-induced cocaine craving. *Drug Alcohol Depend.* **49:** 95–104 (1998).
85. E.M. Kouri, M. Stull, and S.E. Lukas. Nicotine alters some of cocaine's subjective effects in the absence of physiological or pharmacokinetic changes. *Pharmacol. Biochem. Behav.* **69:** 209–217 (2001).
86. S.G. Carmella, A. Borukhova, D. Desai, and S.S. Hecht. Evidence for endogenous formation of tobacco-specific nitrosamines in rats treated with tobacco alkaloids and sodium nitrite. *Carcinogenesis* **18:** 587–592 (1997).
87. X. Du, C.A. Squier, M.J. Kremer, and P.W. Wertz. Penetration of N-nitrosonornicotine (NNN) across oral mucosa in the presence of ethanol and nicotine. *J. Oral Pathol. Med.* **29:** 80–85 (2000).
88. T. Vihavainen, T.R. Relander, R. Leiviska, M. Airavaara, R.K. Tuominen, L. Ahtee, and T.P. Piepponen. Chronic nicotine modifies the effects of morphine on extracellular striatal dopamine and ventral tegmental GABA. *J. Neurochem.* **107:** 844–854 (2008).
89. T. Vihavainen, M. Piltonen, R.K. Tuominen, E.R. Korpi, and L. Ahtee. Morphine-nicotine interaction in conditioned place preference in mice after chronic nicotine exposure. *Eur. J. Pharmacol.* **587:** 169–174 (2008).
90. A. Haghparast, A. Khani, N. Naderi, A.M. Alizadeh, and F. Motamedi. Repeated administration of nicotine attenuates the development of morphine tolerance and dependence in mice. *Pharmacol. Biochem. Behav.* **88:** 385–392 (2008).

91. R. Spiga, J. Schmitz, and J. Day. Effects of nicotine on methadone self-administration in humans. *Drug Alcohol Depend.* **50:** 157–165 (1998).
92. A.K. Chaturvedi. Effects of mecamylamine, nicotine, atropine and physostigmine on the phencyclidine-induced behavioral toxicity. *Pharmacol. Biochem. Behav.* **20:** 559–566 (1984).
93. N.L. Vadlamani, R.B. Pontani, and A.L. Misra. Effect of chronic nicotine pre-treatment on phencyclidine (PCP) disposition in the rat. *Arch. Int. Pharmacodyn. Ther.* **265:** 4–12 (1983).
94. J.P. Zacny. Behavioral aspects of alcohol-tobacco interactions. *Recent Dev. Alcohol* **8:** 205–219 (1990).
95. T. Narahashi, B. Soderpalm, M. Ericson, P. Olausson, J.A. Engel, X. Zhang, A. Nordberg, W. Marszalec, G.L. Aistrup, L.G. Schmidt, U. Kalouti, A.M. Smolka, and L. Hedlund. Mechanisms of alcohol-nicotine interactions: alcoholics versus smokers. *Alcohol Clin. Exp. Res.* **25:** 152 S–156 S (2001).
96. E.J. Pantuck, R. Kuntzman, and A.H. Conney. Decreased concentration of phenacetin in plasma of cigarette smokers. *Science* **175:** 1248–1250 (1972).
97. E.J. Pantuck, K.C. Hsiao, A. Maggio, K. Nakamura, R. Kuntzman, and A.H. Conney. Effect of cigarette smoking on phenacetin metabolism. *Clin. Pharmacol. Ther.* **15:** 9–17 (1974).
98. W.J. Jusko. Role of tobacco smoking in pharmacokinetics. *J. Pharmacokinet. Biopharm.* **6:** 7–39 (1978).
99. R. Kuntzman, E.J. Pantuck, S.A. Kaplan, and A.H. Conney. Phenacetin metabolism: effect of hydrocarbons and cigarette smoking. *Clin. Pharmacol. Ther.* **22:** 757–764 (1977).
100. L.G. Miller. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin. Pharm.* **9:** 125–135 (1990).
101. S.K. Garg and T.N. Ravi Kiran. Effect of smoking on phenylbutazone disposition. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **20:** 289–290 (1982).
102. N.L. Benowitz, G.A. Fitzgerald, M. Wilson, and Q. Zhang. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *J. Am. Coll. Cardiol.* **22:** 1159–1167 (1993).
103. A.A. Weber, S. Liesener, A. Schanz, T. Hohlfeld, and K. Schror. Habitual smoking causes an abnormality in platelet thromboxane A2 metabolism and results in an altered susceptibility to aspirin effects. *Platelets* **11:** 177–182 (2000).
104. R.J. Cipolle, R.D. Seifert, B.A. Neilan, D.E. Zaske, and E. Haus. Heparin kinetics: variables related to disposition and dosage. *Clin. Pharmacol. Ther.* **29:** 387–393 (1981).
105. J.R. Kuykendall, M.D. Houle, and R.S. Rhodes. Possible warfarin failure due to interaction with smokeless tobacco. *Ann. Pharmacother.* **38:** 595–597 (2004).
106. K. Bachmann, R. Shapiro, R. Fulton, F.T. Carroll, and T.J. Sullivan. Smoking and warfarin disposition. *Clin. Pharmacol. Ther.* **25:** 309–315 (1979).
107. H.D. Desai, J. Seabolt, and M.W. Jann. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS. Drugs* **15:** 469–494 (2001).
108. S. Mihailescu and R. Drucker-Colin. Nicotine, brain nicotinic receptors, and neuropsychiatric disorders. *Arch. Med. Res.* **31:** 131–144 (2000).
109. E.R. Lyon. A review of the effects of nicotine on schizophrenia and antipsychotic medications. *Psychiatr. Serv.* **50:** 1346–1350 (1999).
110. E.J. Pantuck, C.B. Pantuck, K.E. Anderson, A.H. Conney, and A. Kappas. Cigarette smoking and chlorpromazine disposition and actions. *Clin. Pharmacol. Ther.* **31:** 533–538 (1982).
111. M. Chetty, R. Miller, and S.V. Moodley. Smoking and body weight influence the clearance of chlorpromazine. *Eur. J. Clin. Pharmacol.* **46:** 523–526 (1994).
112. L. Pan, S.R. Vander, M.T. Rosseel, J.A. Berlo, N. De Schepper, and F.M. Belpaire. Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. *Ther. Drug Monit.* **21:** 489–497 (1999).
113. K. Shimoda, T. Someya, S. Morita, G. Hirokane, T. Noguchi, A. Yokono, M. Shibasaki, and S. Takahashi. Lower plasma levels of haloperidol in smoking than in nonsmoking schizophrenic patients. *Ther. Drug Monit.* **21:** 293–296 (1999).

114. P.J. Perry, D.D. Miller, S.V. Arndt, D.A. Smith, and T.L. Holman. Haloperidol dosing requirements: the contribution of smoking and nonlinear pharmacokinetics. *J. Clin. Psychopharmacol.* **13:** 46–51 (1993).
115. C. Haring, W.W. Fleischhacker, P. Schett, C. Humpel, C. Barnas, and A. Saria. Influence of patient-related variables on clozapine plasma levels. *Am. J. Psychiatry* **147:** 1471–1475 (1990).
116. N.H. Seppala, E.V. Leinonen, M.L. Lehtonen, and K.T. Kivisto. Clozapine serum concentrations are lower in smoking than in non-smoking schizophrenic patients. *Pharmacol. Toxicol.* **85:** 244–246 (1999).
117. M. Hasegawa, R. Gutierrez-Esteinou, L. Way, and H.Y. Meltzer. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. *J. Clin. Psychopharmacol.* **13:** 383–390 (1993).
118. J.M. Meyer. Individual changes in clozapine levels after smoking cessation: results and a predictive model. *J. Clin. Psychopharmacol.* **21:** 569–574 (2001).
119. L.K. Oyewumi. Smoking cessation and clozapine side effects. *Can. J. Psychiatry* **43:** 748– (1998).
120. E. Skogh, F. Bengtsson, and C. Nordin. Could discontinuing smoking be hazardous for patients administered clozapine medication? A case report. *Ther. Drug Monit.* **21:** 580–582 (1999).
121. T. Haslemo, P.H. Eikeseth, L. Tanum, E. Molden, and H. Refsum. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. *Eur. J. Clin. Pharmacol.* **62:** 1049–1053 (2006).
122. H.R. Ochs, D.J. Greenblatt, and E.S. Burstein. Lack of influence of cigarette smoking on triazolam pharmacokinetics. *Br. J. Clin. Pharmacol.* **23:** 759–763 (1987).
123. K. Otani, N. Yasui, H. Furukori, S. Kaneko, H. Tasaki, T. Ohkubo, T. Nagasaki, K. Sugawara, and K. Hayashi. Relationship between single oral dose pharmacokinetics of alprazolam and triazolam. *Int. Clin. Psychopharmacol.* **12:** 153–157 (1997).
124. M. Hossain, E. Wright, R. Baweja, T. Ludden, and R. Miller. Nonlinear mixed effects modeling of single dose and multiple dose data for an immediate release (IR) and a controlled release (CR) dosage form of alprazolam. *Pharm. Res.* **14:** 309–315 (1997).
125. H.R. Ochs, D.J. Greenblatt, and M. Knuchel. Kinetics of diazepam, midazolam, and lorazepam in cigarette smokers. *Chest* **87:** 223–226 (1985).
126. R.R. Miller. Effects of smoking on drug action. *Clin. Pharmacol. Ther.* **22:** 749–756 (1977).
127. D.J. Greenblatt, M.D. Allen, J.S. Harmatz, and R.I. Shader. Diazepam disposition determinants. *Clin. Pharmacol. Ther.* **27:** 301–312 (1980).
128. H.R. Ochs, D.J. Greenblatt, A. Locniskar, and J. Weinbrenner. Influence of propranolol coadministration or cigarette smoking on the kinetics of desmethyldiazepam following intravenous clorazepate. *Klin. Wochenschr.* **64:** 1217–1221 (1986).
129. U. Klotz, G.R. Avant, A. Hoyumpa, S. Schenker, and G.R. Wilkinson. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J. Clin. Invest.* **55:** 347–359 (1975).
130. P.V. Desmond, R.K. Roberts, G.R. Wilkinson, and S. Schenker. No effect of smoking on metabolism of chlordiazepoxide. *N. Engl. J. Med.* **300:** 199–200 (1979).
131. H.R. Ochs, D.J. Greenblatt, and H. Otten. Disposition of oxazepam in relation to age, sex, and cigarette smoking. *Klin. Wochenschr.* **59:** 899–903 (1981).
132. A. Rostami-Hodjegan, S. Nurminen, P.R. Jackson, and G.T. Tucker. Caffeine urinary metabolite ratios as markers of enzyme activity: a theoretical assessment. *Pharmacogenetics* **6:** 121–149 (1996).
133. A.N. Kotake, D.A. Schoeller, G.H. Lambert, A.L. Baker, D.D. Schaffer, and H. Josephs. The caffeine CO2 breath test: dose response and route of N- demethylation in smokers and nonsmokers. *Clin. Pharmacol. Ther.* **32:** 261–269 (1982).
134. C.R. Brown, P. Jacob, III, M. Wilson, and N.L. Benowitz. Changes in rate and pattern of caffeine metabolism after cigarette abstinence. *Clin. Pharmacol. Ther.* **43:** 488–491 (1988).
135. A.H. Oliveto, J.R. Hughes, S.Y. Terry, W.K. Bickel, S.T. Higgins, S.L. Pepper, and J.W. Fenwick. Effects of caffeine on tobacco withdrawal. *Clin. Pharmacol. Ther.* **50:** 157–164 (1991).

136. N.L. Benowitz, S.M. Hall, and G. Modin. Persistent increase in caffeine concentrations in people who stop smoking. *BMJ* **298:** 1075–1076 (1989).
137. E.S. Martin, III, M.L. Crismon, and P.J. Godley. Postinduction carbamazepine clearance in an adult psychiatric population. *Pharmacotherapy* **11:** 296–302 (1991).
138. F.R. Buhler, K. Vesanen, J.T. Watters, and P. Bolli. Impact of smoking on heart attacks, strokes, blood pressure control, drug dose, and quality of life aspects in the International Prospective Primary Prevention Study in Hypertension. *Am. Heart J.* **115:** 282–288 (1988).
139. P. Bolli, F.R. Buhler, and J.K. McKenzie. Smoking, antihypertensive treatment benefit, and comprehensive antihypertensive treatment approach: some thoughts on the results of the International Prospective Primary Prevention Study in Hypertension. *J. Cardiovasc. Pharmacol.* **16 Suppl 7:** S77–S80 (1990).
140. L. Wilhelmsen, G. Berglund, D. Elmfeldt, T. Fitzsimons, H. Holzgreve, J. Hosie, P.E. Hornkvist, K. Pennert, J. Tuomilehto, and H. Wedel. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J. Hypertens.* **5:** 561–572 (1987).
141. G. Hitzenberger, P. Fitscha, T. Beveridge, E. Nuesch, and W. Pacha. Effects of age and smoking on the pharmacokinetics of pindolol and propranolol. *Br. J. Clin. Pharmacol.* **13:** 217 S–222 S (1982).
142. T. Walle, U.K. Walle, T.D. Cowart, E.C. Conradi, and T.E. Gaffney. Selective induction of propranolol metabolism by smoking: additional effects on renal clearance of metabolites. *J. Pharmacol. Exp. Ther.* **241:** 928–933 (1987).
143. J.L. Holtzman, C.E. Weeks, D.C. Kvam, D.A. Berry, L. Mottonen, B.P. Ekholm, S.F. Chang, and G.J. Conard. Identification of drug interactions by meta-analysis of premarketing trials: the effect of smoking on the pharmacokinetics and dosage requirements for flecainide acetate. *Clin. Pharmacol. Ther.* **46:** 1–8 (1989).
144. P.M. Huet and J. Lelorier. Effects of smoking and chronic hepatitis B on lidocaine and indocyanine green kinetics. *Clin. Pharmacol. Ther.* **28:** 208–215 (1980).
145. O. Grech-Belanger, M. Gilbert, J. Turgeon, and P.P. LeBlanc. Effect of cigarette smoking on mexiletine kinetics. *Clin. Pharmacol. Ther.* **37:** 638–643 (1985).
146. C. Lambert, P. Larochelle, and S.P. du. Effects of phenobarbital and tobacco smoking on furosemide kinetics and dynamics in normal subjects. *Clin. Pharmacol. Ther.* **34:** 170-175 (1983).
147. H.I. Vapaatalo, P.J. Neuvonen, A. Tissari, R. Mansner, and M.K. Paasonen. Effect of cigarette smoking on diuresis induced by furosemide. *Ann. Clin. Res.* **3:** 159–162 (1971).
148. K. Kolendorf, J. Bojsen, and S.L. Nielsen. Adipose tissue blood flow and insulin disappearance from subcutaneous tissue. *Clin. Pharmacol. Ther.* **25:** 598–604 (1979).
149. P. Klemp, B. Staberg, S. Madsbad, and K. Kolendorf. Smoking reduces insulin absorption from subcutaneous tissue. *Br. Med. J. (Clin. Res. Ed.)* **284:** 237– (1982).
150. S. Madsbad, P. McNair, M.S. Christensen, C. Christiansen, O.K. Faber, C. Binder, and I. Transbol. Influence of smoking on insulin requirement and metabolic status in diabetes mellitus. *Diabetes Care* **3:** 41–43 (1980).
151. E.R. Mathiesen, U. Soegaard, and J.S. Christiansen. Smoking and glycaemic control in male insulin dependent (type 1) diabetics. *Diabetes Res.* **1:** 155–157 (1984).
152. Boston Collaborative Drug Surveillance Program. Decreased clinical efficacy of propoxyphene in cigarette smokers. *Clin. Pharmacol. Ther.* **14:** 259–263 (1973).
153. H. Jick. Smoking and clinical drug effects. *Med. Clin. North Am.* **58:** 1143–1149 (1974).
154. C.C. Seltzer, G.D. Friedman, A.B. Siegelaub, and M.F. Collen. Smoking habits and pain tolerance. *Arch. Environ. Health* **29:** 170–172 (1974).
155. D.P. Vaughan, A.H. Beckett, and D.S. Robbie. The influence of smoking on the intersubject variation in pentazocine elimination. *Br. J. Clin. Pharmacol.* **3:** 279–283 (1976).
156. M. Keeri-Szanto and J.R. Pomeroy. Atmospheric pollution and pentazocine metabolism. *Lancet* **1:** 947–949 (1971).
157. J.H. Hull, J.W. Findlay, J.F. Rogers, R.M. Welch, R.F. Butz, and J.A. Bustrack. An evaluation of the effects of smoking on codeine pharmacokinetics and bioavailability in normal human volunteers. *Drug Intell. Clin. Pharm.* **16:** 849–854 (1982).

158. Q.Y. Yue, T. Tomson, and J. Sawe. Carbamazepine and cigarette smoking induce differentially the metabolism of codeine in man. *Pharmacogenetics* **4:** 193–198 (1994).
159. J.F. Rogers, J.W. Findlay, J.H. Hull, R.F. Butz, E.C. Jones, J.A. Bustrack, and R.M. Welch. Codeine disposition in smokers and nonsmokers. *Clin. Pharmacol. Ther.* **32:** 218–227 (1982).
160. B. Ali, S. Kaur, A. Kumar, and K.P. Bhargava. Comparative evaluation of stimulatory effects of oral tobacco and nicotine consumption on hepatic microsomal N-demethylations. *Biochem. Pharmacol.* **29:** 3087–3092 (1980).
161. L.E. Mather, G.T. Tucker, A.E. Pflug, M.J. Lindop, and C. Wilkerson. Meperidine kinetics in man. Intravenous injection in surgical patients and volunteers. *Clin. Pharmacol. Ther.* **17:** 21–30 (1975).
162. S.M. Lesko, L. Rosenberg, D.W. Kaufman, S.P. Helmrich, D.R. Miller, B. Strom, D. Schottenfeld, N.B. Rosenshein, R.C. Knapp, J. Lewis, and . Cigarette smoking and the risk of endometrial cancer. *N. Engl. J. Med.* **313:** 593–596 (1985).
163. J.A. Baron. Smoking and estrogen-related disease. *Am. J. Epidemiol.* **119:** 9–22 (1984).
164. J.J. Michnovicz, R.J. Hershcopf, H. Naganuma, H.L. Bradlow, and J. Fishman. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *N. Engl. J. Med.* **315:** 1305–1309 (1986).
165. F.E. Crawford, D.J. Back, M.L. Orme, and A.M. Breckenridge. Oral contraceptive steroid plasma concentrations in smokers and non- smokers. *Br. Med. J. (Clin. Res. Ed.)* **282:** 1829–1830 (1981).
166. R. Kanarkowski, K.M. Tornatore, R. D'Ambrosio, M.J. Gardner, and W.J. Jusko. Pharmacokinetics of single and multiple doses of ethinyl estradiol and levonorgestrel in relation to smoking. *Clin. Pharmacol. Ther.* **43:** 23–31 (1988).
167. M.P. Vessey, L. Villard-Mackintosh, and H.S. Jacobs. Anti-estrogenic effect of cigarette smoking. *N. Engl. J. Med.* **317:** 769–770 (1987).
168. L.G. Miller. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin. Pharmacokinet.* **17:** 90–108 (1989).
169. R. Burkman, J.J. Schlesselman, and M. Zieman. Safety concerns and health benefits associated with oral contraception. *Am. J. Obstet. Gynecol.* **190:** S5–22 (2004).
170. C. Seibert, E. Barbouche, J. Fagan, E. Myint, T. Wetterneck, and M. Wittemyer. Prescribing oral contraceptives for women older than 35 years of age. *Ann. Intern. Med.* **138:** 54–64 (2003).
171. I. Schiff. Use of oral contraceptives by women who smoke. *Am. J. Obstet. Gynecol.* **180:** S341–S342 (1999).
172. Welty, D., Pool, W., Woolf, T., Posvar, E., and Sedman, A. The effect of smoking on the pharmacokinetics and metabolism of Cognex in healthy volunteers. *Pharm. Res.* **10**: S334–(1993).
173. J.R. Schein. Cigarette smoking and clinically significant drug interactions. *Ann. Pharmacother.* **29:** 1139–1148 (1995).
174. J.R. Powell, J.F. Thiercelin, S. Vozeh, L. Sansom, and S. Riegelman. The influence of cigarette smoking and sex on theophylline disposition. *Am. Rev. Respir. Dis.* **116:** 17–23 (1977).
175. S.N. Hunt, W.J. Jusko, and A.M. Yurchak. Effect of smoking on theophylline disposition. *Clin. Pharmacol. Ther.* **19:** 546–551 (1976).
176. W.J. Jusko, J.J. Schentag, J.H. Clark, M. Gardner, and A.M. Yurchak. Enhanced biotransformation of theophylline in marihuana and tobacco smokers. *Clin. Pharmacol. Ther.* **24:** 405–410 (1978).
177. B.L. Lee, N.L. Benowitz, and P. Jacob, III. Cigarette abstinence, nicotine gum, and theophylline disposition. *Ann. Intern. Med.* **106:** 553–555 (1987).
178. P.R. Mayo. Effect of passive smoking on theophylline clearance in children. *Ther. Drug Monit.* **23:** 503–505 (2001).
179. J.R. Hughes. Comorbidity and smoking. *Nicotine & Tobacco Research* **1:** S149–S152 (1999).
180. N. Breslau. Psychiatric comorbidity of smoking and nicotine dependence. *Behav. Genet.* **25:** 95–101 (1995).
181. *Preventing Tobacco Use Among Young People; A Report of the Surgeon General,*U.S. Government Printing Office, Washington, DC, 1994,

182. N.G. Schneider, E. Lunell, R.E. Olmstead, and K.O. Fagerstrom. Clinical pharmacokinetics of nasal nicotine delivery. A review and comparison to other nicotine systems. *Clin. Pharmacokinet.* **31:** 65–80 (1996).
183. N.L. Benowitz, H. Porchet, L. Sheiner, and P. Jacob, III. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin. Pharmacol. Ther.* **44:** 23–28 (1988).
184. J.H. Choi, C.M. Dresler, M.R. Norton, and K.R. Strahs. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine. Tob. Res.* **5:** 635–644 (2003).

Chapter 15
Anabolic Doping Agents

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Abstract This chapter discusses the different types of doping agents that have been used since the pre-Christian era, such as hallucinogenic mushrooms and alcohol, up to those currently used by athletes today. Today, articles 2.1 through 2.8 of the World Anti-Doping Code, define doping as the violation of one or more of these articles through the use of prohibited substances or methods. In the present discussion on anabolic doping agents, the classes of banned substances covered include stimulants, anabolic agents, peptide hormones, and β_2-adrenoceptor agonists, as well as masking and antiestrogenic agents. The pharmacokinetics, pharmacodynamics, and toxicology of these substances will be discussed along with some potential historical consequences of the use of certain doping agents by both axis and allied forces during World War II, and the terrible consequences that might be attributed to their use.

Keywords Doping • Anabolic • Performance enhancement • Athletics

Introduction: History of Performance Enhancers

The term "doping" is derived from a stimulant drink called "dop" that was used in the eighteenth century during tribal ceremonies in South Africa [1]. During the late 1800s, the term "doping" in the English language took on a different meaning where it referred to a performance-reducing narcotic potion used in racehorses. More

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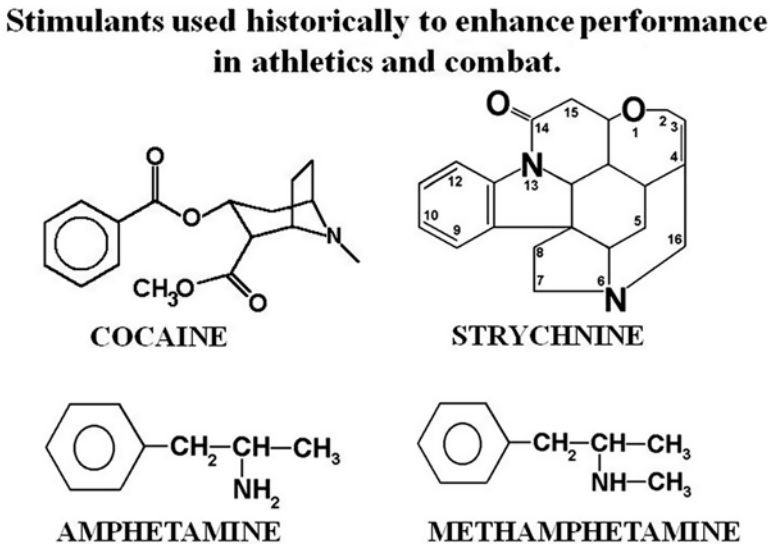


Fig. 15.1 List of stimulants commonly used by both athletes and warfighters to enhance performance

recently, doping refers to the use of any synthetic (e.g., synthetic anabolic steroids, recombinant hormones, genetic manipulation, etc.) or natural product to enhance the performance of athletes [1].

The desire to gain an upper edge in athletic competition and war can be traced back into antiquity. During the pre- to early Christian era, the Berserkers, ancient Germanic warriors, were known for their savagery and frenzied rage in battle [2]. Modern scholars believe that prior to battle, they would consume hallucinogenic mushroom (Bufotein from the fungus *Amanita muscaria*) and/or massive quantities of alcohol. The early Greeks used hallucinogenic mushrooms and the CNS stimulant strychnine in order to gain an edge in battle and in Olympic competition. Gladiators were known to use stimulants to stave off fatigue during their gladiatorial battles. It was not until the end of the sixteenth century that Europeans learned of caffeine-containing drugs.

The use of stimulants such as strychnine, cocaine, and caffeine became more prevalent in sports during the nineteenth century. In 1879, during the "6 Days" races, the competitors used a wide variety of prescriptions to give them the edge they needed. French racers used mixtures of different caffeine bases, while Belgians preferred sugar cubes dipped in ether. Sprinters, from all over the world, preferred using nitroglycerine. In 1886, a French cyclist used a "speedball," a mixture of cocaine and heroin, only to become the first recorded death from the use of performance-enhancing drugs. In 1904, Olympic marathon runner Thomas Hicks nearly died when he used a mixture of brandy and strychnine to enhance his performance. In boxing around the end of the nineteenth century, the combination of brandy and cocaine was used along with strychnine in order to gain an edge in performance (Fig. 15.1) [3, 4].

During the early twentieth century, strychnine was replaced by amphetamines as the preferred performance-enhancing drug. German chemist Edeleano first synthesized amphetamine in 1887. Thirty-two years later, Japanese scientist Ogata synthesized methamphetamine, although it was not until the early 1930s that a clinical use for the amphetamine (benzedrine) was found. Increasing human performance during the Second World War was a common practice for both the Allied and Axis powers. Between 1939 and 1945, the stimulant methamphetamine [*methedrine* (England) and *pervitine* (Germany)] was used to increase a soldier's endurance on long marches or while conducting night flights. Although safer than strychnine, serious side effects were still associated with the use of stimulants [4, 5].

This use of amphetamines was not limited to just the troops. Reports indicate that Hitler was being treated by his physician Dr. Theodor Morell with a special nutritional "cocktail." Always suspicious, the *SS* became concerned about Hitler's health and perhaps their potential loss of prestige to Morell, they secretly had the "cocktail" analyzed. Results from those tests helped to justify the concerns that the *SS* had about the "cocktail" and Hitler's health when they discovered that along with the host of vitamins, etc., was methamphetamine [6]. Reports from Hitler's physicians and those close to him [7] indicated that Hitler had parkinsonian-like symptoms that developed around mid-1941. Speculation on the causes of Hitler's condition ranged from idiopathic parkinsonism, which seemed more likely, to the less plausible postencephalitic parkinsonism. However, other potential causes of his neurological disorder might include his abuse of "Antigas pills" and an amphetamine-dependence [7]. For the Nazi's and their campaign in the east, this news could not have come at a worst time. The Wermacht was in the midst in of the battle for Stalingrad and winter was coming on. It is possible that the through the dependence on methamphetamine, Hitler's irrational insistence on not withdrawing troops from Stalingrad resulted in the catastrophic loss of the battle and subsequently the war [6, 8].

Up to the 1930s, the only performance enhancement drugs used by athletes or soldiers were stimulants or hallucinogens. The identification of androstanediol and testosterone as anabolic and androgenic steroids and their subsequent isolation ushered in a new era with respect to performance enhancement. During the later part of the 1930s and throughout the Second World War, nations of the Axis and Allied powers sought to enhance the endurance and alertness of their armies through the use of pharmaceutical adjuvants such as the amphetamines (amphetamine and methamphetamine). Stimulants enabled soldiers to function on minimal rest, endure reduced rations and long marches, or provide maximal performance during combat. Although the use of stimulants dates back to Greece and the Roman Empire, the use of anabolic steroids to "create" a more powerful warrior began in Nazi Germany. It is alleged that in an attempt to enhance the endurance, strength, and aggressiveness of his elite troops, Adolf Hitler ordered the use of the hormone testosterone. It is further alleged that Hitler administered testosterone to himself. If true, the combination of anabolic steroids and methamphetamine could have contributed significantly to many of the irrational political and military decisions made by Hitler.

In a move similar to Hitler's, Josef Stalin also allegedly ordered the use of anabolic steroids and stimulants for Soviet troops. It is unclear whether he also used these

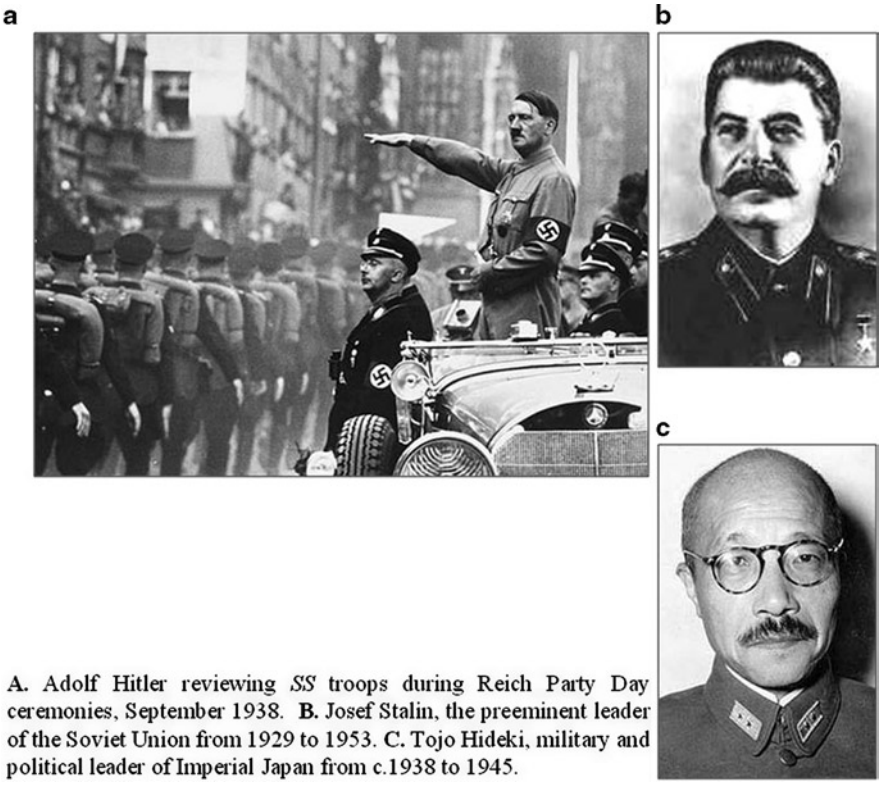
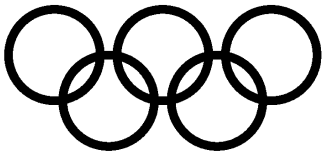


Fig. 15.2 (**a**) Adolf Hitler reviewing *SS* troops during Reich Party Day ceremonies, September 1938. (**b**) Josef Stalin, the preeminent leader of the Soviet Union from 1929 to 1953. (**c**) Tojo Hideki, military and political leader of Imperial Japan from c. 1938 to 1945

drug combinations on himself. In the case of Japan, it is unclear whether Tojo Hideki ordered Imperial troops to use anabolic steroids and amphetamines. However, when one takes into consideration the close ties that existed between Nazi Germany and Imperial Japan, and the fact that methamphetamine was first synthesized in Japan, it seems likely that anabolic steroids were employed (Fig. 15.2a–c) [2].

The unfortunate flaw in "pharmaceutically enhanced troops" is that with continual usage of amphetamines and anabolic steroids at high doses, the likelihood of a psychotic episode and violence would undoubtably increase. In times of war when adrenalin (β_1, β_2-adrenoceptor agonist) is surging, i.e., the soldiers' "blood is up," there is little doubt that the magnitude of these violent outbursts could be horrific in nature. The combination of steroid usage along with stimulants may have contributed to some of the excesses attributed to the *SS*, Soviet, and Imperial Japanese troops, as well as any others who may have used excessive amounts of stimulants and/or anabolic steroids. Although an extreme example of potential hazards that may be encountered when heavy steroid usage is coupled with frequent use of stimulants, it serves as a stern warning for those who embrace the popular fitness craze of the last decades of the twentieth century.

The Olympics: Since the 1970s, the media has been reporting among athletes. In particular, reports from the USA indicate that the highest frequency of steroid abuse occurs among male (95%) athletes (65%) who are usually football players, weight lifters, or heavy weight wrestlers. These users are usually attending a metropolitan school with greater than 700 students, usually a minority student, and most likely to have received the drugs via a black market (60%) source [5]. Furthermore, the magnitude of this problem is on an international scale. To determine the frequency of use of doping agents in college students from five European Union countries (Finland, France, Germany, Greece, and Italy) and Israel, the students were given an anonymous standardized survey that indicated a rate of usage (at least once) was 2.6%, while a previous study suggested that over 15% of the students used substances on the WADA (World Anti-Doping Agency) list prohibited substances [1, 9]. In study conducted by Wanjek et al. [9] in 2004, students from 16 schools (five regular schools, four secondary schools, three sport schools, and four vocational schools) located in Germany were given a survey to provide reliable data regarding doping usage and future interventions. The usage distributions were: 0.7% anabolic androgenic steroids (AAS), 0.4% growth hormones, 2.4% stimulants, 13.2% cannabis, 0.1% diuretics, 2.2% cocaine/heroin, and 0.3% erythropoietin [9]. Interestingly, the study further showed that nonathletes (N = 490) reported a 5% higher substance use than that of the recreational athletes (N = 1,254) and a nearly threefold greater usage than that of competitive athletes (N = 497) [9]. Clearly, this problem is not isolated to a few countries, but rather is epidemic in its proportions.



On an international scale, many of the elite athletes (Olympic/professional sports) can obtain doping agents through various sources including their colleagues, team managers, the black market, and unethical physicians. This is especially true where it is considered a criminal act to use these drugs for nonmedical purposes [1]. The question is how to reduce the use of these agents among athletes at all levels. Those individuals (coaches and general physicians) who can have the greatest impact on the illegal use of doping agents often have a limited knowledge of doping and offer a poor defense against their use. In contrast, the Internet offers a vast resource for information supporting the uncontrolled use of doping agents (ranging from androgenic anabolic steroids to recombinant hormones) to give the individual the competitive edge [1]. Furthermore, despite sophisticated anti-doping testing programs implemented by professional sports and competitive sports organizations to reduce the magnitude of usage, the situation is becoming more out of control resulting in an epidemic of doping cases. Examples of this out-of-control usage can be found in the news. The 2008 Beijing Games as with previous Olympics saw their share of doping incidences. In April of 2009, CNN reported that the IOC's drug testing program revealed that six athletes tested positive for the erythropoietic-stimulating agent CERA (continuous erythropoiesis receptor activator). Likewise, the Tour de

France has frequently been in the news as a result of their cyclists testing positive for EPO and CERA as well as major league professional sports in the USA where wide spread steroid usage has raised concerns about the legitimacy of current records.

International Olympic Committee (IOC) and the World Anti-Doping Agency (WADA) List of Banned Anabolic Agents and Stimulants

The World Anti-Doping Agency (WADA) is an independent international organization that was created in 1999 to promote, coordinate, and monitor the fight against doping in sport in all its forms through harmonizing anti-doping policies in all sports and all countries [10, 11]. WADA's priorities are stated by the agency as being focused "on several areas emanating from the responsibilities given to the Agency by the Code and reflect the importance of a comprehensive approach to the fight against doping in sports." These areas include: (1) code compliance monitoring; (2) cooperation with law enforcement; (3) science and medicine to promoting global research to identify and enhance detection of doping substance; (4) develop and maintain the Anti-doping Development Management System (ADAMS); (5) to facilitate the coordination of regional anti-doping organizations; (6) education and doping prevention.

Doping is defined by WADA as being one or more of the following [1, 10, 11]: (1) presence of a prohibited substance or its metabolites or markers in an athlete's bodily specimen; (2) the use or attempted use of a prohibited substance or a prohibited method; (3) refusing, or failing without compelling justification, to submit to sample collection after notification, as authorized in applicable anti-doping rules or otherwise evading sample collection. WADA indicates various categories of substances and methods that are prohibited.

Categories of banned substances include:

- Stimulants
- Anabolic Agents
- Peptide Hormones
- BETA-2 Agonists Note: Only clenbuterol and salbutamol, when its concentration in urine is greater than 1,000 ng/mL
- Masking Agents and Agents with Antiestrogenic Activity

Categories of prohibited methods include:

- Enhanc\ement of Oxygen Transfer
- Pharmacological, Chemical, and Physical Manipulation
- Gene Doping

A. *Sympathomimetic Stimulants*: Amfepramore, amfetamine, amphetamines (amphetamine, benzphetamine, methamphetamine), caffeine, cathine, ephedrine, cocaine, cropropamide, crothetamide, etafedrine, ethamivan, fencamfamine, fenetylline, furfenorex, mefenorex, methoxyphenamine, methylephedrine, methylphenidate,

morazone, nikethamide, pemoline, pentetrazol, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, pipradrol, prolintane, propylhexedrine, pyrovalerone, strychnine, and related compounds.

All stimulants (including both their D- & L-optical isomers, where relevant) are prohibited, except imidazole derivatives for topical use and those stimulants included in the 2009 Monitoring Program*.

* The following substances included in the 2009 Monitoring Program (bupropion, caffeine, phenylephrine, phenylpropanolamine, pipradol, pseudoephedrine, synephrine) are not considered as Prohibited Substances.

B. Anabolic Androgenic Steroids (AAS) (2009 World Anti-Doping Code):

1. *For purposes of this discussion, exogenous anabolic androgenic steroids (AAS) are defined as those substances which are generally not produced in the body while endogenous AAS refers to natural substances that are generally produced in the body.*
   (a) Exogenous AAS including: 1-androstendiol; 1-androstenedione; bolandiol; bolasterone; boldenone; boldenone; calusterone; clostebol; danazol; dehydrochlormethyl-testosterone; desoxymethyltestosterone; drostanolone; ethylestrenol; fluoxymesterone; formebolone; furazabol; gestrinone; 4-hydroxytestosterone; mestanolone; mesterolone; methenolone; methandienone; methandriol; methasterone; methyldienolone; methyl-1-testosterone; methylnortestosterone; methyltrienolone; methyltestosterone; mibolerone; nandrolone; 19-norandrostenedione; norboletone; norclostebol; norethandrolone; oxabolone; oxandrolone; oxymesterone; oxymetholone; prostanozol; quinbolone; stanozolol; stenbolone; 1-testosterone; tetrahydrogestrinone; trenbolone and other substances with a similar chemical structure or similar biological effect(s)
   (b) Endogenous AAS (when administered exogenously): androstenediol; androstenedione; dihydrotestosterone; prasterone (dehydroepiandrosterone, DHEA); testosterone and the following metabolites and isomers: 5α-androstane-3α,17α-diol; 5α-androstane-3α,17β-diol; 5α-androstane-3β,17α-diol; 5α-androstane-3β,17β-diol; androst-4-ene-3α,17α-diol; androst-4-ene-3α,17β-diol; androst-4-ene-3β,17α-diol; androst-5-ene-3α,17α-diol; androst-5-ene-3α,17β-diol; androst-5-ene-3β,17α-diol; 4-androstenediol; 5-androstenedion; epi-dihydrotestosterone; epitestosterone; 3α-hydroxy-5α-androstan-17-one; 3β-hydroxy-5α-androstan −17-one; 19-norandrosterone; 19-noretiocholanolone.
2. β_2-Adrenoceptor Agonists: bambuterol, clenbuterol, fenoterol, formoterol*, reproterol, salbutamol*, salmeterol*, terbutaline*, and related substances. (*Inhalation authorized as described in Article [I.A.]).

C. *Peptide Hormones, Mimetics, and Analogues*: human chorionic gonadotropin* (hCG), pituitary and synthetic gonadotropins* (LH), corticotrophins (ACTH, tetracosactide), growth hormone (hGH), insulin-like growth factor (IGF-1), erythropoietin (EPO), insulin (permitted only to treat athletes with insulin-dependent diabetes),

clomiphene*, cyclofenil*, tamoxifen*, aromatase inhibitors*. (*Note: Use prohibited in males).

D. β-*Adrenoceptor Antagonists (Beta-Blockers)*. Acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, bunolol, carteolol, celiprolol, esmolol, labetalol, levobunolol, metipranolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, timolol

Anabolic Steroids (Androgens)

Early investigations into anabolic steroids can be dated back to the late 1700s, when John Hunter published observations on castration-induced loss of male sex accessory organs. Later studies, conducted in 1849 by Berthold, showed that transplanting a portion of testes into castrated roosters prevented the signs of castration. Thus, the result of this research further described the relationship between the testes and male secondary sex characteristics [5]. In an attempt to thwart the effects of aging, the physiologist Brown-Séquard (1889) prepared and self-administered extracts made from testicles. It was believed that aging was caused by failure of testicular function, and he was convinced that these injections not only reinvigorated him, but also restored his capacity to work. It was not until the 1930s that Koch and his colleagues were able to develop assays to determine androgenic activity with the growth response of the capon's comb [5].

In 1931, Butenandt used Koch's activity assay to help him isolate and identify 15 mg of crystalline androsterone from 15,000 L of male human urine. A year later, Butenandt correctly deduced the structural formula of androsterone by using only 25 mg of isolated crystal. Butenandt's work was finally confirmed in 1934 by Ruzicka when he successfully synthesized androsterone. Work by others showed that androsterone's activity could be enhanced significantly through the process of esterification. Furthermore, the reduction of androsterone to androstanediol was found to increase the hormone's activity by 2- to 3-fold. In 1935, David and his colleagues isolated the principle androgenic steroid, testosterone, from rat testicles and correctly elucidated its structure. Dr. Charles Kochakian, also in 1935, discovered that androstenedione possessed both androgenic and anabolic properties. These properties, however, were only significant in castrated dogs and were much weaker than the effects of testosterone [5, 12].

Understanding the chemistry of the anabolic steroids came about, in a great part, with the development of better techniques for analytical and activity assays. Activity assays, such as the growth response of the capon's comb, provided Koch and his coworkers with a valuable approach to accurately establish the degree of anabolic activity associated with crystals derived from human male urine. Subsequent work showed that testosterone, the prototypical anabolic steroid, was produced in the greatest quantity and had the highest degree of androgenic and anabolic activity of all the endogenous steroids tested. However, later work showed that dihydrotestosterone (DHT), the active form of testosterone in tissue, actually had the greatest potency while having the same affinity for the androgen receptor as testosterone [5, 12].

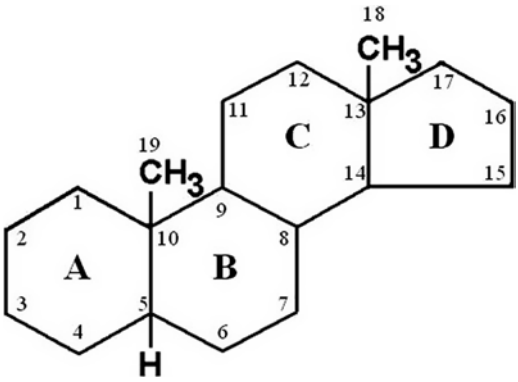


Fig. 15.3 The 19-carbon phenanthrene nucleus forms the skeleton common to steroids

Chemistry

Structure

Naturally occurring steroids are generally relatively flat molecules derived from cholesterol and are of low molecular weight. The basic framework common to all steroids is the 19-carbon phenanthrene (cyclopentanoperhydrophenanthrene) nucleus formed by three hexagonal carbon rings (A, B, and C) attached to a cyclopentane ring (D). Also common to most steroids are two angular methyl groups at positions 18 and 19, and a hydrogen atom at position 5 (Fig. 15.3). For fully saturated molecules, each carbon in the basic ring structure is either attached to two hydrogen atoms, or a hydrogen atom and another carbon atom are associated with a joining ring structure. Another feature common to the basic steroid ring structure is the presence of angular methyl groups (C18 and C19) at positions 10 and 13 of the phenanthrene nucleus. These two methyl groups serve as points of reference regarding the spatial orientation of other groups in the steroid nucleus [13, 14].

This basic structure, the phenanthrene nucleus, is found in several different naturally occurring steroidal compounds including sterols (e.g., cholesterol), bile acids (e.g., cholanic acid), corticosteroids, cardiac glycosides (e.g., digitoxigenin), and the sex hormones (estrogens and androgens). Aromatization of the phenanthrene nucleus at positions 5 and 6 on the hexagonal B ring and the addition of an alkyl side chain (carbons 20–27) at position 17 of the pentagonal carbon ring (D) yields cholesterol, the parent to all steroids. However, removal of part of the alkyl side chain at position 17 of cholesterol gives rise to C21-compounds of the pregnane series (progestins and corticosteroids). Subsequently, the total removal of the alkyl side chain produces C19-steroids of the androstane series (including the androgens), while the loss of the C19 angular methyl group following aromatization yields the estrane series, to which the estrogens belong [13, 14].

Structurally, endogenous and synthetic androgens are characterized by differences in specific functional groups (e.g., hydroxy, keto(oxo), and aldehydes) attached to the phenanthrene and cyclopentane rings. The most frequent sites for modifications of the basic ring structure occur at positions 3, 4, 5 of ring A, and position 17 of the cyclopentane ring, while modifications at positions 11, 18, 20, and 21 are also common (Fig. 15.4). Dehydroepiandrosterone (DHEA, 3β-hydroxyandrost-5-en-17-one), a precursor to testosterone and a commonly used nutritional supplement, has hydroxyl and oxygen groups at positions 3 and 17, respectively. It is interesting to note that endogenous levels of DHEA decrease with age and possess antioxidant properties. Another nutritional supplement, androstenedione (4-androstene-3,17-dione), has hydroxyl groups at positions 3 and 17, and a double bond at positions 4 and 5. Furthermore, the presence of hydrogen at position 5 changes testosterone (17β-hydroxy androstan-3-one to the cellularly active form dihydrotestosterone (stanolone, 17β-hydroxy-5α-androstan-3-one) [13, 14].

Stereochemistry

Of the 1,850 drugs regularly prescribed by physicians, approximately 56% possess a chiral center. In contrast, approximately 99% of the naturally occurring chiral pharmaceutical compounds have a single pharmacologically active enantiomer. Enantiomers can vary greatly in their pharmacological effects upon target tissue(s) due to differences in their pharmacodynamic and/or pharmacokinetic parameters because of variations in their binding to receptors or metabolizing enzymes. Furthermore, the less active enantiomer (distomer) may interfere with the more biologically active species (eutomer) through competitive inhibition. Thus, the distomer may potentially bind to sites other than its primary receptor, thereby potentially causing adverse effects or altering the distribution and/or the activity of the eutomer, resulting in decreased or increased effect or toxicity [14, 16].

In general, androgens are relatively flat molecules that have functional groups that can be oriented either in equatorial or axial positions. Thus, this type of structure can potentially give rise to numerous asymmetrical sites, e.g., chiral centers, yielding molecules with the same chemical formula but different three-dimensional structures.

Groups that are in the same plane as the angular methyl groups (positions 18 and 19) are referred to being in the β-configuration and are represented by a solid line, while groups on the opposite side of the plane are in the α-configuration and are represented by a dashed line. Those groups that are *trans* to one another are on opposite sides of the molecule while those that are *cis* are on the same side. In all naturally occurring steroid hormones, the spatial relationship between rings B/C and C/D is in the *trans* configuration. However, the fusion of the A and B rings into either a *cis* or *trans* conformation can significantly increase the complexity of their stereochemistry [13, 14].

Research into receptor binding and binding to metabolizing enzymes has shown that a chiral preference exists. In particular, investigations into antiandrogen activity (for blocking androgen-induced prostate enlargement) with drugs such as casodex

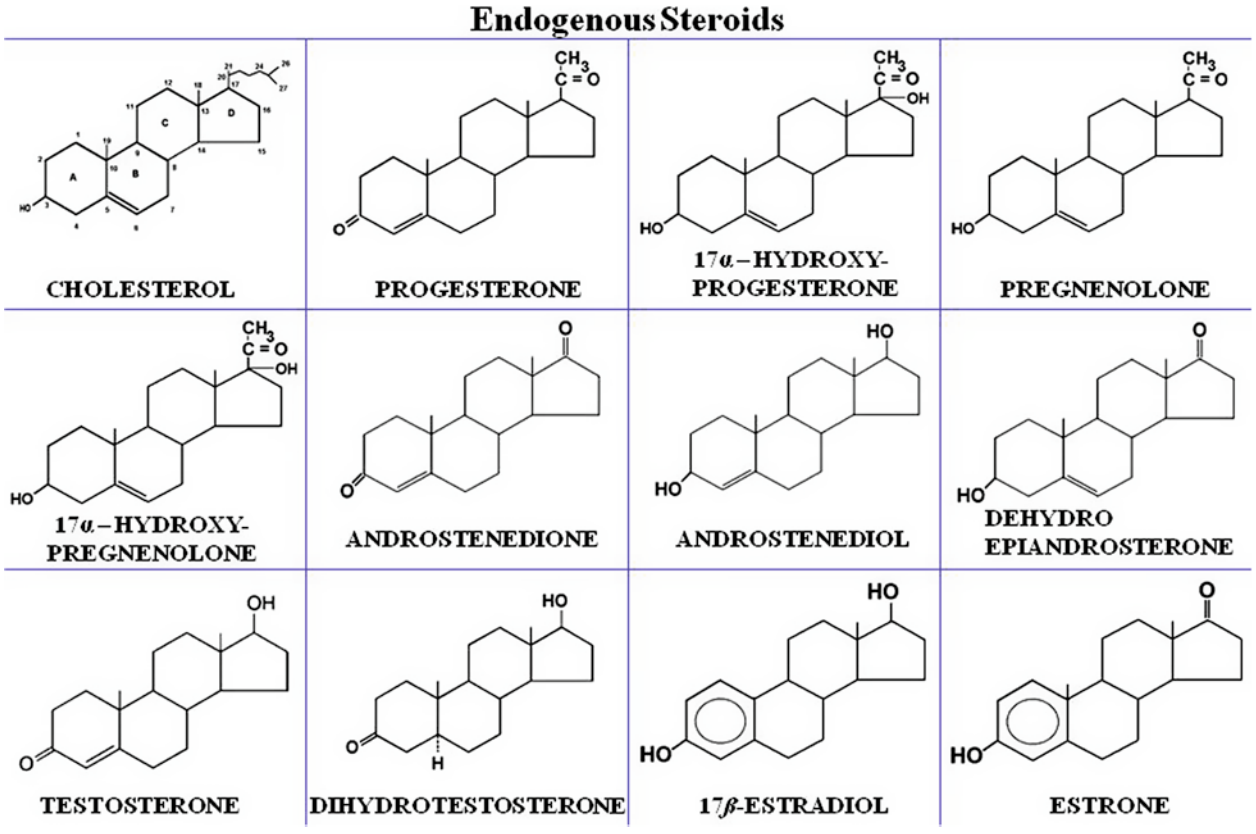


Fig. 15.4 Endogenous steroid hormones. Note the common 19-carbon phenanthrene nucleus making up the steroids. (Budavari et al. [15])

have shown a 30-fold greater effect for the (−)-*R* enantiomer over that of the (+)-*S* species [17]. However, chiral research into the anabolic and androgenic properties of the androgens to date has not been addressed.

Basic Physical Properties [10]

See Tables 15.1 and 15.2 and Fig. 15.5.

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

Androgens are classified as a controlled substance under the Anabolic Steroids Control Act of 1990 and have been assigned to Schedule III. There have been no reports of acute overdosing with androgens.

Treatment with natural androgens taken either orally or by intramuscular injections is cleared rapidly by the liver and thus is not clinically effective. Modification of the position 17 hydroxyl group on testosterone by esterification renders the molecule more lipophilic. Through such modifications, variations in the aliphatic chains directly affect the solubility and rate of absorption of the androgen. Furthermore, analogues such as these are usually made up in oil and injected intramuscularly. In contrast, androgen esters are rapidly metabolized, thereby releasing the parent molecule to act at receptor site.

Esters of testosterone that are used clinically in the U.S.A. are propionate, cypionate, and enanthate and have equal potency for their androgenic and anabolic activities. However, analogues of testosterone have been synthesized to enhance the anabolic properties over that of the androgenic (Table 15.3). In cases of hypopituitarism, androgen replacement therapy begins at puberty with a long-acting androgen, such as the enanthate ester of testosterone, in doses of 50 mg intramuscularly (IM) every 4 weeks. Subsequent treatments should be given every 3 and then every 2 weeks, with changes taking place in 3-month intervals. Doses are then changed to 100 mg every 2 weeks until the individual is mature. For adults, the dosage is approximately 200 mg at 2-week intervals. It should be noted that the propionate ester has a relatively short half-life and is normally not considered suitable for long-term treatment, while the undecanoate analogue can be given orally (40 mg/day) but can give rise to liver adenomas. The use of other androgen preparations for replacement therapy includes fluoxymesterone and methyltestosterone. An alternative route of administration for testosterone or its analogues is via transdermal patches or gels.

In contrast to the doses used in replacement therapy, many athletes and their coaches believe that anabolic steroids taken in megadose quantities (e.g., doses that are 10- to 200-fold greater than the normal daily production) will increase the

Table 15.1 Basic physical properties of selected steroids

Drug	Chemical formula	Chemical name	Synonym/salt name
Cholesterol	C27 H46 O	(3β)-Cholest-5-en-3-ol	
Danazol	C22 H27 N O2	(17 alpha)-pregna-2,4-dien-20-yno[2,3-d]-isoxazol-17-ol	Danocrine
Dihydrotestosterone	C19 H30 O2	17β-Hydroxy-5 alpha-androstan-3-one	DHT, stanolone
Fluoxymesterone	C20 H29 F O3	(11β,17β)-9-fluoro-11,17-di-hydroxy-17-methylandrost-4-en-3-one	Oxymesterone
Methyltestosterone	C20 H30 O2	17-Hydroxy-17-methylandrost-4-en-3-one	Androsan
Nandrolone	C18 H26 O2	(17β)-17-Hydroxyestr-4-en-3-one	19-Nortesterone
Nandrolone salts			
Cyclohexanecarboxylate	C25 H36 O3	19-Nortestosterone hexahydrobenzoate	Norlongandron, nor-durandron
Cyclohexanepropionate	C27 H40 O3	19-Nortestosterone cyclohexylpropionate	Sanabolicum
Decanoate	C28 H44 O3	19-Nortestosterone decanoate	Durabolin, deca-durabol, retabolil
p-Hexyloxyphenylpropionate	C33 H46 O4	19-Nortestosterone-3-(p-hexyloxyphenyl) propionate	Anador, anadur
Phenpropionate	C27 H34 O3	19-Nortestosterone β-phenylpropionate	Activin, durabolin, durabol, strabolene
Propionate	C21 H30 O3	19-Nortestosterone propionate	Norybol-19, nortesto
Oxandrolone	C19 H30 O3	5 alpha, 17 β-hydroxy-17-methyl-2-oxaandrostan-3-one	Anavar
Oxymetholone	C21 H32 O3	(5 alpha,17 β)-17-Hydroxy-2-(hydroxymethylene)-17-methyl androstan-3-one	Anadrol
Testosterone	C19 H28 O2	17β-Hydroxy androstan-3-one	
Testosterone salts			
17-Chloral hemiacetal	C21 H29 Cl3 O3	17β-(2,2,2-Trichoro-1-hydroxyethoxy) androst-4-en-3-one	Caprosem
17 β-Cypionate	C27 H40 O3	17β-(3-Cyclopentyl-1-oxopropoxy) androst-4-en-3-one	Depovirin, pertestis, testergon

(continued)

Table 15.1 (continued)

Drug	Chemical formula	Chemical name	Synonym/salt name
Enanthate	C26 H40 O3	17β-[(1-Oxoheptyl)oxyl]-androst-4-en-3one	Testosterone heptoate, androtardyl
Nicotinate	C25 H31 N O3	17β-[(3-Pyridinylcarbonyl)oxy]androst-4-en-3- one	Bolfortan
17-Phenylacetate	C27 H34 O3	17β-[(Phenylacetyl)oxyl]androst-4-en	Perandren phenylacetate
Propionate	C22 H32 O3	delta4-Androstene-17 β-propionate-3-one	Anertan, enarmon
Stanozolol	C21 H32 N2 O	(5alpha,17 β)-17-methyl-2′H-androst-2-eno[3,2-c]-pyrazol-17-ol	Androstanazole

Source: Budavari et al. [15]

Table 15.2 Basic physical properties of selected steroids

Drug	MW (g/mol)	Melting point (°C)	Melting point solvent/other	Solubility	UVMax (nm)
Cholesterol	386.64	149	–	Nearly insoluble in water (0.2 mg/dL), slightly soluble in alcohol, ether 0.36 g/mL, chloroform 0.22 g/mL, pyridine 0.67 g/mL	–
Danazol	337.46	224–227	–	Insoluble in water. Soluble in alcohol, ether, chloroform, petroleum ether, oils	–
Dihydrotestosterone	290.43	177–179	–	Soluble in ethanol (8.0 mg/mL), acetone, ether, alcohol, and ethyl acetate. Practically insoluble in water (<0.5 mg/mL)	–
Fluoxymesterone	336.45	270	–	Soluble in pyridine, slightly soluble in acetone and chloroform. Sparingly soluble in methanol and practically insoluble in water, ether, benzene, and hexanes	240
Methyltestosterone	302.44	161–166	–	Soluble in alcohol, methanol, ether, and other organic solvents. Sparingly soluble in vegetable oil and practically insoluble in water	–
Nandrolone	274.40	112–124	Dimorphic crystals	Soluble in alcohol, ether, and chloroform	241
Nandrolone salts					
Cyclohexanecarboxylate	384.56	88–89	Petroleum ether	–	–
Cyclohexanepropionate	412.61		–	–	–
Decanoate	428.65	32–35	White to yellow crystals	Nandrolone decanoate is practically insoluble in water but is soluble in ethanol, ether, acetone, chloroform, and oils	–

(continued)

Table 15.2 (continued)

Drug	MW (g/mol)	Melting point (°C)	Melting point solvent/other	Solubility	UVMax (nm)
p-Hexyloxyphenylpropionate	506.72	53–55	–	–	–
Phenpropionate	406.56	95–96	–	–	–
Propionate	330.47	55–60	Aqueous methanol or isopropyl ether	–	240
Oxandrolone	306.45	235–238	–	–	–
Oxymetholone	332.48	178–180	Ethyl acetate	–	285
Testosterone	288.41	155	–	Insoluble in water. Soluble in alcohol, ether, and other organic solvents	238
Testosterone salts					
17-Chloral hemiacetal	435.83	200–201	Ethyl ether	–	241
17β-Cypionate	412.59	101–102	–	Soluble in oils	–
Enanthate	400.58	36–38	–	–	–
Nicotinate	393.51	187–188	Acetone	Soluble in dilute HCl and other dilute mineral acids	–
17-Phenylacetate	406.54	129–131	Hexane	–	–
Propionate	344.49	118–122, 117–183	Alcohol + water, methanol	Insoluble in water. Freely soluble in alcohol, ether, and other organic solvents. Soluble in vegetable oils	–
Stanozolol	328.48	230–242	Alcohol	Soluble in alcohol and chloroform	223

Source: Budavari et al. [15]

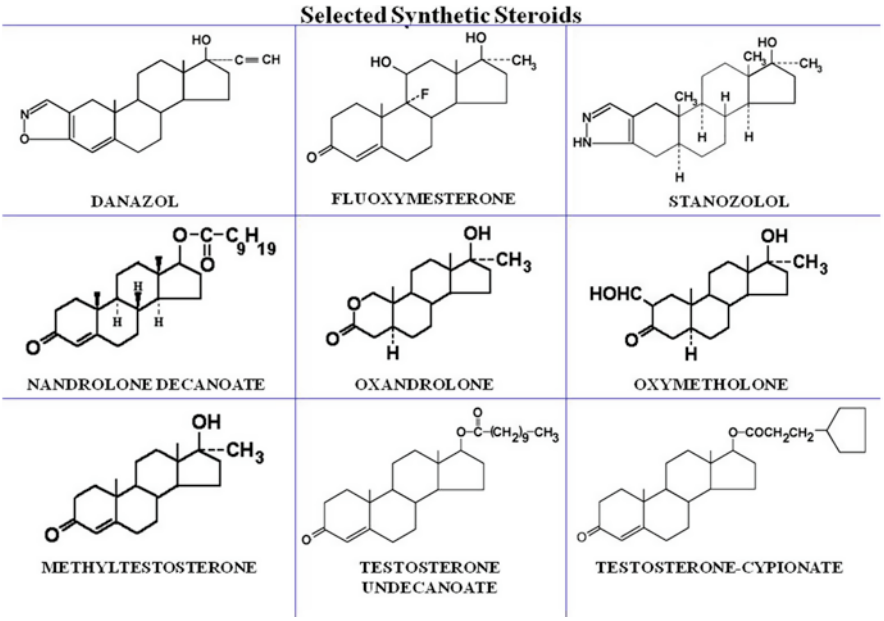


Fig. 15.5 Selected synthetic steroids. Again note the common 19-carbon phenanthrene ring structure commonly found in all steroids. (Budavari et al. [15])

Table 15.3 Anabolic and androgenic potencies of selected androgens

Selected androgen	Androgenic:anabolic activity
Methyltestosterone	1:1
Nandrolone decanoate	1:1
Nandrolone phenpropionate	1:1
Testosterone	1:1
Testosterone cypionate	1:1
Testosterone enanthate	1:1
Testosterone propionate	1:1
Fluoxymestrone	1:2
Metandienone	1:3
Oxymetholone	1:3
Drostanolone propionate (dromostanolone propionate)	1:3–1:4
Stanozolol	1:3–1:6
Ethylestrenol	1:4–1:8
Oxandrolone	1:3–1:13

individual's overall performance by increasing skeletal muscle mass and strength as well as their aggressiveness. In women, these anabolic effects have been observed, but in males, questions have been raised regarding the benefits gained from using anabolic steroids. Earlier versions of pharmacology texts such as Katzung's *Basic and Clinical Pharmacology* and Goodman and Gilman's *The Pharmacological*

Basis of Therapeutics [18] have argued that the benefits gained, if any, from using anabolic steroids are far outweighed by the risk of adverse effects. Furthermore, it was argued at that time that the use of anabolic steroids in megadose quantities does not cause an increase in skeletal muscle mass, strength, or performance, and that the weight gain observed was the result of fluid retention. However, subsequent research utilizing proper controls showed that significant increases in skeletal muscle mass and strength could be achieved in healthy male subjects (18–35 years) when treated weekly with testosterone enanthate at levels greater than 125 mg (125, 300, or 600 mg) per week. This was especially true for individuals who were combining strength exercises along with receiving testosterone treatment [18, 19]. Additionally, testosterone's effects on lean body mass (decreased fat content and increased muscle mass) and muscle strength were found to be dose dependent. Treatments of 25, 50, 125, 300, or 600 mg of testosterone enanthate in the presence of a gonadotropin-releasing hormone (to suppress endogenous testosterone secretions) over a period of 20 weeks resulted in plasma testosterone levels of 2.5, 3.1, 5.4, 13.5, and 23.7 ng/mL. Thus, it was observed that a positive correlation exists between the dose–response and plasma testosterone levels with respect to the overall anabolic effects. Furthermore, results from these studies show that higher plasma testosterone levels (>5.4 ng/mL) were required to render an anabolic effect in males. However, with the higher plasma testosterone levels that are necessary to gain the desired anabolic effects, there comes the risk of detection (Table 15.4).

In hormone replacement therapy, for example with testosterone enanthate, a dose of 75–100 mg/week would be sufficient for treating a hypogonadal man, while a dose of 200–250 mg/week has been used in trial studies as a male contraceptive. However, for those abusing anabolic steroids, doses ranging up to 1,000 mg/week over a cycle of 6 weeks to 7 years (continuous usage) for power lifters have been reported. Androgens such as oxandrolone, oxymetholone, methandrostenolone, and stanozolol (orally active) and testosterone enanthate and nandrolone decanoate (parenterally administered) are commonly abused while mesterolone, testerone undecanoate, and methenolone thus far appear to be of lesser significance with respect to androgen abuse [20–22].

Since anabolic steroids are not routinely included in drug of abuse (DAU) screens, the chances for an individual who is not actively competing in athletic events to be caught are significantly less than if they were abusing cannabis (pot), amphetamines (speed), or cocaine (crack, etc.) [23]. However, those individuals who are routinely use anabolic steroids risk detection when competing in athletic events because of the sensitivity of the analytical tests now being employed. This is especially true when considering that the limit of detection (LOD) for testosterone and testosterone metabolites is significantly less than the plasma levels necessary to render an anabolic effect [23, 24]. In an attempt to avoid detection and to maximize the anabolic activity of androgens, the use of multiple androgens simultaneously (stacking) has been employed. In an epidemiological study focused on the frequency and nature of androgen abuse, results indicated that 38.3% used injectable androgens (61.7% did not) and 43.7% used a stacked androgen regiment. Furthermore, their results indicated that a direct correlation existed between the number of cycles

Table 15.4 Routes of administration for selected anabolic agents (total number of users = 175) (NIDA report, www.nida.nih)

	No. of reported cases	No. of reported cases (%)
Drugs: oral use		
Methandrostenolone	79	35.3
Oxandrolone	55	24.6
Stanozolol[a]	43	19.2
Oxymetholone	18	8.0
Ethylestrenol	8	3.6
Methyltestosterone	7	3.1
Methenolone acetate[a]	7	3.1
Fluoxymesterone	3	1.3
Other	4	1.8
Total number of cases	224	100
Drugs: parenteral use		
Testosterone esters	88±4	40.9
Nandrolone esters	77±5	35.8
Methenolone esters[a]	14	6.5
Stanozolol[a]	15	7.0
Testosterone (aqueous)	6	2.8
Boldenone undecylenate	4	1.9
Methandriol dipropionate	7	3.3
Other	4	1.9
Total number of cases	215	100
Other drugs: non-steroidal		
Chorionic gonadotropin	4	25.0
Growth hormone	3	18.8
Diuretics	3	18.8
Thyroid hormones	2	12.5
Testolactone/tamoxifen	1	6.3
Others	3	18.8
Total number of cases	16	100

Note: steroids may be stacked in varying combinations (see Table 15.5 for Stacking Schedule)
[a]Route used not clearly established

of androgen usage with both an increasing frequency of stacking and use of injectable androgens [25].

Stacking Schedules [26]

Another point of variation among androgen users was the length of cycles. In the before mentioned epidemiological study, it was shown that the length of cycles generally varied from 6 to greater than 13 weeks. The study also showed that with greater usage, cycle lengths increased. From a user's point of view, the stacking of similar drugs together in order to achieve a desired anabolic effect can have several advantages over that of a single drug. These advantages may include:

Table 15.5 Example of a recommended stacking schedule using a combination of transdermal and oral dosing regiments using dermagain, equibolan, and maxeron

Cycle week	Transdermal application (noran drostene & andros tene) (mL/day)	Oral drug 1 (1,4-andro stadienedione) (pills/day)	Oral drug 2 (5α-androstanediol) (pills/day)
1	4		
2	4		
3	4	6	
4	4	6	
5		6	6
6		6	6
7			6
8			6

1. The use of lower doses, thereby reducing the risk of adverse side effects associated with high doses of a single drug
2. The ability to select aspects of desired effects of one drug to offset the less desirable effects of another while maintaining sufficient combined levels to achieve an effective dose
3. To avoid or lessen the chance of being caught using anabolic agents by keeping detectable drug levels less than the limit of detection

For an anabolic stacking regiment to work effectively, dosing should be conducted in staggered cycles. Normal dosing cycles are usually 4 or 8 weeks in length, but cycles 12 weeks in length are occasionally used. When employing the different dosing cycles, breaks (drug abstinence) of 2, 4, or 6 weeks, respectively, are strongly recommended in order to allow the body's endocrine system to recover (Table 15.5).

Drug Usage: Preparations and Routes of Administration Overview

A consequence of taking exogenous androgens in normal males with adequate plasma testosterone levels is the reduction of endogenous testosterone levels. Additionally, exogenous testosterone causes the suppression of gonadotropin-releasing hormone and follicle-stimulating hormone.

- *Androstenedione. [Andro-Max, Androstat 100, 50 and 100 mg].* Androstenedione is an endogenous steroid precursor that is acted upon by the enzyme 17β-hydroxysteroid dehydrogenase to produce testosterone. Synthesis of androstenedione is significantly increased in both men and women following intense anaerobic exercise such as running sprints. Today, androstenedione is widely marketed as an over-the-counter dietary supplement intended to bolster endogenous levels in the hopes of building skeletal muscle mass. Another factor that has increased interest in androstenedione has been with the baseball slugger from the Saint Louis

Cardinals Mark McGwire when he admitted using it in 1998. Whether androstenedione causes increased muscle mass, especially when used concomitantly with exercise, remains unclear. However, basic and clinical research is required to better understand the dynamics of the hormone/anabolism relationship and to better establish the efficacy (if any) of anabolic supplements. In clinical trials conducted by King et al. [19] and Broeder et al. [27], they tested androstenedione and androstenediol for their physiological and hormonal effects. In these studies, male subjects (ages 19–29 years and 35–65 years, respectively) were given 200 or 300 mg/day of androstenedione or androstenediol over an 8- or 12-week period. They found that androstenedione causes a transient increase in plasma testosterone levels (16% increase during the first month and then levels returned to baseline), but did not result in any increase in muscle mass or strength. It was concluded that the manufacture's recommended dosages do not produce any appreciable gains in muscle strength. Additionally, the consequences from using androstenedione and/or androstenediol supplements at the prescribed amounts were significant increases in plasma dehydroepiandrosterone sulfate levels, increases in the amount of estrogen-related compounds, decreases in testosterone synthesis through downregulation, and adverse changes in blood lipid profiles (changes in cholesterol: increased LDL and decreased HDL). Additionally, it was noted that there was an increased risk of coronary heart disease. It should be noted that since androstenediol and androstenedione are hormones, their use is banned from athletic competition by the IOC, NCAA, NFL, and the USOC [10, 28].

- *Indications and Dosages*: Although the use of androstenedione as an ergogenic agent for the treatment of andropause has not been approved for use by the FDA, it may prove useful in the future for treating such conditions. (Andropause is associated with decreases in serum testosterone levels that results in cognitive impairment, lack of energy, loss of bone and muscle mass, increased frailty, loss of balance, sexual dysfunction, and a decrease in the individual's overall general well-being.) Androstenedione is administered orally usually with meals [28, 29].

  The suggested doses for androstenedione as a nutritional ergogenic supplement in athletes are 50–100 mg/day orally. However, clinical studies in adult male volunteers (ages 19–65) suggest that the manufacture's recommended doses fail to achieve any appreciable gains in muscle strength or endurance (during resistive exercises).

  The suggested dosage of androstenedione in males for the treatment of documented andropause is 300 mg/day orally for a period of 7 days. It has been shown that treatment with androstenedione results in increased testosterone levels during the first 4 weeks of treatment, then subsequently drops to baseline levels with prolonged treatment (>4 weeks). However, no results from clinical studies support the use of androstenedione in the treatment of andropause.
- *Danazol. [Danocrine®, Danazol (USP), Danocrine Capsules (CAP 50, 100, 200 mg)]*. Danazol, a synthetic steroid derived from ethisterone (ethinyl testosterone), possesses weak androgenic effects and is antiestrogenic. Danazol acts indirectly on the pituitary to lower estrogen production through reducing the output of both luteinizing and follicle-stimulating hormones. Danazol also binds

to tissue sex hormone receptors, thereby rendering its antiestrogenic, anabolic, and weak androgenic activities. The use of danazol is banned from athletic competition by the IOC, NCAA, and the USOC [10, 28].

- *Pharmacokinetics*. Danazol is administered orally with meals, but plasma levels do not increase proportionally with an increase in dosage. Peak danazol concentrations usually occur in approximately 2 h, but significant treatment time is required for the onset of the therapeutic effects. Daily doses over a period of 6–8 weeks are required for treating anovulation or amenorrhea and treatment of 1–3 months for the pain to subside in fibrocystic breast disease. Danazol is extensively metabolized in the liver to its primary metabolite 2-hydroxymethyl ethisterone, and both are excreted in the urine. The elimination half-life for danazol is 4–5 h [28].
- *Indications and Dosages*. Danazol is indicated for the treatment of angioedema, endometriosis, and fibrocystic breast disease. Although not an approved use by the FDA, danazol can also be used to treat idiopathic thrombocytopenic purpura [145–147]. However, danazol's mechanism of action for treating idiopathic thrombocytopenic purpura is unclear. Investigations conducted by Ahn [25], Fujisawa et al. [26], and Otawa et al. [27] suggest that danazol acts on cell membranes, potentially making them less sensitive to osmotic lysis or by modifying the patient's immune response. Other uses for danazol include treating postcoital contraception, and premenstrual syndrome (PMS) [28].

  For the prophylactic treatment of hereditary angioedema in adults, danazol is given orally in an initial dose of 200 mg/day. Depending on the patient's response, subsequent doses may be reduced to half at intervals of 1–3 months, or increased by 200 mg/day if the patient suffers an attack of angioedema during treatment. However, if danazol is used to treat traumatic angioedema, attempts should be made periodically to reduce or discontinue treatment [28].

  For treating mild cases of endometriosis in adults, danazol is given orally during menstruation in two divided doses of 200–400 mg/day. In moderate to severe cases of endometriosis, danazol is initially given orally during menstruation in two divided doses of 800 mg/day. Depending on the patient's response, subsequent doses may be reduced gradually. However, daily doses should be given over a period of 3–6 months, with treatment not extending beyond 9 months.

  For the treatment of fibrocystic breast disease in adults, danazol is given orally during menstruation in two divided doses of 100–400 mg/day. Depending on the patient's response, dosages are adjusted accordingly. It should be noted that therapy should be continued uninterrupted over a period of 6 months, independent of whether the symptoms are relieved or eliminated. The continuation of treatment over this time is important in order to insure the elimination of nodularity.

  The use of danazol in adults for the treatment of chronic idiopathic thrombocytopenic purpura, PMS maladies, and emergency postcoital contraception is not approved by the FDA. However, for the treatment of chronic idiopathic thrombocytopenic purpura, a dosage of 200 mg orally 3-times/day over a period of 6 months has been recommended. For the treatment of maladies [e.g., mastalgia, bloating and weight gain (greater than a 1.4-kg increase in weight), anxiety, and

depression] associated with premenstrual syndrome (PMS), the recommended dosage in adults is 50–100 mg orally 2 times/daily. To achieve the best results, the dose should be titrated. For emergency postcoital contraception, doses of 800–1,200 mg orally every 12 h for two doses and a dose of 800 mg orally every 12 h for three doses have been suggested. However, further studies are required because of contradictory data.

- *Dihydrotestosterone (DHT)***.** *[Andractim™]*. DHT is classified as a schedule III controlled substance, banned by the NCAA, IOC, and USOC [10, 28]. DHT is the active metabolite of testosterone believed to be the primary anabolic agent in target tissues (e.g., skeletal muscle and the prostrate).
- *Pharmacokinetics*. Results from phase III testing of transdermal DHT patches in hypogonadal men (ages 21–65 years) indicate treatment for 24 h produces peak concentrations after 13 h (reaching a plateau between 12–18 h). On the other hand, peak testosterone levels were achieved in 8 h [30]. Serum DHT levels increased from hypogonadal to normal physiological concentrations within 24 h of treatment. Following removal of the patches, plasma DHT levels dropped back down to its baseline hypogonadal range. The half-life for DHT was reported to be approximately 2.83 ± 0.97 h, while that for testosterone was 1.29 ± 0.71 h. Using a sequential crossover design for transdermal DHT, there was negligible variation in uptake from the different application sites (abdomen, back, chest, shin, thigh, or upper arm). However, this was not true for testosterone.
- *Indications and Dosages*. In individuals who have AIDS, DHT is being studied for reversing AIDS-related wasting of muscle mass. Previous attempts to use testosterone to treat AIDS-related wasting were unsuccessful because it is thought that AIDS patients lack 5α-reductase, the enzyme responsible for converting testosterone into DHT in target tissues [28]. Furthermore, DHT may be the hormone responsible for stimulating an increase in appetite and is currently in phase III clinical trials as a topical agent for treatment of low circulating testosterone levels (andropause) in men and AIDS-related wasting syndrome [21, 29, 31]. Another benefit gained from the use of topical DHT is that this route of administration avoids the pain associated with IM testosterone injections [22].

  The suggested dosage to be used by AIDS patients to attenuate the AIDS-related wasting syndrome or hypogonadal men is unclear at this time. However, topical doses of 16, 32, and 64 mg/day have been studied in phase III trials [28, 29, 31].
- *Fluoxymesterone. [Fluoxymesterone (Tab 10 mg), Halotestin® (Tab 2, 5, 10 mg), Android-F®, Hysterone®, Ora-Testryl® (10 mg)]*. Fluoxymesterone is an orally administered androgen and is classified as a schedule III controlled substance, banned by the NCAA, IOC, and USOC [10, 28]. Fluoxymesterone promotes normal growth, the development of male sex organs, and the development of secondary sex characteristics. It has twice the anabolic potency as testosterone and has an androgenic-to-anabolic potency ratio of 1:2. Furthermore, since fluoxymesterone inhibits the formation of estrogen, it could potentially serve as a potent doping agent [28].
- *Pharmacokinetics*. In a clinical study conducted with fluoxymesterone, 10-mg tablets were administered to six male subjects either orally or buccally. Peak

serum fluoxymesterone levels of 40–150 ng/mL were achieved in 1–2 h, with a half-life of approximately 2.0 h [32, 33].

- *Indications and Dosages*: Fluoxymesterone is indicated for the treatment of inoperable breast carcinoma and hypogonadism in men. The recommended dosage in adults for treating hypogonadism via androgen replacement therapy is 5 mg orally 1–4 times/daily for a total of 5–20 mg/day. For the treatment of inoperable breast cancer in adults, the recommended dosage is 10–40 mg/day orally. The doses should be divided. Fluoxymesterone can also be used to prevent postpartum breast engorgement. Although this usage is not approved by the FDA, it is suggested that 2.5 mg of fluoxymesterone should be administered orally to adults after delivery, then 5–10 mg orally per day in divided doses for a period of 4–5 days. Fluoxymesterone comes in tablet form in doses of 2, 5, and 10 mg [28].
- *Methyltestosterone. [(Tablets 10, 25 mg) Android-10®, Testred®, Virilon® (Inj soln 200 mg/mL), and Methitest™]*. Methyltestosterone is an orally administered androgen and is classified as a schedule III controlled substance, banned by the NCAA, IOC, and USOC [10, 28]. Methyltestosterone is a synthetic analogue of testosterone designed to be administered orally without loss of bioactivity, and was first approved for use by the FDA as a topical ointment in 1939 and as an oral androgenic agent in 1940. When compared to testosterone, methylation at the 17 carbon position reduces the rate at which methyltestosterone is metabolized in the liver. Androgens are important for stimulating RNA polymerase and subsequent protein production is important in the development of male sex traits. During puberty, androgens promote the growth and development of skeletal muscle, and the redistribution of body fat [28].
- *Pharmacokinetics*. Methyltestosterone is administered either orally or buccally. When methyltestosterone is administrated orally, it undergoes the first-pass effect in the liver where it is metabolized at a rate approximately 50% greater than buccally. Peak serum methyltestosterone levels are achieved after about 2 h, with a half-life of approximately 2.5–3.5 h. The glucuronide and sulfate conjugates are eliminated primarily by renal excretion, with a small degree of the drug unchanged.
- *Indications and Dosages*. Methyltestosterone is indicated for the management of congenital or acquired hypogonadism and can be used for the treatment of delayed puberty and erectile dysfunction. Methyltestosterone is also useful for the treatment of breast carcinoma in postmenopausal women because of its antiestrogenic effects.
- Methyltestosterone comes either in capsule or tablet form. The oral dosage required for androgen replacement therapy as well as treatment for erectile dysfunction (impotence) or hypogonadism in adult males is 10–50 mg/day. When taken buccally (i.e., dissolved in buccal cavity), the dose is 5–25 mg/day. In treating delayed puberty in adolescent males, the recommended dosage is 5–25 mg/day orally or 2.5–12.5 mg/day buccally. Treatment occurs over a period of 4–6 months. In treating breast cancer in adult women, the recommended dosage is 50 mg/day up to four times per week orally or 25 mg/day up to four times per week buccally. Once the desired response is observed usually within

2–4 weeks, the dosage can be reduced to 25 mg twice daily. It should be noted that high doses of methyltestosterone over a long period could result in nonreversible masculine changes in women.

- *Nandrolone. [Androlone-D 100®, Deca-Durabolin®, Neo-Durabolic®, Anabolin™ LA, Andryl™, Durabolin®, Hybolin™, Nandrocot™, Deca-durabolin Injection (Inj Sol 100 mg/2 mL); Nandrolone Decanoate Injection (Inj Sol 50 and 100 mg/mL)]*. Nandrolone is an orally administered androgen and is classified as a schedule III controlled substance, which is banned by the NCAA, IOC, and USOC [10, 28]. Nandrolone is a synthetic androgen used in the treatment of osteoporosis and the anemia associated with chronic renal failure. Nandrolone increases hemoglobin and the mass of red blood cells. However, with the advent of recombinant human erythropoietin, the use of nandrolone in treating the aforementioned anemia is declining. Additionally, since nandrolone produces an anabolic effect, it is used as a doping agent to build muscle mass, increase bone density, and stimulate appetite. Furthermore, nandrolone might also enhance erythropoietic-stimulating factor to increase the production of erythrocyte production. Other effects associated with nandrolone include increased levels of low-density lipoproteins (LDL) and decreased levels of high-density lipoproteins (HDL) [28].
- *Pharmacokinetics*. Intramuscular administration of nandrolone is slowly released at a relatively constant rate over a period of 4 days. Peak concentrations occur in approximately 3–6 days for a dose of 100 mg IM. Plasma esterases hydrolyze nandrolone decanoate to its highly lipid-soluble free form, nandrolone. Nandrolone is metabolized in the liver and has a half-life of 6–8 days. The clearance rate of nandrolone is 1.6 L/h/kg body weight.
- *Indications and Dosages*. Nandrolone is indicated for the treatment of the anemia arising from chronic renal failure. Nandrolone can also be used to treat wasting conditions as well as to counter the effects of osteoporosis, but these usages are not approved by the FDA. For treating anemia, nandrolone should be taken at intervals of 3–4 weeks for up to 12 weeks. If a second treatment-cycle is required, a 4-week interval between cycles should be employed. Additionally, because of its erythropoietic effects, adequate iron is required for maximal drug response. For treating the anemia associated with chronic renal failure, adult and adolescent (age 14 years or more) males and females are administered intramuscularly 50–200 mg and 50–100 mg, respectively, at intervals of 1–4 weeks. In children (2–13 years), the recommended dosage of nandrolone is 25–50 mg IM [28].
- Nandrolone may be used intramuscularly (50 mg IM every 3–4 weeks) for the treatment of osteoporosis in postmenopausal women, where it acts to inhibit bone resorption and increases bone density. It should be noted that this usage is not approved by the FDA.
- *Oxandrolone. [Oxandrin®; come in 2.5 mg tablets]*. It should be noted that oxandrolone is a schedule C-III controlled substance and is subsequently banned from athletic competition by the IOC, NCAA, NFL, and the USOC [10, 28]. Oxandrolone is a potent synthetic analogue of testosterone that has approximately eight-times the anabolic activity of its parent compound. The ratio of anabolic to androgenic activity (testosterone:oxandrolone) is approximately 1:3–1:13, making

oxandrolone the most potent of the androgens (Table 15.3). The deletion of the angular methyl group at the C-19 position results in the molecule's greater androgenic potency. Oxandrolone in combination with adequate calories has been used to promote weight gains in individuals with chronic wasting diseases such as Duchenne's muscular dystrophy, COPD, and AIDS [28, 34–36]. Androgens have also proven useful in maintaining muscle mass and body weight in trauma cases or in cases where patients suffered severe burns [28].

At normal prescribed doses, oxandrolone is not ergogenic. It is unclear due to conflicting evidence whether anabolic steroids significantly increase athletic performance when used in high doses. Oxandrolone has been shown to promote increases in lean body mass (increased muscle mass and strength) that is lost with the stoppage of treatment. Oxandrolone is not aromatized to estrogen, thus works directly as an androgen. Furthermore, oxandrolone decreases protein catabolism possibly by competitively inhibiting glucocorticoid receptors or interfering with the glucocorticoid responsive element.

- *Pharmacokinetics*. Oxandrolone is administered orally and is rapidly absorbed. Oxandrolone is highly bound (9–97%) to plasma proteins and has a bioavailability of approximately 97%. Hepatic metabolism of oxandrolone is markedly slower than that of testosterone or other androgens due to the modification of ring A (lack of a 4-ene function) and 17α-alkylation. The elimination half-life for oxandrolone is approximately 9.4 h, and peak plasma concentrations are higher than methyltestosterone. Oxandrolone is excreted primarily in the urine as the unchanged parent drug (approximately 28%) and unconjugated product [28].
- *Indications and Dosages*. It is important to note that when treating wasting conditions with oxandrolone (or any other androgen), proper nutrition is essential. Oxandrolone is indicated for the treatment of wasting syndromes associated with chronic diseases and lack of nutrition. Oxandrolone has also been suggested for use in the treatment of AIDS-related wasting syndrome, Duchenne muscular dystrophy, growth failure, and Turner's syndrome. However, these uses have not been approved by the FDA [28, 37]. Oxandrolone is indicated for treating wasting conditions (cachexia, resulting from chronic disease and/or infection, severe trauma, prolonged glucocorticoid treatment, or extensive surgery), thereby promoting weight gain and increased protein synthesis. Furthermore, treatment would be indicated within those individuals who fail to maintain normal body weight. The usual recommended oral dosage in adults is 2.5 mg, taken 2–4 times daily (5–10 mg/day) over a period of 2–4 weeks. Depending on how the patient responds, the treatment may be repeated as needed. If necessary, the dosage may be increased up to 20 mg/day. However, the patient's response to treatment will determine the dose and duration of treatment. In children, the recommended oral dose is 0.1 mg/kg (0.045 mg/pound) body weight/day over a period of 2–4 weeks. However, the dosage should not exceed the adult dosage.

  To treat the wasting syndrome associated with AIDS and the accompanying muscle weakness (not FDA-approved usage), an oral dosage of 5–15 mg/day over 16 weeks has been investigated in adults [38]. Dosages of 15 mg/day were shown to enhance weight gain while the 5 mg/day treatment group and placebo-controls

experienced either weight maintenance or loss in body weight, respectively. In these subjects, there was not any measurable improvement in muscle strength.

In other clinical studies conducted in children and adolescents suffering from chronic diseases and/or failure of growth (e.g., Duchenne muscular dystrophy, HIV infection, Turner's syndrome in females, and delayed pubertal development in males), oxandrolone was used orally at doses of 0.1 mg/kg/day (0.05 mg/kg/day for Turner's syndrome) over a period of 12 weeks [28, 37, 39]. Results indicated that treatment with oxandrolone was successful in countering the weight loss and decreases in muscle mass associated with HIV. With stoppage of treatment, body weight was maintained but there was a decrease in muscle mass.

Treatment with oxandrolone (0.1 mg/kg/day, males) significantly improved muscle strength in children with Duchenne muscular dystrophy, and significantly improved the velocity of growth in boys with delayed pubertal development. Likewise, oxandrolone (0.05 mg/kg/day) significantly increased the rate of growth and final height in girls with Turner's syndrome. Additionally, the concomitant treatment with oxandrolone and growth hormone resulted in a greater final height than with oxandrolone alone.

- *Oxymetholone. [Anadrol®, Anapolon®; come in 50 mg tablets]*. Oxymetholone is an orally administered androgen and is classified as a schedule III controlled substance, banned by the NCAA, IOC, and USOC [10, 28]. Oxymetholone, like nandrolone, acts to enhance the production and excretion of erythropoietin, thereby increasing the red blood cell count. In contrast to nandrolone, oxymetholone produces a greater degree of hepatotoxicity.
- *Indications and Dosages*. Oxymetholone is used for the treatment of anemias resulting from aplastic anemia (acquired or congenital), decreased production of red blood cells, bone marrow failure, myelofibrosis, and hypoplastic anemias arising from myelotoxic drugs. Additionally, oxymetholone has been used to treat wasting conditions associated with chronic diseases. In 1997, Anadrol-50 was discontinued. Oxymetholone is not meant to replace other therapeutic approaches to counter anemias such as iron, folic acid, vitamin B-12, and/or pyridoxine replacement therapy, and blood transfusions.

  In adults and children, the recommended oral dosage is 1–5 mg/kg body weight/day. Normally, a dose of 1–2 mg/kg/day is effective but higher doses may be required. As with all androgens, therapy should be tailored to the individual's needs and overall response. Treatment should be given over a period of 3–6 months with careful monitoring of hepatic functions. Following remission in patients with congenital aplastic anemia, a continued maintenance dose is usually sufficient to maintain normal red blood cell counts.
- *Stanozolol. [Winstrol®, Winstrol® V (2 mg Tablets)]*. Stanozolol is an orally administered androgen and is classified as a schedule III controlled substance, banned by the NCAA, IOC, and USOC [10, 28]. It has been used in the treatment of hereditary angioedema, and has been used as an anabolic agent to promote increases in muscle mass, enhance performance, and reverse catabolism. Stanozolol was approved for use by the FDA in 1962 with 4.5-times greater anabolic potency than testosterone. Additionally, the anabolic activity for stanozolol is 3- to 6-fold greater than its

androgenic effects. Stanozolol, as with the other anabolic agents, requires sufficient chloric and protein intake in order to maintain a positive nitrogen balance.

- *Indications and Dosages*. Stanozolol is indicated for use in the treatment of hereditary angioedema. The recommended oral dosage in adults is initially 2 mg taken 3 times/day. The dosage should be decreased when the frequency of attacks has lessened. A maintenance dose of 2 mg/day or every other day should be taken orally at intervals of 1–3 months.
- *Testosterone. (Andro®, AndroGel®, depoAndro®, Depo®-Testosterone, Androderm®, Testoderm®, Testoderm TTS®, Testopel®, Andro Cyp™, Andro-L.A.®, Delatest®, Depandrate™, Depandro®, Duratest™, Durathate™, Histerone™, Meditest™, Testa Span™, Testamone™, Testerone™, Testolin™, Testro™, Testro™ AQ, Testro™ LA.; Testosterone (PELLET 75 mg, INJ SUSP 50 mg/cc); Testerone suspension (INJ SUSP 50 mg/mL); Testosterone propionate injection (INJ SOL 100 mg); Depo testosterone injection (INJ SOL 200 mg/mL); Testoderm system transdermal (FILM ER 4 mg/day); Androderm (FILM ER 2.5 mg/day)).* Testosterone is the principal endogenous androgen and is classified as a schedule III controlled substance, banned by the NCAA, IOC, and USOC [10, 28]. It was first approved for use in 1939 by the FDA and can be administered parenterally in two dosage forms (regular and delayed release), by transdermal application, or through the implantation of sterile pellets (released over a period of 3–6 months). Testosterone is metabolized in the liver at a relatively fast rate, thus prompting the search for androgens with prolonged action, as with the analogue methyltestosterone. Androgens are important for stimulating RNA polymerase and subsequent protein production important in the development of male sex traits. During puberty, androgens promote the growth and development of skeletal muscle, and the redistribution of body fat [28].
- *Pharmacokinetics*. Oral administration of testosterone would result in the drug being absorbed from the GI tract and being extensively metabolized in the liver (first-pass effect). Since the bioavailability of testosterone is low when taken orally, analogues of testosterone (e.g., methyltestosterone) have been synthesized to act as a prodrug (prohormone) when taken orally, releasing testosterone as the active metabolite when metabolized in the liver. However, the usual routes of administration for testosterone include: intramuscularly (IM), absorption by transdermal patches, absorption by topical gel application, and pellet implant [21, 28].
- *Intramuscularly Route (IM).* When testosterone undecanoate is taken orally for replacement therapy in hypogonadal men, multiple doses are required on a daily basis to achieve the desired effect. Additionally, the resulting serum testosterone levels can vary by a wide margin potentially due to variations in absorption from the GI tract and the rapid metabolism of testosterone in the liver. However, the administration of testosterone esters (e.g., testosterone undecanoate) via an IM route offers a more sustained duration of action lasting from 2 to 4 weeks, owing to its slow absorption from the injection site. Testosterone esters are less polar than testosterone and are absorbed at a slower rate.

  In pharmacokinetic studies conducted in orchidectomized cynomolgus monkeys (*Macaca fascicularis*), Partsch et al. [40] showed that a single IM injection (10 mg/kg) of testosterone undecanoate produced first day mean serum levels of

58 ±18 nmol/L and levels of 40–68 nmol/L for a period of 45 days. Testosterone levels remained normal over another 56 days. However, IM injections of testosterone enanthate (10 mg/kg) produced higher initial plasma testosterone levels (100–177 nmol/L) than the undecanoate out to day 5, then significantly decreased to low normal levels after 31 days. Clinical studies with testosterone undecanoate in Klinefelter's syndrome patients were conducted by Zhang et al. [22]. In these studies, they showed plasma testosterone levels to increase from 10 nmol/L (hypogonadal levels) to 47.8 ± 10.1 and 54.2 ± 4.8 nmol/L following IM injection of 500-mg or 1,000-mg testosterone undecanoate, respectively.

- *Subcutaneous Implantable Pellets.* Subcutaneous testosterone pellets have duration of action that ranges from 3 to 4 months to approximately 6 months.

Topical Absorption [28].

- *Gels.* Dosing once a day (24 h doing interval) with a topical testosterone skin gel or ointment, 10% of the applied dosage is systemically absorbed. This information suggests that the skin acts as a reservoir for sustained-release of testosterone. Differences in skin color may affect the amount of drug absorbed into the skin-reservoir. It is important to note that with higher melanin concentrations in dark skin, higher drug concentrations will be observed than in skin of a lighter color.
- *Transdermal Patches.* Skin patches can be applied to areas of the scrotum, arm, back, or upper buttocks. The scrotum provides an area that is fivefold more permeable than other areas. From scrotal patches, serum testosterone concentrations peak after 2–4 h and plateau following 3–4 weeks.
- *Indications and Dosages*. Testosterone is indicated for the treatment of breast cancer, delayed puberty, erectile dysfunction, and hypogonadism. Although not approved for use by the FDA, testosterone has also been suggested for the treatment of AIDS-associated wasting syndrome, anemia, and microphallus.
- *Androgen Replacement Therapy for the Treatment of Erectile Dysfunction (Impotence).* In adult males, the recommended dosage of testosterone suspension or testosterone propionate is 10–25 mg (IM) 2–3 times/week, while 50–400 mg (IM) once every 2–4 weeks is recommended for testosterone cypionate or enanthate.
- *Androgen Replacement Therapy for Hypogonadism (primary and hypogonadotropic types).* In adult males, the recommended dosage of testosterone suspension or testosterone propionate is 10–25 mg (IM) 2–3-times/week, while 50–400 mg (IM) once every 2–4 weeks is recommended for testosterone cypionate or enanthate. In children, to initiate pubertal growth, 40–50 mg/m^2 is administered IM. Treatment is continued until the growth rate drops to prepubertal levels. The recommended treatment for the terminal growth phase is 100 mg/m^2 IM until growth stops. Continuing treatment (100 mg/m^2 IM) at a dosage rate of 2/month will maintain virilization.

Biosynthesis of Endogenous Androgens

The principal site for the synthesis of endogenous androgens (e.g., dehydroepiandrosterone (DHEA) or testosterone) in men is in the leydig cells of the testes

where approximately 95% of all the androgens are produced. In particular, androgens are synthesized in the mitochondria of leydig cells. In addition to the testes, androgens are also synthesized in the cortex of adrenal glands. The primary androgen synthesized in the adrenals is androstenedione, a precursor to testosterone and dihydrotestosterone. In males, the adrenal cortex accounts for only about 5% of the total hormone produced in the body. In contrast, the adrenal cortex in females accounts for the majority of androgens (e.g., DHEA) produced, while theca follicular cells of the ovaries are secondary for androgen production. The mean production rates of testosterone and dihydrotestosterone (DHT) in normal healthy males are 0.07 and 0.03 mg/day, respectively, while in females, the corresponding rates of production are 0.03 and 0.006 mg/day [13, 41, 42].

The synthesis of testosterone (Fig. 15.6) in the testis is initiated by the conversion of plasma cholesterol and acetate [13, 41, 42]. The resulting cholesterol esters are acted on by the enzyme *20,22-desmolase* in the rate-limiting step to form the intermediate pregnenolone. This rate-limiting step in the synthesis of testosterone is most likely subject to regulation by gonadotropins. In turn, pregnenolone undergoes conversion to progesterone by *3*β*-OH-steroid dehydrogenase* (*3*β*-HSD)*. Pregnenolone and progesterone are both acted on by the enzyme *17-hydroxylase* forming 17-OH-pregnenolone and 17-OH-progesterone, respectively. Similarly, the enzyme *17,20-desmolase* is responsible for catalyzing the conversion of 17-OH-pregnenolone and 17-OH-progesterone to dehydroepiandrosterone (DHEA) and androstenedione, respectively. DHEA and androstenedione both undergo 17β-dehydroxylation by *17*β*-OH-steroid dehydrogenase* to form androstenediol and testosterone. Androstenediol is further acted upon by the enzyme *3*β*-OH-HSD* to yield testosterone [13, 41, 42].

Mechanism of Action

All of the androgens produce their effect through binding to high-affinity steroid receptors free in the cytoplasm (Fig. 15.7). Once bound, the hormone–receptor complex translocates into the nucleus and binds to DNA. Other possible interactions may include the passing of the steroid molecule into the nucleus and binding with a nuclear receptor, or possibly dissociating from the steroid receptor and directly interacting with DNA. However, it has been shown that the rate-limiting step in binding steroid hormones to the receptor is not either the cytoplasmic concentration of the steroid or steroid–receptor complex, but the number of cytoplasmic receptors. In the nucleus, anabolic steroids enhance gene transcription resulting in the production of specific mRNA. The mRNA passes out into the cytoplasm, binds to the rough endoplasmic reticulum, and induces protein synthesis. In addition to an anabolic/androgenic action on tissue, catabolic activity is inhibited. Whether inhibition of catabolic activity occurs in the nucleus through inhibiting the transcription of catabolic enzymes or in the cytoplasm is unclear [13, 41, 42].

When androgen receptors are present in a tissue, the tissue is said to be androgen sensitive. Receptor levels in skeletal muscle have been reported to range between 0.5 and 3.0×10^{-12} moles per mg protein, while in the prostrate receptor, levels may be 25-fold greater. Nearly all of the testosterone content in tissues such as the prostate,

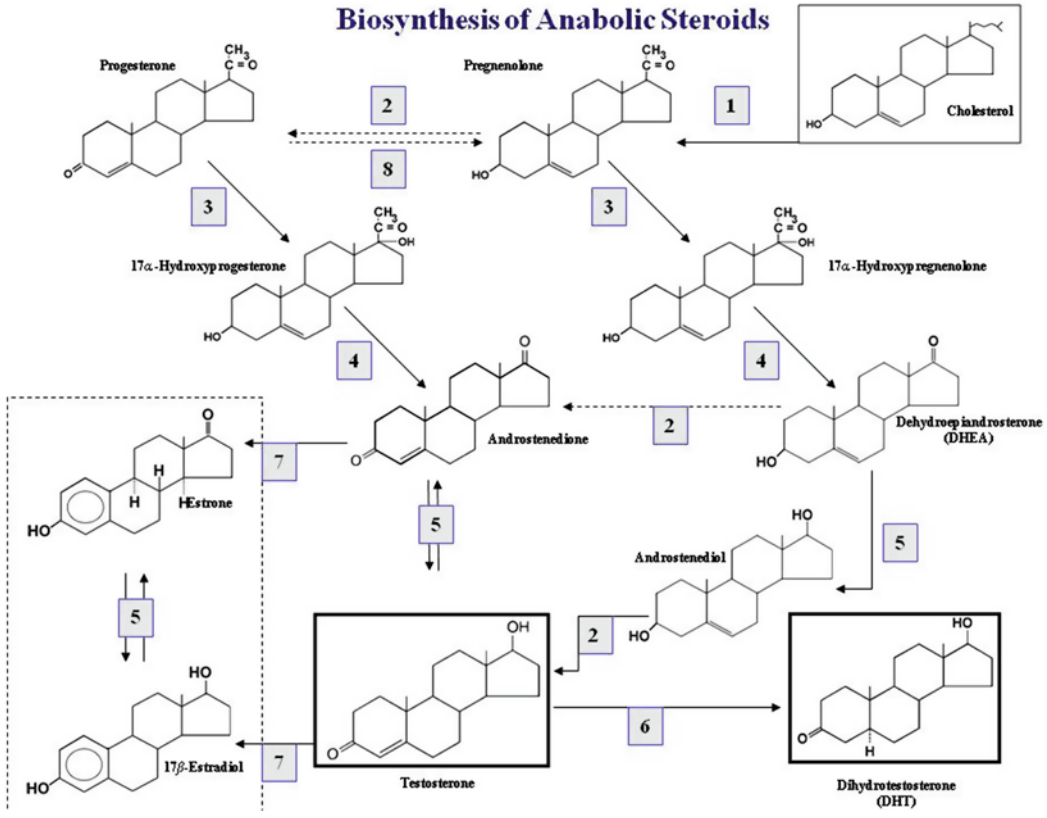


Fig. 15.6 The biosynthesis of anabolic steroids. Enzymes used in testosterone synthesis from cholesterol. ***1*** 20,22 Desmolase, ***2*** 3β-OH-steroid dehydrogenase (3-β-HSD), ***3*** 17β-hydroxylase, ***4*** 17,20 desmolase, ***5*** 17β-OH-steroid dehydrogenase (17-β-HSD), ***6*** 5α-reductase, ***7*** Aromatase, ***8*** 5β-reductase

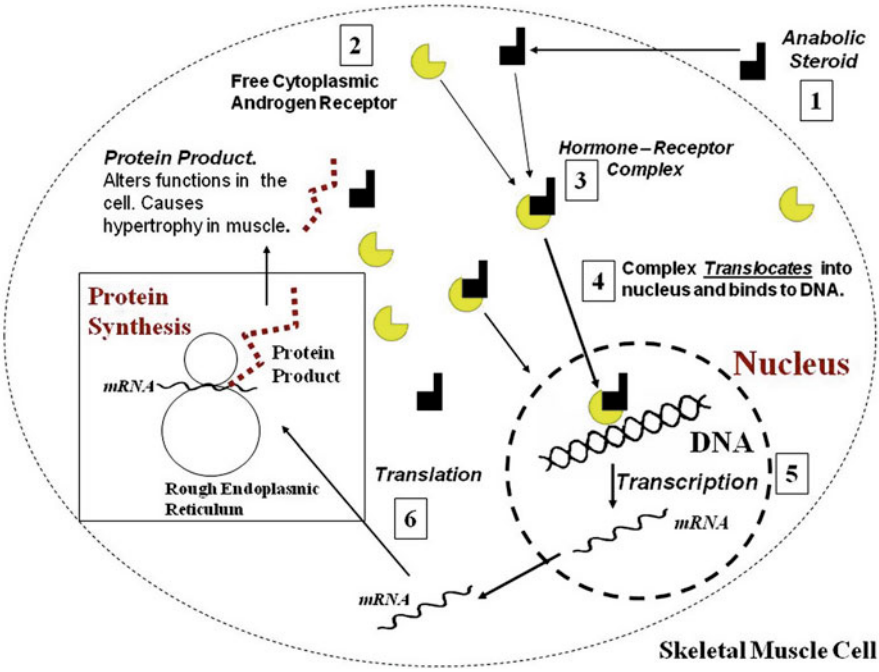


Fig. 15.7 Mechanism of action: receptor signal transduction

seminal vesicles, and pubic skin is metabolized to DHT, the active form of testosterone that binds to the nuclear androgen receptors. However, in other tissues (e.g., kidneys, testis, and skeletal muscle) that contain little 5α-reductase, testosterone binds directly to the receptor. DHT is 2.5–10 times more potent than testosterone in bioassays (such as capon's comb) and binds to the receptor with a 2- to 3-fold higher affinity (K_d=0.25–0.5 nM DHT and K_2=0.4–1.0 nM testosterone). In skeletal muscle, DHT activity is attenuated by the enzyme 3α-hydroxysteroid oxidoreductase, which converts DHT to the less active androgen 5α-androstane-3,17β diol. Thus, bioconversion of DHT and other androgens limits their effectiveness in skeletal muscle. A final point to consider for androgen activity is the feedback control mechanism utilizing the testosterone metabolite estradiol (Fig. 15.8). Estradiol acts to enhance catabolic activity in tissue, thereby attenuating the effects of high levels of testosterone or its analogues [14, 43, 44].

Transport and Metabolism

Transport

Endogenous hormones that are released into the blood stream subsequently act on remote target tissues responsible for muscle growth and secondary sex characteristics. Once entering the plasma, testosterone becomes bound to carrier proteins and

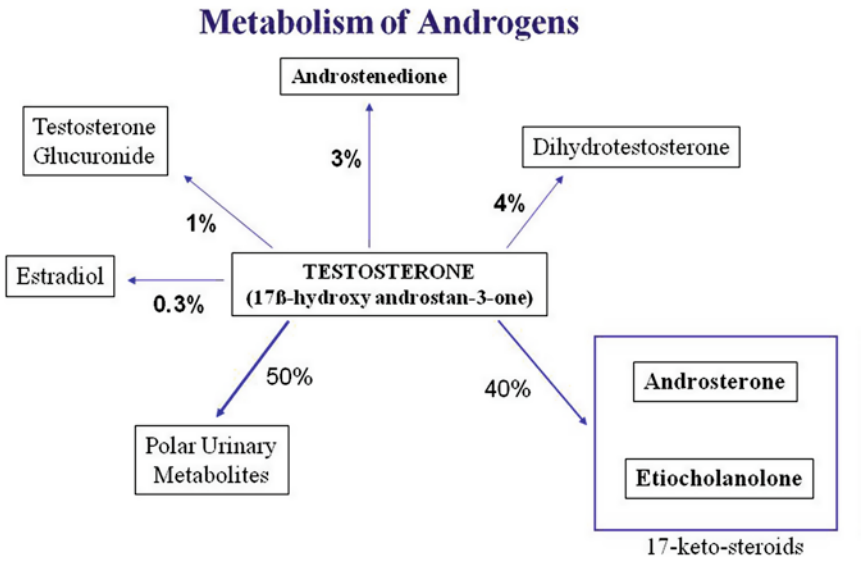


Fig. 15.8 The different products associated with androgen metabolism

is transported to the liver where the complex undergoes catabolism. Of these carrier proteins, testosterone binds to the sex hormone–binding globulin (SHBG), also known as the testosterone-estradiol-binding globulin (TeBG) [13, 41]. In plasma, approximately 2–3% of testosterone and DHT circulates as unbound (e.g., free), bound to SHBG (~60%), or bound to albumin (~37%). In women, estradiol is also carried by SHBG, while in men, it is carried by albumin since testosterone and DHT saturate all of the available sites on SHBG. The primary route for testosterone to enter cells is via simple diffusion. However, it is unclear whether testosterone that is bound to SHBG is able to enter cells. It is important to note that changes in the circulating pool of SHBG will have an effect on the proportion of free testosterone in the plasma available to enter target cells. Because testosterone has such a short biological half-life, alkylation (for oral usage) or esterification (for injectable steroids) of the molecule is required in order to prolong its half-life, by slowing down its rate of metabolism [13, 42, 45].

Metabolism (Table 15.6 – Metabolites, Fig. 15.8)

The primary site for the metabolism of testosterone and other androgens is in the liver. In both testosterone and androstenedione, the double bond located between C4 and C5 is reduced, yielding two stereoisomers with a chiral center at C5. The isomers of androstenedione are etiocholanolone (5β-isomer) and androsterone (5α-isomer). Other isomers that are formed from the hydrogenation of the C-3 keto group include the 3α-hydroxysteroids (androsterone and etiocholanolone) and the

Table 15.6 Major metabolites of selected androgens

Androstenedione	Danazol	Dihydrotestosterone	Fluoxymesterone	Methyltestosterone
Testosterone	Delta-1-2-hydroxymethyl-ethisterone	Androstanediol	6-Hydroxyfluoxy-mesterone	6β-Hydroxymethyl-testosterone
Estrone	2-Hydroxymethyl-ethisterone		6,16-Dihydroxyfluoxy-mesterone equine[a]	
		Glucuronidated at positions 3 & 17		

Nandrolone	Oxandrolone	Oxymetholone	Stanozolol	Testosterone
19-Norandrosterone		17β-Hydroxy-17 α-methyl-5α-androstan-3-one (mestanolone)	16β-Hydroxystano-zolol	Dihydrotestosterone
19-Noretiocholanolone		17β-Hydroxy-17α-methyl-2,3-seco-5α-an-drostan-2,3-dioic acid		Estradiol
		3α, 17β-Hydroxy-17α-methyl-5α-androstan-2β-carboxylic acid		Etiocholanolone

[a]No first-pass effect and cannot be converted to estrogen

Table 15.7 Percent usage of anabolic steroids amongst middle and high school students (NIDA report, www.nida.nih)

	Grades		
	8th	10th	12th
Year	% Use	% Use	% Use
1991	1.90	1.80	2.10
1999	2.70	2.70	2.90
2000	3.00	3.50	2.50
	% Change	% Change	% Change
1991–1999	0.80	0.90	0.80
1999–2000	0.30	0.80	–0.40
1991–2000	1.10	1.70	0.40

3β-hydroxysteroid (epiandrosterone). Of these 17-keto-steroids, the 3α-hydroxysteroids are found in the highest concentration in the urine. Another metabolite of testosterone, epitestosterone, is the 17α-hydroxy androstan-3-one enantiomer of testosterone. In normal adult men, it has been reported that approximately 5–25 mg of 17 keto-steroids is excreted in the urine over a 24-h period [13, 20, 42].

In addition to the aforementioned metabolites of testosterone, testosterone is also metabolized into a series of hydroxylated (positions 3, 15, and 16) polar compounds that are conjugated to sulfuric and glucuronic acids and excreted in the urine and bile. In addition to the metabolites, approximately 250 mg/day is excreted into the urine unchanged.

Alkylation at position 17 on the D ring for orally active androgens provides a measure of protection against the first-pass clearance in the liver. These drugs include oxandrolone, oxymetholone, methandrostenolone, and stanozolol for the orally active drugs and testosterone enanthate and nandrolone decanoate for the parenterally administered nonmethylated androgens containing a 17-β ester period [13, 20, 42].

Toxicology: Adverse Reactions and Contraindications

Use of anabolic steroids, as well as other anabolic agents, is occurring at an increased rate in other segments of the population. The "Monitoring the Future" study conducted by the National Institute on Drug Abuse (NIDA) is an annual survey of drug abuse among American adolescents. Results from this study showed a 6% decrease among 12th grade students in associating the magnitude of health risk with the use of anabolic steroids. Over a period of 8 years (from 1991 to 1999), significant increases in anabolic steroid usage were observed among adolescents (Table 15.7). More alarmingly, between the years 1998 and 1999, a greater increase in steroid abuse was noted among middle school aged students. Other reports from Merck indicated that in the USA, the rate of anabolic steroid use in male high school students ranged from 6 to 11%. Surprisingly, this relatively high percentage of users

included a number of nonathletes. Additionally, it was reported that steroid usage among female high school students was approximately 2.5%. Furthermore, nonsteroidal anabolic agents such as β_2-adrenergic agonists, growth factors, and growth hormone are now being used in combination with anabolic steroids in order to gain a more desirable anabolic effect [46].

Results from these studies indicate a rising belief that the gains associated with taking steroids far outweigh any potential risks. A national survey revealed that the most common reasons given for using steroids were to improve athletic performance and/or improve their appearance, and no doubt their self-esteem. This willingness among adolescents to use anabolic steroids reflects a failure of society to recognize the severity of problem among the young and/or a lack of programs that sufficiently address the dangers associated with steroid abuse [43, 47].

Since 1969, based on seized Stasi (East Germany's State Security Service) records, an extensive doping program (State Plan 14.25) was in existence in the DDR, primarily with the intent of humiliating West Germany at the 1972 Munich Olympics. This East German program may have involved as many as 10,000 athletes, of which many received doping agents without their knowledge. Furthermore, it appears that the practice of state-sponsored doping programs was prevalent throughout the Eastern Block countries such as Czechoslovakia, Bulgaria, and the USSR, as well as China. However, Germany is the only country to launch judicial investigations into past doping offenses with the intent of prosecution. Following the fall of the Berlin Wall and the reunification of Germany, the true extent of nationally sponsored anabolic doping programs became evident [44, 48].

Today, these former athletes are presenting a host of problems attributed to the use of multiple doping agents (e.g., turinabol, human growth hormone, etc.) that range from liver damage and ovarian inflammation to infertility, tumors, and a continual deterioration of their health. From the use of massive doses of anabolic/androgenic steroids in young female athletes, they have been reported to experience an inhibition of gonadotropin secretion, growth of facial hair, muscle mass, and other virilization traits. It is important to note that virilization occurring in such young women tends to be irreversible (e.g., deepening of voice and clitoral enlargement), even after discontinuation of androgens. Additionally, the impact of massive androgen doses has been reported to cause changes in sexual preference in some women.

In studies conducted in women, it was noted that 100 mg of either dehydroepiandrosterone (DHEA) or androstenedione caused plasma testosterone levels to increase by at least six times that of normal human females. This treatment-induced increase in plasma testosterone levels had a duration of 2 h, with peak levels lasting for only a few minutes. In another study conducted with men, it was found that plasma testosterone levels rose by 211% and 237% when treated with either 50 or 100 mg of androstenedione, respectively [19, 27, 49, 50]. Androstenedione is classified and sold as a dietary supplement. Because dietary supplements are sold containing androgens, one must be alert to the possibility of accidental exposure or alterations to endogenous androgen levels [51, 52].

Contraindications

In general, these drugs are schedule C-III controlled substances and are all banned by the NCAA, USOC, and IOC [10, 28]. They are sold (with the exception of androstenedione) as prescription only and are categorized as: pregnancy category X (should never be used during pregnancy or in children).

Androstenedione

Androstenedione is contraindicated in children, cholestasis, females, hepatic disease, and hepatitis. It should never be used during pregnancy or in cases of prostate cancer.

Danazol

Danazol is contraindicated for the elderly, and in cases of migraine or prostatic hypertrophy. Should never be used in cases of breast cancer, breast-feeding, cardiac disease, elderly, hepatic disease, migraine, porphyria, pregnancy, prostatic hypertrophy, renal disease, seizure disorder, vaginal bleeding.

Dihydrotestosterone

Unclear at this time.

Fluoxymesterone

Fluoxymesterone is contraindicated in cases of cardiac, hepatic, and renal diseases, men with breast or prostate carcinomas, pregnancy, prostatic hypertrophy, porphyria, and tartrazine dye hypersensitivity.

Methyltestosterone and Testosterone

Testosterone is contraindicated in cases of accidental exposure in women to patients using testosterone gels or creams. Both are contraindicated in women who are breast-feeding or pregnant, children, hypercalcemia, diabetes mellitus, coronary artery disease, diabetes mellitus, females, heart failure, myocardial infarction, and prostatic hypertrophy. It should never be used in cases of breast or prostate cancer, intravenous administration, cardiac, hepatic and renal diseases, soya lecithin hypersensitivity, and tartrazine dye hypersensitivity.

Nandrolone

Nandrolone decanoate is contraindicated in breast-feeding, children, coronary artery disease, diabetes mellitus, heart failure, hypercalcemia, myocardial infarction, and prostatic hypertrophy. It should never be used in cases of benzyl alcohol hypersensitivity, breast cancer, cardiac and hepatic diseases, females, intravenous administration, pregnancy, and prostate cancer.

Oxandrolone

Contraindicated in cases of arteriosclerosis, breast cancer, breast-feeding, cardiovascular diseases (cardiac disease, coronary artery disease, heart failure, myocardial infarction, peripheral edema), children, cholestasis, diabetes mellitus, females, hepatic and renal diseases, hypercalcemia, hypercholesterolemia, jaundice, peripheral edema, polycythemia, pregnancy, prostate cancer, and prostatic hypertrophy.

Oxymetholone

Oxymetholone is contraindicated in cases of breast carcinoma, diabetes, kidney disease (nephrosis, nephrotic phase of nephritis), pregnancy, prostate carcinoma, and seizure disorders. Oxymetholone (Anadrol-50) was discontinued in 1997.

Stanozolol

Stanozolol is a schedule C-III controlled substance and is contraindicated in cases of breast carcinoma, diabetes, kidney disease (nephrosis, nephrotic phase of nephritis), pregnancy, prostate carcinoma, and seizure disorders.

General Adverse Effects [28]

Some of the most common side effects include hirsutism, male pattern baldness, acne, increased serum cholesterol and decreased HDL. *Testosterone enanthate*, for example, also affects body fluids and electrolytes by causing retention of water, sodium, chloride, potassium, calcium, and inorganic phosphates. The hematological effects of testosterone enanthate include suppression of clotting factors II, V, VII, and X, producing bleeding in patients on anticoagulant therapy, and polycythemia. Other adverse effects include nausea, cholestatic jaundice, alterations in liver function tests, headaches, anxiety, depression, altered libido, and generalized paresthesia. Infrequently, testosterone enanthate can cause hepatocellular neoplasms, hepatitis, inflammation, and anaphylactic reactions. High doses of anabolic steroids have been implicated in causing cancer and behavior changes including steroid “roid” rage [53].

Endocrine and Urogenital [28]

- *Males.* In men, the most common side effects associated with androgen usage include: gynecomania (an excessive desire for women), and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages.
- *Females.* In women, the most common side effects associated with androgen therapy are: amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement. The observed changes in voice and clitoral enlargement are usually irreversible even after discontinuation of androgens. In pregnant women, treatment with androgens causes virilization of the external genitalia in female fetuses.

Specific Adverse Effects of Selected Androgens [28]

Androstenedione

Androstenedione can cause feminization (indirect effect through its metabolites estradione and 17β-estradiol), priapism, secondary malignancy, and virilization (direct anabolic action of androstenedione).

Danazol

Acne, alopecia, amenorrhea, bleeding, cholestasis, diaphoresis, edema, elevated hepatic enzymes, erythema multiforme, flushing, Guillain–Barre syndrome, headache, hirsutism, hoarseness or deepening of voice, hypercholesterolemia, jaundice, maculopapular rash, nausea/vomiting, peliosis hepatis, pharyngitis, photosensitivity, pruritus, pseudotumor cerebri, seborrhea, Stevens–Johnson syndrome, stroke, teratogenesis, thromboembolism, thrombosis, urticaria, visual impairment, and weight gain [144, 145].

Dihydrotestosterone (DHT)

DHT causes male pattern baldness; other adverse effects are unclear at this time.

Fluoxymesterone

Amenorrhea, anxiety, change in libido, cholestatic jaundice, clitoral enlargement, depression, edema, elevated hepatic enzymes, excessive frequency and duration of erections, gynecomastia, headache, hirsutism, hoarseness or deepening of voice, hypercalcemia, male pattern baldness, nausea/vomiting, oligospermia, peliosis hepatis, suppression of clotting factors, and virilization.

Methyltestosterone

Acne, alopecia, amenorrhea, anxiety, depression, elevated hepatic enzymes, epididymitis, epiphyseal closure, erythrocytosis, feminization, gynecomastia, hepatitis, hypercalcemia, hypercholesterolemia, jaundice, libido increase/ decrease, nausea and vomiting, oligomenorrhea, peliosis hepatis, peripheral edema, priapism, prostatic hypertrophy, secondary malignancy, virilization, and weight gain.

Nandrolone

Nandrolone can cause: acne, acneiform rash, alopecia, amenorrhea, clitoral enlargement, decreased ejaculate volume, depression, diarrhea, edema, elevated hepatic enzymes, epididymitis, epiphyseal closure, excitability, feminization, fluid retention, gynecomastia, hepatic failure, hepatic necrosis, hepatitis, hepatoma, hirsutism, hoarseness or deepening of voice, hypercalcemia, hypercholesterolemia, impotence, injection site reaction, insomnia, jaundice, libido increase/decrease, mastalgia, menstrual irregularity, nausea and vomiting, oligomenorrhea, oligospermia, peliosis hepatis, penile enlargement, peripheral edema, priapism, prolonged bleeding time, prostatic hypertrophy, secondary malignancy, sodium retention, teratogenesis, testicular atrophy, virilization, and weight gain.

Oxandrolone

Oxandrolone can cause: acne, amenorrhea, cholestasis, clitoral enlargement, clotting factor deficiency, coagulopathy, depression, edema, elevated hepatic enzymes, epididymitis, excitability, feminization, fluid retention, gynecomastia, hepatic necrosis and failure, hepatitis, hepatoma, hirsutism, hoarseness or deepening of voice, hypercalcemia, hypercholesterolemia, hyperkalemia, hypernatremia, hyperphosphatemia, impotence, insomnia, jaundice, libido increase/decrease, menstrual irregularity, oligomenorrhea, oligospermia, peliosis hepatis, penile enlargement, peripheral edema, polycythemia, priapism, prolonged bleeding time, prostatic hypertrophy, secondary malignancy, teratogenesis, testicular atrophy, virilization, and weight gain.

Oxymetholone

Oxymetholone can cause: acne, blood lipid changes, cholestatic jaundice, clitoral enlargement, diarrhea, edema, excitation, glucose intolerance, gynecomastia, hirsutism, hoarseness or deepening of voice, inhibition of testicular function, insomnia, liver cell tumors, nausea and vomiting, oligospermia, peliosis hepatis, testicular atrophy, and virilization.

Stanozolol

Stanozolol can cause: acne, blood lipid changes, cholestatic jaundice, clitoral enlargement, diarrhea, edema, excitation, glucose intolerance, gynecomastia, hirsutism, hoarseness or deepening of voice, inhibition of testicular function, insomnia, liver cell tumors, nausea and vomiting, oligospermia, peliosis hepatis, testicular atrophy, and virilization.

Testosterone

Testosterone can cause: acne, alopecia, amenorrhea, anxiety, depression, elevated hepatic enzymes, epididymitis, epiphyseal closure, erythema, erythrocytosis, feminization, gynecomastia, headache, hepatitis, hypercalcemia, hypercholesterolemia, injection site reaction, insomnia, jaundice, libido increase/ decrease, mastalgia, nausea and vomiting, oligomenorrhea, peliosis hepatis, peripheral edema, priapism, prostatic hypertrophy, pruritus, secondary malignancy, skin discoloration, skin irritation, virilization, and weight gain.

Mechanisms of Interactions [28]

The Following Classes of Drugs May Interact with Androgens When Administering Concurrently

It should be noted that chronic usage of androgens has been shown to lead to dependency and the abuse of other drugs such as alcohol, cocaine, amphetamines, and opioids. Furthermore, studies have shown that androgens are frequently used in varying combinations along with other anabolic agents such as clenbuterol, growth hormone, and nutritional supplements.

Anticoagulants, NSAIDs, and Salicylates

Androgens such as danazol, fluoxymesterone, methyltestosterone, methandrostenolone, nandrolone, and testosterone have been reported to interact with anticoagulants, NSAIDs, and salicylates by potentiating their anticoagulant effects. With anticoagulants such as warfarin, concomitant usage of androgens can cause an increase in plasma warfarin levels. The specific mechanism by which this takes place is unknown, but it appears not to be related to displacement from plasma proteins. Patients receiving oral anticoagulant, NSAIDs, or salicylate therapy require close monitoring especially when androgens are started or stopped.

Antidiabetic Drugs and Insulin

Androgens have been shown to decrease blood glucose levels in diabetics, thereby lowering insulin requirements.

ACTH, Corticosteroids, High-Sodium Foods, and Sodium-Containing Drugs

The interaction of androgens with drugs that promote sodium retention or foods that have high sodium content should be avoided because of risk of edema. Furthermore, individuals with hepatic or cardiac disease should avoid these combinations due to risk of hepatotoxicity, stroke (as a result of hypertension), or heart attack.

Alcohol (Ethanol)

Although alcohol does not have any ergogenic effects, it can reduce the anxiety level or tremors prior to competition. Furthermore, it has been shown that ethanol metabolism may interfere with steroid metabolism by interacting with steroid oxidoreductions. In addition to interfering with steroid metabolism, alcohol may potentiate other effects related with androgen abuse. In clinical studies conducted to determine whether personality psychopathology is common among anabolic steroid users, illicit androgen users were compared with age-matched alcoholics and two control groups. Results from these studies showed that androgen users had increased risk for personality psychopathology when compared with community controls. Furthermore, illicit androgen users also demonstrated significant antisocial traits in a manner similar to the alcoholic group [28, 54].

Pregnant female athletes who are taking androgens and alcohol risk fetal alcohol syndrome (FAS). The testosterone metabolite estradiol has been shown to synergistically interact with ethanol causing renal damage such as hydronephrosis in the developing fetus of humans and animal models. Additionally, renal damage may persist due to suppression of testosterone-stimulated renal growth and development in the fetus.

Amphetamines (Amphetamine and Methamphetamine)

Abuse of amphetamines and androgens has been well documented with regard to increasing aggressive and antisocial behavior. In addition, a consistent clinical feature associated with methamphetamine-induced organic mental disorders included an organic delusional syndrome with paranoid ideation and hallucinations. Furthermore, with methamphetamine abuse, a high propensity for violence is very common. Similarly, violent and aggressive tendencies have been commonly observed in androgen abusers. However, information on the combined effect of androgens and amphetamines on aggressive behavior is lacking and further research is required [4].

The potential consequences arising from the combined use of amphetamines and androgens were addressed initially in the introduction. During the Second World War, all the armies used amphetamines routinely to help increase the soldier's endurance and alertness, thereby giving them an edge in combat. Additionally, when amphetamines were presumably used in combination with other behavior-modifying drugs such as alcohol and/or androgens, the likelihood of a psychotic episode and violence could be greatly enhanced (either in severity or frequency). This would be especially true if these drugs are taken chronically and at high doses.

In studies focused on investigating the effects of androgens on reward in the brain of male rats, results suggested that although androgens do not appear to change the rewarding properties of brain stimulation, they might impact the sensitivity of the brain reward systems. This observation was achieved by implanting electrodes in the lateral hypothalamus using the rate–frequency curve shift paradigm of brain stimulation reward. It was found that androgenic effects on the brain reward system in male rats, when methandrostenolone was given singly or as part of a "cocktail" over a period of 2 weeks, had no effect on either the reward or performance of intracranial self-stimulation. However, when a "cocktail" consisting of testosterone cypionate, nandrolone decanoate, and boldenone undecylenate was given over a period of 15 weeks, the bar press rate (to stimulate the electrode) increased slightly but significantly. Treatment with amphetamine prior to and after the 15-week androgen protocol significantly increased the rate–frequency curve shift. From these results, the investigators were able to conclude that androgens may enhance the sensitivity of the brain to amphetamine-induced brain reward properties [53].

Other areas of research have indicated that amphetamines inhibit spontaneous and human chorionic gonadotropin (hCG)–stimulated testosterone secretion in the testes by in part increasing cAMP production and decreasing Ca^{2+} channel activity.

Antiviral Nonnucleoside Reverse Transcriptase Inhibitor Drugs Used in Treating AIDS

AIDS patients who are taking the antiviral nonnucleoside reverse transcriptase inhibitors (NNRTIs) agents such as deavirdine, efavirenz, and nevirapine may interact with some anabolic steroid treatments. Results from a study conducted by the Liverpool HIV Pharmacology Group from the University of Liverpool in conjunction with Bristol-Myers Squibb Pharma indicated that no clinically significant interaction occurred with nandrolone, while it was unclear whether any potential interactions with oxandrolone would take place. On the other hand, treatment with the androgens, namely, stanazolol and testosterone, may require close monitoring regarding alterations in drug dosage or the timing of administration [28].

Antiviral Protease Inhibitors

AIDS patients who are taking the antiviral protease inhibitors such as amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir may interact with some

anabolic steroid treatments. Results from a study conducted by the Liverpool HIV Pharmacology Group from the University of Liverpool in conjunction with Bristol-Myers Squibb Pharma indicated that no clinically significant interaction occurred with *nandrolone*, while it was unclear whether any potential interactions with *oxandrolone* would take place. On the other hand, treatment with the androgens *stanazolol* and *testosterone* may require close monitoring regarding alterations in drug dosage or the timing of administration.

Adrenoceptor Agonists

The synergistic effects of clenbuterol and anabolic steroids appear to cause in myocardial infarctions, potentially resulting from coronary spasms. In laboratory animals, there is little information on the anabolic interactions taking between the beta-2-adrenergic agonists clenbuterol and salbutamol and the androgens. Clenbuterol had no effect on blood testosterone levels. However, treatment with clonidine (alpha-2 adrenoceptor agonist) and dobutamine (beta-1-adrenoceptor agonist with some beta-2 activity, $\beta_1 >>> \beta_2$) caused increases in blood testosterone levels [55, 56].

Other studies conducted in intact and castrated male and female Sprague Dawley rats showed clenbuterol's anabolic effects were highest in males and least in females. In general, the efficacy of clenbuterol's anabolic activity was (from highest to lowest): *intact males* > *castrated males* > *castrated females* > *intact females*. These data suggest an anabolic interaction (potentiation or synergism) may occur between clenbuterol and endogenous androgens or that estrogens may interfere with clenbuterol's anabolic effects [55]. However, the exact nature of this interaction remains unclear and further research is needed.

Cannabinoids

No known anabolic effects or interaction with androgens.

Carbamazepine

Danazol can inhibit carbamazepine metabolism and cause an elevation of plasma carbamazepine levels to potentially toxic concentrations.

Clonidine

In animals, the effects of clonidine on alpha-2 adrenergic-induced changes in blood pressure, catecholamine, and growth hormone release were modified by testosterone. In man, however, testosterone is unable to modulate clonidine's effects. However, testosterone was able to restore basal noradrenergic activity in hypogonadal men.

Cocaine

In selected populations, cocaine and androgens are among the most commonly abused substances. In laboratory studies conducted with rats, cocaine and/or androgen (nandrolone decanoate) treatment when given alone or in combination produced increased aggression. It was found that low-dose (2 mg) androgens taken over a relatively longer period (4 weeks) produced even greater aggression than the high intermittent dosed group (20 mg twice weekly). When animals were given combined optimal doses of cocaine and nandrolone, aggression scores showed that a greater percentage of animals exhibited aggression than did animals receiving a single drug, while the level of aggression did not change. Thus, the investigators concluded that the drugs did indeed interact to produce unique effects in development of aggression. Furthermore, cocaine studies conducted in humans (acute) and laboratory animals (chronic) showed that aggression levels were enhanced. It should be noted, however, that further investigations are needed to fully elucidate the complex interactions of cocaine and androgens on aggressive behavior. Additionally, combining androgens and cocaine with ethyl alcohol may contribute to increased levels of aggression [57–59].

Growth Hormone

Contrary to other reports, the presence of testosterone had no effect on the plasma concentration of growth hormone or its secretion.

Imipramine

The coadministration of the tricyclic antidepressant imipramine with methyltestosterone could result in a dramatic paranoid response in four out of five patients.

Opioids

Narcotic analgesics are not ergogenic but can serve to allow athletes to compete in competition with severe injuries. However, the nature of any interactions with androgens is unclear. The non-scheduled opioid agonist/antagonist nalbuphine hydrochloride has been associated with usage-dependence among androgen users. From the findings of Wines et al. [60], nalbuphine may represent a new drug of abuse among athletes.

It has been suggested that prolonged use of high-dose androgens may induce a dependency that may involve endogenous opioid systems. A study conducted in rhesus monkeys showed that although the monkeys showed signs of opioid withdrawal when given naloxone (to counter morphine treatments), naloxone was not able to induce any signs of withdrawal symptoms during testosterone treatment.

Thus, it does not seem likely that high-dose androgen treatment enhances endogenous opioid activity in rhesus monkeys in a manner resulting in opioid dependence or tolerance.

Oxyphenbutazone

The coadministration of oxyphenbutazone, an antirheumatic analgesic rarely used today, along with androgens results in elevated serum oxyphenbutazone levels. Oxyphenbutazone has anti-inflammatory, antipyretic, analgesic, and uricosuric actions that can provide symptomatic relief from pain. In general, oxyphenbutazone and its parent molecule phenbutazone have been withdrawn from North America and most European markets due to its toxicity.

Summary of Drug Interactions

Testosterone Might Interact with Corticosteroids, Insulin, and Other Agents [28]

- Concomitant use of testosterone with these compounds may enhance the formation of edema: ACTH, betamethasone (acetate and sodium phosphate), cortisone acetate, dexamethasone (and dexamethasone acetate and sodium phosphate), fludrocortisone acetate, hydrocortisone (and hydrocortisone acetate, sodium phosphate, and sodium succinate), methylprednisolone (acetate and sodium succinate), prednisolone (acetate, sodium phosphate, and tebutate), prednisone, triamcinolone (and triamcinolone acetonide, diacetate, and hexacetonide).
- In diabetic patients, the use of testosterone (or other androgens) may result in the lowering of blood glucose levels and subsequently insulin requirements. Thus, the concomitant use of androgens with insulin formulations could result in excessive lowering of blood glucose levels: insulin, human: (zinc suspension, NPH, regular, regular and NPH mixture), insulin: (NPH, regular, zinc crystals, zinc suspension), insulin aspart (human regular), insulin glargine, insulin lispro (human), insulin lispro protamine (human).
- Concomitant use of testosterone with oxyphenbutazone may result in elevated serum levels of oxyphenbutazone.
- Concomitant use of testosterone cypionate (injectable) with propranolol hydrochloride may result in an increased clearance of propranolol.

Synthetic Androgens (e.g., Danazol, Fluoxymesterone, Methyltestosterone, Nandrolone, Oxymetholone, Oxandrolone, Stanozolol) Might Interact with Corticosteroids, Oral Anticoagulants, Oral Hypoglycemic Agents, and Other Agents

- Concomitant use of androgens (e.g., *danazol, fluoxymesterone, methyltestosterone, nandrolone, oxymetholone, oxandrolone, stanozolol*) with corticosteroids may

enhance the formation of edema: ACTH, betamethasone (acetate and sodium phosphate), cortisone acetate, dexamethasone (and dexamethasone acetate and sodium phosphate), fludrocortisone acetate, hydrocortisone (and hydrocortisone acetate, sodium phosphate, and sodium succinate), methylprednisolone (acetate and sodium succinate), prednisolone (acetate, sodium phosphate, and tebutate), prednisone, triamcinolone (and triamcinolone acetonide, diacetate, and hexacetonide) [28].

- Concomitant use of androgens (e.g., *danazol, fluoxymesterone, methyltestosterone, nandrolone, oxymetholone, oxandrolone, stanozolol*) with oral hypoglycemic agents may result in the inhibition of the metabolism their metabolism (oral hypoglycemic agents): acarbose, chlorpropamide, glimepiride, glipizide, glyburide, metformin hydrochloride, miglitol, pioglitazone hydrochloride, repaglinide, rosiglitazone maleate, tolazamide, tolbutamide, and troglitazone [28].
- Concomitant use of androgens (e.g., *danazol, fluoxymesterone, methyltestosterone, nandrolone, oxymetholone, oxandrolone, stanozolol*) with oral anticoagulants may result in an increased sensitivity to the anticoagulants, thus requiring a decrease in order to maintain desired prothrombin time: dicumarol, warfarin sodium.
- Concomitant use of androgens (e.g., *danazol, fluoxymesterone, methyltestosterone, nandrolone, oxymetholone, oxandrolone, stanozolol*) with oxyphenbutazone may result in elevated serum levels of oxyphenbutazone.
- In males, the use of human chorionic gonadotropin (hCG) is thought to stimulate gonadal testosterone production during and after androgen self-administration [61].

β-Adrenoceptor Agonists

In the 1992 Barcelona Olympics, several athletes from the USA, Germany, China, and Great Britain were asked to leave due to use of banned drugs. Surprisingly, not one of the athletes excused from the games used anabolic steroids, but they were found to have used stimulants such as strychnine or the anabolic agent clenbuterol [43].

Anabolic agents can be used either to enhance athletic performance or to attenuate skeletal muscle atrophy. Muscle atrophy is caused by unloading (unweighting) that can result from prolonged bed rest, joint immobilization, or exposure to the environment of space (microgravity). Under these conditions, mitigation of muscle atrophy and the promotion of muscle growth have been approached pharmacologically by administering anabolic agents such as anabolic steroids, growth hormone, insulin-like growth factors, and β-adrenergic (adrenoceptor) agonists. Of these anabolic agents, β-adrenoceptor agonists are among the least understood. In general, the tissue-specific distribution of β-adrenergic receptors can be summarized as follows: (1) β_1 in the heart; (2) β_2 in lung, vascular tissue, and skeletal muscle; and (3) β_3 in brown adipose tissue of rats [16, 18, 28, 62–64].

Among β_2-adrenoceptor agonists used as anabolic agents in humans or livestock, clenbuterol is by far the most popular. Clenbuterol is a relatively selective

β_2-adrenergic agonist demonstrated to have anabolic effects on skeletal muscle. Developed primarily for the treatment of asthma, clenbuterol has also been used to enhance performance by athletes and body builders and to increase lean body mass in animals raised for food. Controlled clinical studies involving β-agonist-induced muscle effects in adult humans have been rare and results have been ambiguous. In one study, effects on muscle size were not detected although strength recovery after orthopedic surgery was improved. Clenbuterol has been shown to enhance growth and reduces atrophy in unloaded and denervated hind-limb muscles of young rats whose muscles are still growing. In the former studies, and in sexually mature female rats, there is evidence for a drug-induced shift from slow-twitch (type I) toward fast-twitch (type II) fiber types in the slow-fiber-rich soleus muscle. Normal, pregnant, rats fed a diet containing clenbuterol show increases in the wet weight of all hind-limb muscles tested except the soleus. Until the current study, there have been no reports of clenbuterol's effects on the hind-limb muscles of fully mature male rats. Additionally, the confounding effects of growth in these mature animals are naturally reduced in comparison to younger animals. Furthermore, studies conducted with mature rats are more likely to reflect the responses of adults undergoing disuse atrophy resulting from bed rest, injury, surgery, or microgravity [16, 62–64, 148].

Chemistry

The parent molecule to sympathomimetic drugs is phenylethylamine that is comprised of a phenyl ring with an ethylamine side chain (Fig. 15.9). Variations in the molecular structure of these agents are made to alter the drug's metabolism in order to prolong the drug's activity, to enhance the drug's affinity to α- and β-adrenoceptors as well as the pharmacokinetic activity. Modifications to the phenylethylamine parent molecule include substitutions on: (1) the phenyl ring, (2) the terminal amino group, and (3) the α and β carbons on the ethylamine side chain [18, 65].

Substitutions made at positions 3 and 4 on the phenyl ring of phenylethylamine with -OH groups yield the endogenous catecholamines dopamine, norepinephrine, and epinephrine. The least modified molecule, dopamine, is the catecholamine version of phenylethylamine and has greater affinity for the D_1 and D_2 dopamine receptors ($D_1 = D_2$) than for adrenoceptors ($D >> \beta >> \alpha$). Subsequent modifications at other positions can alter the specificity of the molecule for a particular receptor type. These modifications would include:

Structure of β_2-Adrenoceptor Agonists [18, 65]

Phenyl Ring Substitutions

Substitutions on the phenyl ring can significantly alter the potency and half-life of a drug. For example, epinephrine and phenylephrine only differ by a hydroxyl

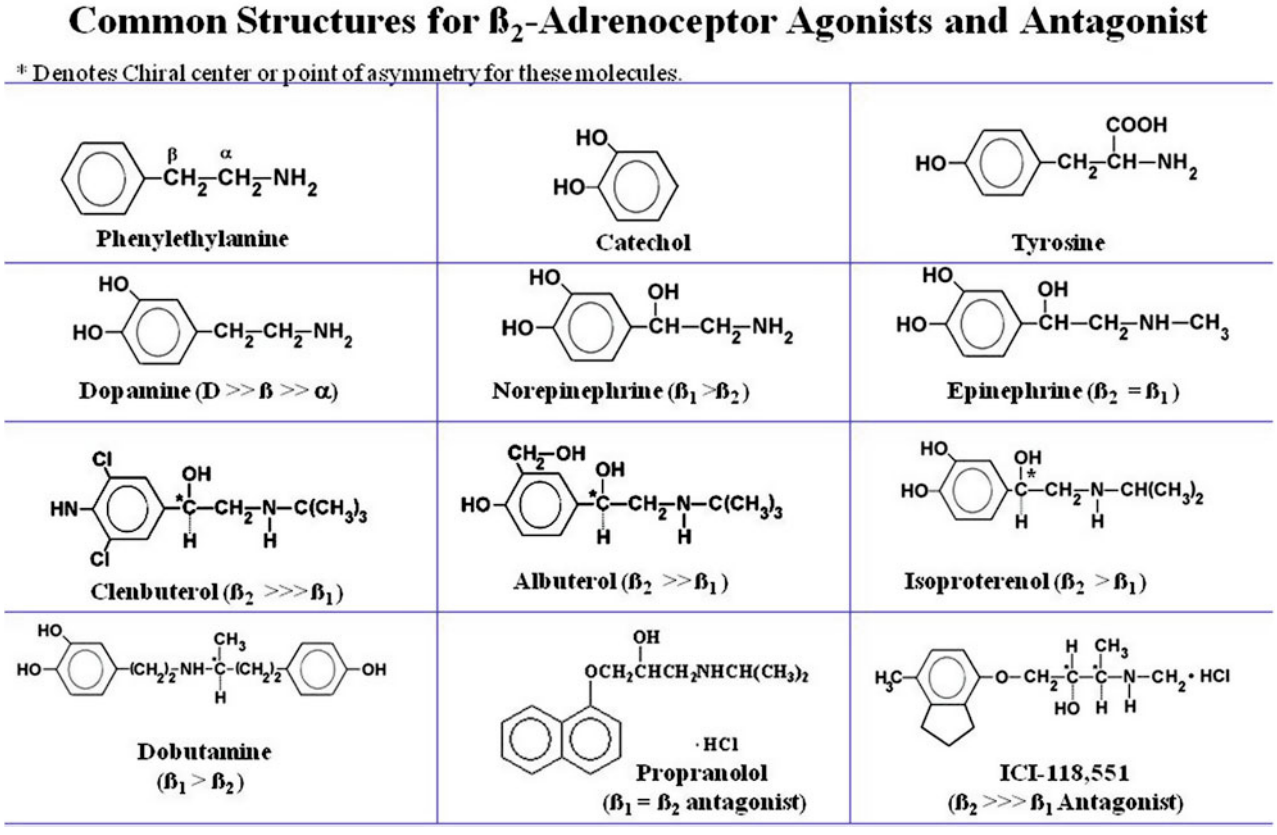


Fig. 15.9 Common structures for both endogenous and synthetic β2-adrenoceptor agonists and antagonist. (Budavari et al. [15])

group at position 4 of the phenyl ring. Loss of the hydroxyl at position 4 for phenylephrine significantly altered the molecule's adrenoceptor affinity: increasing for α (α_1>α_2) and near-complete loss for β (α>>>>β) except when concentrations are very high.
Additional to altering the molecule's potency at either α- or β-adrenoceptors, catecholamines are subject to metabolism by catechol-O-methyltransferase (COMT, see section on metabolism). Along with the loss of both hydroxyl groups at positions 3 and 4, the molecule's half-life is increased as well as its distribution into the central nervous system or other tissues and organ systems.

α-Carbon Substitutions

Substitutions on the α carbon of the ethylamine side chain will interfere with metabolism by blocking oxidation of the site by monoamine oxidase (MAO). Blocking metabolism at the α carbon position tends to increase the molecule's half-life, as is the case with ephedrine and amphetamine.

β-Carbon Substitutions

Most of the β-adrenoceptor agonists have hydroxyl groups substituted at the β-carbon position on the ethylamine side chain. It is believed that the presence of the hydroxyl group might be important with respect to storage of the molecule in neural vesicles.

Amino Group Substitutions

Substitutions on the amino group with alkyl chains have a tendency to enhance β-adrenoceptor activity and selectivity. The presence of a methyl group on amino group of norepinephrine yields the hormone epinephrine. Epinephrine has greater affinity for β_2-adrenoceptors than norepinephrine. Increasing the size of the substituent on the amino group increases the molecule's selectivity toward β_2-adrenoceptors, while decreasing selectivity for α-adrenergic receptors. Thus, the presence of an isopropyl (isoproterenol) or isobutyl (albuterol, clenbuterol) group on the amino terminus increases β-adrenoceptor selectivity.

Stereochemistry

It should be noted that of the drugs regularly prescribed by physicians, more than half possess at least one chiral center. In contrast, approximately 99% of the naturally occurring chiral pharmaceutical compounds have a single pharmacologically active enantiomer. Enantiomers can vary greatly in their pharmacological effects upon target tissue(s) due to differences in their pharmacodynamic and/or pharmacokinetic parameters because of variations in their binding to receptors or metabolizing enzymes [16].

Determining the identity of the active enantiomer (eutomer) in racemic drugs is important because of the potential for avoiding undesirable side effects associated with the less active enantiomer (distomer). As is the case with most β_2-adrenoceptor agonists such as clenbuterol and salbutamol, they are commercially available as a racemic mixture (1:1 ratio) of the two enantiomers, (−)-*R* and (+)-*S*. Whether one or both of the enantiomers contribute to a drug's principal action or to its toxic side effect(s) must be determined on a drug-by-drug basis [16].

Furthermore, the less active enantiomer (distomer) may interfere with the activity of the more biologically active species (eutomer) through competitive inhibition. Thus, the distomer may potentially bind to sites other than its primary receptor, thereby potentially causing adverse effects or alter the distribution and/or the activity of the eutomer, resulting in decreased or increased effect or toxicity. Thus, this type of structure can potentially give rise to numerous asymmetrical sites, e.g., chiral centers, yielding molecules with the same chemical formula but different three-dimensional structures [14, 16].

Basic Physical Properties

See Tables 15.8 and 15.9 for physical properties.

Pharmacology and Kinetics

Drug Usage: Sympathomimetic Preparations and Routes of Administration

Sympathomimetic agents such as albuterol (salbutamol) or clenbuterol are important pharmaceutical agents for the treatment of asthma. In general, these agents cause the relaxation of bronchial smooth muscle and inhibit the release of bronchial-constricting substances released from mast cells. The prototypic endogenous sympathomimetic agent epinephrine is a rapidly acting bronchodilator that has been used to treat asthma and anaphylactic shock. Epinephrine can be given as a subcutaneous injection (0.4 mL of a 1:1,000 solution) or inhaled as a microaerosol delivered from a pressurized canister (320 μg per puff). Additionally, epinephrine is contained within some local anesthetic preparations as a vasoconstrictor (1:50,000, 1:100,000, or 1:200,000 dilutions), constricting cutaneous vessels and prolonging the local anesthetic action.

Albuterol (Accuneb™, Proventil®, Proventil® HFA, Ventolin®, Ventolin® HFA, Ventolin® Rotahaler®, Ventolin® Syrup, Volmax®, Proventil®, Repetabs®, Respirol Rx™, Salbutamol™, Ventolin® Nebules®, Ventolin® Rotacaps®, Ventolin® HFA, Xopenex)

Albuterol and levalbuterol [the (−)-*R* enantiomer of albuterol and more potent than the racemic mixture] are β_2-selective adrenoceptor agonists ($\beta_2 >> \beta_1 >>>>> \alpha$) used in the treatment of acute bronchospasm, asthma, and act as a prophylaxis for

Table 15.8 Basic physical properties of β-agonists and other selected drugs

Drug	Chemical formula	Chemical name	Synonym/salt name
Albuterol	$C_{13}H_{21}NO_3$	Alpha1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol	Salbutamol
Albuterol sulfate	$C_{26}H_{44}N_2O_{10}S$		Aerolin, proventil
Cimaterol	$C_{12}H_{17}N_3O$	2-Amino-5-[1-hydroxy-2-[(1-methylethyl)amino] ethyl] benzonitrile	–
Clenbuterol	$C_{12}H_{18}C_{12}N_2O$	4-Amino-3,5-dichloro-alpha-[[(1,1-dimethylethyl) amino] methyl]benzene methanol	NAB 365
Clenbuterol HCl	$C_{12}H_{19}Cl_3N_2O$	–	NAB 365 Cl, spiropent, ventipulmin
Cocaine	$C_{17}H_{21}NO_4$	[1R-(exo,exo)]3-(Benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester	Free base
Cocaine HCl	$C_{17}H_{22}Cl\ NO_4$	–	HCl
Isoproterenol	$C_{11}H_{17}NO_3$	4-[1-Hydroxy-2-[(1-methylethyl)-amino]ethyl]-1, 2-b enzenediol	Isoprenaline
Isoproterenol HCl (racemic)	$C_{11}H_{18}Cl\ NO_3$	–	Aerotrol, euspiran
Isoproterenol sulfate dihydrate (racemic)	$C_{22}H_{36}N_2O_{10}S$	–	Aludrin, isomist, propal
The (1) enantiomer (free base)	–	–	–
The (1) enantiomer (HCl)	–	–	–
The (1) enantiomer of isoproterenol (d-) bitartrate dihydrate	–	–	Isolevin
Mabuterol	$C_{13}H_{18}Cl\ F_3\ N_2\ O$	4-Amino-3-chloro-alpha-[[(1,1-dimethylethyl) amino] methyl]-5-trifluoromethyl) benzenemethanol	–
Mabuterol hydrochloride (racemic)	$C_{13}G_{19}\ C_{12}\ F_3\ N_2\ O$	–	–
Individual (d) and (l) enantiomers of Mabuterol hydrochloride	–	–	–

Phenylpropanolamine (PPA)	C_9H_{14} Cl N O	Alpha-(1-aminoethyl)benzenmethanol-HCl	–
Propranolol	$C_{16}H_{21}NO_2$	1-[(1-Methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol	–
Propranolol HCl	$C_{16}H_{22}ClNO_2$	–	–
Strychnine	$C_{21}H_{22}$ N_2 O_2	Strychnidin-10-one	–
Terbutaline	$C_{12}H_{19}$ N O_3	5-[2-[1,1-Dimethylethyl)amino]-1-hydroxyethyl]-1,3-benzenediol	Brethaire, brethine, bricanyl, butaliret, monovent, terbasmin, terbul
Terbutaline-sulfate	(C_{12} H_{19} N O_3) 2-H_2 S O_4	–	–

Source: Budavari et al. [15]

Table 15.9 Basic physical properties of β-agonists and other selected drugs

Drug	MW (g/mol)	Melting point (°C)	Melting point solvent/other	Solubility/notes
Albuterol	239.31	151, and 157–158	Crystal powder	Salbutamol is soluble in most organic solvents. Salbutamol is also marketed as the pure R enantiomer and is called levalbuterol
Albuterol sulfate				The sulfate salt is soluble in aqueous solutions
Cimaterol	219.29	159–161	–	–
Clenbuterol	277.18	177–179	–	Clenbuterol (free base) is soluble in methanol. Soluble in alcohol
Clenbuterol HCl	313.64	174–176	Colorless microcrystalline power	The salt is very soluble in water, alcohol, methanol, slightly soluble in chloroform; insoluble in benzene; LD50 in mice, rats, guinea pigs 176,315, and 67.1 mg/kg orally; 27.6, 35.3, and 12.6 mg/kg IV
Cocaine	303.35	98	monoclinic tablets from alcohol	One gram dissolves in 600 mL water and 270 mL water at 80°C. Soluble in 6.5 mL alcohol, 0.7 mL chloroform, 3.5 mL ether, 12 mL oil turpentine, 12 mL olive oil, 30–50 mL liquid petrolatum. Also soluble in acetone, ethyl acetate, carbon disulfide. LD50 I.V. in rts: 17.5 mg/kg
Cocaine HCl	339.82	195	Crystals, granules, or powder	Numbs tongue on application, slightly bitter tasting. One gram dissolves in 0.4-mL water or 3.2-mL cold water. Dissolves in 2-mL hot alcohol, 12.5-mL chloroform. Cocaine HCl also soluble in glycerol and acetone. Insoluble in ether or oils
Isoproterenol	211.24	155	Crystal powder	–
Isoproterenol HCl (racemic)	247.72	170–171	–	1 g dissolves in 3-mL water or in 50 mL of 95% ethanol. Less soluble in absolute ethanol, practically insoluble in chloroform, ether, and benzene. In a 1% aqueous solution, isoproterenol has a pH of about 5 and will turn to a brownish-pink color upon exposure to air or in an alkaline solution

Isoproterenol sulfate dihydrate (racemic)	520.59	128	–	One gram dissolves in approximately 4 mL of water and is only slightly soluble in alcohol. Practically insoluble in chloroform, ether, and benzene
The (1) enantiomer (free base)	–	164–165	–	–
The (1) enantiomer (HCl)	–	164–165	–	–
The (1) enantiomer of isoproterenol (d-) bitartrate dihydrate	–	80–83	–	–
Mabuterol	310.75	–	–	Related to Clenbuterol
Mabuterol hydrochloride (racemic)	345.21	205–206	–	Fairly soluble in water. Related to Clenbuterol. LD50 in male and female mice and rats is 220.8, 119.9, 319.9, and 305.6 mg/kg orally; 41.5, 51.1, 26.4, and 28.1 mg/kg IV
Individual (d) and (l) enantiomers of mabuterol hydrochloride	–	194	–	–
Phenylpropanolamine (PPA)	187.67	101–102/190–194	Free base/HCl salt	PPA is soluble in water and alcohol, and practically insoluble in ether, chloroform, and benzene. The LD50(rat) for PPA is 1,490 mg/kg
Propranolol	259.34	96	Crystals	Crystals from HCl salt are soluble in water. Practically insoluble in ether, benzene, ethyl acetate. The LD50 in mice: 565 mg/kg orally, 22 mg/kg IV, and 107 mg/kg IP
Propranolol HCl		163–164	Crystals	–
Strychnine	334.42	275–285	Crystals	The pKa at 25°C is 8.26, and 1 g is soluble in 182-mL ethanol, 6.5-mL chloroform, 150-mL benzene, 250-mL methanol, 83-mL pyridine, and slightly soluble in water. The LD50 in rats: 0.96 mg/kg by slow IV infusion
Terbutaline	225.29	119–122	Absolute ether	–
Terbutaline-sulfate	323.37	246–248	–	The pKal is 8.8, pKa2 is 10.1, and the pKa3 is 11.2. The solubility at 25°C is greater than 20 mg/mL in water, 0.1 N HCl and NaOH. In ethanol the solubility is 1.2 mg/mL and in methanol 2.7 mg/mL

Source: Budavari et al. [15]

bronchospasms. In the treatment of asthma or other chronic obstructive airway disease, albuterol acts as a bronchodilator to alleviate the restriction in the airway. Albuterol has a more prolonged bronchodilatory effect than either isoproterenol or metaproterenol, but less of cardiostimulatory effect than terbutaline. Albuterol comes as *tablets* (4 or 8 mg, see note A), *inhalation aerosols* (6.8- or 17-g canisters containing 80 or 200 metered inhalations, respectively; see note B.), inhalation solution (0.5% solution in 20-mL amber bottle). [Note: (a). Albuterol 4- or 8-mg tablets: comes as timed release (2 or 4 mg in the coating for immediate release, 2 or 4 mg in the core for delayed release) as 4.8 or 9.6 mg of albuterol sulfate. (b). Albuterol 6.8- or 17-g canisters deliver 100 μg of albuterol at the valve and 80 μg at the mouthpiece] [28, 66].

Albuterol can be given orally (solution, tablet, or capsule form) or via an oral inhalation route (metered-dose inhaler). There are numerous treatment regimens that include orally (immediate-release tablets or solution and extended-release tablets), oral inhalation (using Rotahaler inhalation device with inhalation capsules), and oral inhalation using an albuterol nebulizer solution.

- *Oral treatment (immediate-release tablets or oral solution)*. The normal adult dose is 2–4 mg every 6–8 h. The maximum dose in adults and adolescents should not exceed 32 mg/day. In children 6–12 years and the elderly, 2 mg of albuterol should be taken every 6–8 h with maximum doses of 24 and 32 mg/day, respectively. In children under 6 years, they should receive an initial dose of 0.1 mg/kg orally every 8 h, not to exceed 8 mg/day. This dose can be increased to 0.2 mg/kg every 8 h if the desired effect is not achieved, but should not exceed 12 mg/day.
- *Oral treatment (extended-release tablets)*. It should be noted that treatment with 4 mg of the extended-release tablets every 12 h is equivalent to 2 mg of the immediate-release tablets every 6 h. The normal adult dose of the extended-release tablets is 4–8 mg every 12 h. The maximum dose in adults and adolescents should not exceed 16 mg/12 h. In children under 6 years, they should receive an initial dose of 0.3–0.6 mg/kg orally per day, not to exceed a maximum of 8 mg/day.
- *Oral inhalation Treatment. Metered-Dose Inhaler*. Treatment with inhalation doses in adults and children (4 years and above) should be 90–180 μg (1–2 puffs) every 4–6 h as needed. *Capsule and Rotahaler Inhaler.* Treatment with capsule inhalation doses in adults and children (4 years and above) should be 200 μg (per capsule) every 4–6 h. *Albuterol Nebulizer Solution.* Treatment with the nebulizer solution in adults and adolescents should be 2.5 mg every 6–8 h as needed. Treatment should be delivered over a period of 5–15 min. For severe episodes, acute treatment should be 2.5–5 mg initially every 20 min for three doses, followed by doses of 2.5–10 mg every 1–4 h as needed (or 10–15 mg/h by continuous nebulization). In children, treatment should be 1.25–2.5 mg every 4–6 h as needed. As with adults, treatment should be delivered over a period of 5–15 min. Treatment of severe episodes in children should be 0.15 mg/kg (2.5 mg minimum and 5 mg maximum) for three doses every 20 min, followed by 0.15–0.3 mg/kg (10 mg maximum) every 1–4 h as needed [28, 66].

- *Prophylaxis Treatment in the Prevention Exercise-Induced Bronchospasms.* The use of albuterol to prevent the onset of exercise-induced bronchospasms is not recommended. Longer-acting agents such as formoterol, levalbuterol, the (−)-R enantiomer of albuterol, are better suited for this task [28, 67].

Levalbuterol [the (−)-R Enantiomer of Albuterol].
Oral Inhalation Treatment (Nebulizer Solution)

The initial treatment with the nebulizer solution in adults, adolescents, and children (12 years or older) should be 0.63 mg every 6–8 h. Treatment should be given 3 times per day. For severe asthmatic episodes, treatment should be 1.25 mg three times per day. Higher doses should be monitored for adverse effects. In children 6–11 years, the initial dose is 0.31 mg every 6–8 h, three times per day. Routine dosing should not exceed 0.63 mg given three times per day [28].

Amphetamines (Amphetamine, Dextroamphetamine, and Methamphetamine)

As a group, the amphetamines are considered CNS stimulants and their effects are mediated centrally and peripherally through the action of norepinephrine. Amphetamines are used to treat attention-deficit hyperactivity disorder (ADHD), as an appetite suppressant for the treatment of obesity, and narcolepsy. However, amphetamines should be used with caution since there is a great potential for abuse and addiction [28].

Methamphetamine is used for the treatment of ADHD in children under 6 year: 5 mg orally once or twice daily, then increase incrementally by 5 mg/week. Usual effective dose is 20–25 mg orally daily. For adjunctive treatment of obesity in adults, treat with 5 mg orally 30 min prior to each meal, or treat with 10–15 mg orally with the long-acting form every morning. Treatment should be continued for only a few weeks. Methamphetamine (Desoxyn) comes in tablet form at doses of 5, 10, and 15 mg.

Amphetamine is used for the treatment of narcolepsy in children 3–6 years by giving 2.5 mg orally once or twice daily, then increase incrementally by 2.5 mg/day/week until desired response is obtained. In children over 6 years, 5 mg of amphetamine is given orally once or twice daily, then increase incrementally by 5 mg/week until desired response is obtained. For treating narcolepsy in adults, amphetamine is given orally at a dose of 5–20 mg once to three times a day. In children who are being treated for attention-deficit hyperactivity disorder (ADHD), amphetamine is given in a fashion somewhat similar to the treatment of narcolepsy. In children 6–12 years, 2.5-mg amphetamine is given orally twice daily with incremental increases of 5 mg/day/week until the desired response is obtained. In children 12 years or older, 5 mg of amphetamine is given orally twice daily. Incremental increases in dose (10 mg/day/week) are given until the desired response is obtained. Amphetamine comes in tablet form as amphetamine sulfate in doses of 5 or 10 mg.

Clenbuterol

Clenbuterol is an orally active, sympathomimetic agent (not approved for use in USA) that has specificity for β_2-adrenoceptors (β_2>>>β_1>>>>>α), including those in bronchiolar smooth muscle [68, 69]. Owing to its bronchodilator properties, it is used therapeutically to relieve respiratory disorders in humans (10–20 μg/day taken twice daily) and animals (*equine* as bronchodilator: 0.8 μg/kg body weight given twice daily for up to 10 days). Clenbuterol can be administered orally or parenterally in horses, but intramuscular or IV routes can also be used. Clenbuterol also has been used in veterinary medicine and in human clinical trials as a tocolytic agent [68, 70, 71]. In animals, the recommended treatment with clenbuterol, as a tocolytic agent, is equivalent to 0.8 μg/kg bodyweight by a single parenteral injection in horses and 0.8 μg/kg bodyweight orally in cattle [68].

When administered in relatively high therapeutic doses, clenbuterol improves nitrogen retention and thus increases muscle growth. Because clenbuterol also markedly reduces body fat, it has been used illegally by ranchers as a repartitioning agent in beef production, and by athletes, especially body builders, to increase lean body mass [16, 62, 64, 72–74]. Experimentally, clenbuterol inhibits skeletal muscle atrophy secondary to disuse, injury, and denervation. Clinical studies in adult humans have shown clenbuterol to be effective in enhancing strength recovery after orthopedic surgery, without altering muscle size [74]. In rats, clenbuterol increased the rate of protein synthesis in skeletal muscle [75-77]. Thus, clenbuterol therapy could be useful in ameliorating microgravity-induced muscle atrophy in astronauts [16, 62, 64, 78, 79].

Cocaine

Cocaine is a naturally occurring alkaloid used on mucosal tissue (oral, laryngeal, and nasal cavities) as a topical or local anesthetic. It is also used in the eye as an ophthalmic anesthetic [18, 28, 65]. Cocaine acts by decreasing neural permeability to sodium, thereby decreasing the rate of membrane depolarization and nerve conduction. Centrally, cocaine acts similarly to its peripheral effects, but also inhibits the reuptake of norepinephrine, dopamine, and serotonin, making it an indirect agonist. Adverse effects associated with the use of cocaine (e.g., significant local vasoconstriction, euphoria, abuse, dependence, and the potential for violence) prevent its more widespread clinical use [79]. Cocaine is a schedule C-II controlled substance and is banned by the IOC [10, 28].

- *Topical Anesthetic Treatment*. In adults and children (6 years or older), a 1–10% cocaine solution is applied to the tissue via sprays, cotton applicators, packs, or instillation. In general, cocaine should be used in the lowest effective dose. However, 4% solutions of cocaine are used most frequently. It should be noted that more concentrated solutions (>4%) of cocaine can result in systemic toxicity. Furthermore, in elderly or debilitated patients, cocaine doses should be reduced. As a topical, cocaine should not be applied to the eye or administered parenterally [10, 28].

Dobutamine

Dobutamine is a relatively selective β_1-adrenoceptor agonist (β_1>>β_2>>>>α), used for the short-term inotropic treatment of congestive heart failure (low output states), cardiogenic shock, and post cardiac surgery. Dobutamine possesses inotropic, chronotropic, and vasodilatory activities. Dobutamine is administered by IV infusion for a period not exceeding 48 h [28].

- *Intravenous Dosage*. The initial continuous IV infusion with dobutamine (0.5–1 μg/kg/min) in adults, children, infants, and neonates is subsequently titrated every few minutes to a range of 2–20 μg/kg/min (usual maximum). Adjustments to the dosage are made based on the hemodynamic response. Tachycardia or ventricular ectopy may occur when infusion rates exceed 20 μg/kg/min. However, infusion rates up to 40 μg/kg/min may be required in adults, adolescents, and children on rare instances. In the elderly, variable dose-responses to dobutamine may occur; thus, dose should be titrated based on hemodynamic responses [28].

As an anabolic agent, dobutamine has been tested in laboratory animals, but its anabolic responses in muscle and bone were mixed [80, 81]. Additionally, dobutamine has been investigated as one possible agent in offsetting the onset of microgravity-induced skeletal muscle atrophy [82]. However, its effects on skeletal muscle and bone appear to be greater under sedentary conditions than in exercised or trained animals.

Isoproterenol (Isuprel®, Medihaler-Iso™)

Isoproterenol is the prototypic synthetic β-adrenoceptor agonist (β_1= β_2 >>>>>α) approved by the FDA in 1947. It is structurally similar to epinephrine, with inotropic and bronchodilator properties. Isoproterenol is indicated for use in cases of acute bronchospasm, asthma, AV block, bradycardia, cardiopulmonary resuscitation, Stokes-Adams attack, torsade de pointes. Isoproterenol can also be used to treat status asthmaticus, although not approved for this use by the FDA. In general, isoproterenol relaxes the smooth muscle in the lungs and helps to improve breathing by dilating airways. Isoproterenol is administered by inhalation, parenterally, IV injection or infusion, or sublingually [18, 28, 65, 83].

- *Oral Inhalation Treatment. Metered Aerosol*: The oral inhalation dose for the treatment of *acute and mild bronchospasms in adults and children with asthma* is 120–262 μg isoproterenol HCl (1–2 inhalations) 4–6 times/day at 3–4 h intervals. Treatment with isoproterenol sulfate in adults and children is 80–160 μg (1–2 inhalations) 4–6 times/day at 3–4 h intervals. The maximum dose for each is 12 inhalations/24 h. It should be noted that the National Asthma Education and Prevention Program Expert Panel recommends against the use of isoproterenol because it could potentially produce excessive cardiac stimulation. *Nebulizer*: In adults and children, the recommended treatment under normal circumstances with isoproterenol is 6–12 inhalations of a 0.25% solution every 15 min up to

15 min up to three times. The maximum dosage is eight treatments over a period of 24 h. However, the recommended treatment for acute asthma is 5–15 deep inhalations of a 0.5% solution. If necessary, treatment is repeated after 5–10 min. The maximum dosage is five treatments over a period of 24 h. The oral inhalation dose (via metered dose) for the treatment of *acute bronchospasms in adults with chronic obstructive pulmonary disease (COPD)* is 120–262 μg isoproterenol HCl (1–2 inhalations) 4–6 times/day at 3–4 h intervals. The maximum dosage is 12 inhalations/24 h. Treatment in adults and children using a nebulizer is 5–15 deep inhalations of a 0.5% isoproterenol HCl solution. Treatment is repeated if necessary up to every 3–4 h [28].

- *Sublingual Treatment*: In adults, isoproterenol HCl is given in doses of 10–15 mg, 3–4 times/day. In children, the isoproterenol HCl is given in doses of 5–10 mg, 3 times/day. The maximum dosage per day is 60 mg/day in adults and 30 mg/day in children.
- *Intravenous Infusion*: In adults, isoproterenol is given at a dose of 0.01–0.02 mg (0.5–1.0 mL of a 1:50,000 dilution) IV. Treatment is repeated if necessary. It should be noted that with IV infusion, the individual's cardiac functions should be monitored closely. Treatment should be avoided in individuals receiving general anesthesia with cyclopropane or halogenated hydrocarbon anesthetics.
- *Intramuscular (IM) and subcutaneous (SC) treatment*. The treatment of ventricular arrhythmias secondary to AV block in adults is initially 0.2-mg isoproterenol HCl IM, followed by 0.02–1 mg as needed. SC treatment in adults is 0.2 mg initially, followed by treatments of 0.15–0.2 mg as needed. Alternatively, treatment can be given initially by IV bolus of 0.02–0.06 mg, followed by intermittent IV injections of 0.01–0.2 mg [28].

Phenylpropanolamine (PPA; Acutrim®, Dexatrim®, Phenoxine®, Phenyldrine®, Propagest®, Rhindecon®). This Drug Has Been Discontinued in the USA. Note: Elderly Patients Appear to be More Likely to Have Adverse Reactions to Sympathetic Amines

PPA is a nonprescription sympathomimetic agent used as a nasal decongestant, to improve breathing by promoting the drainage of sinus passages, and as an appetite suppressant for the short-term (6–12 weeks) treatment of exogenous obesity. PPA has also been used to treat urinary incontinence (non-FDA-approved use). PPA has been included in cold/cough preparations and formulations for appetite suppression [19, 20, 30].

PPA acts as a CNS stimulant by acting directly on both α and β-adrenoceptors (α > β), as well as indirectly through the release of norepinephrine from its storage sites in the nerve terminal. PPA causes vasoconstriction, and subsequently shrinking swollen nasal mucous membranes. PPA also has an indirect effect on β-adrenoceptors in the heart, producing tachycardia and increased blood pressure [18, 28, 65].

- *Oral dosage using immediate-release tablets or capsules. Adults and adolescents*: The dosage was 20–25 mg orally every 4 h, up to 150 mg/day. In children (6–11 years),

the dosage was 10–12.5 mg orally every 4 h with a maximum of 75 mg/day. In younger children (2–5 years), the dosage for PPA was 6.25 mg orally every 4 h (37.5 mg/day maximum). *Oral dosage-using extended release capsules*. In adults using the extended-release capsules, the dosage was 75 mg orally every 12 h [28].

- *PPA was previously indicated as a short-term (6–12 weeks) appetite suppressant for treating exogenous obesity concomitantly with a weight loss program. Oral dosage (immediate-release tablets or capsules) in Adults:* The dosage used to suppress appetites was 25 mg orally three times daily (up to 75 mg/day). PPA was administered 30 min before meals with 1–2 full glasses of water. Lower doses of 12.5 mg 3 times/daily may be used in individuals sensitive to sympathomimetics or other stimulants.

Propranolol (Betachron®, Inderal®, Inderal® IV, Inderal® LA, Pronol™)

Propranolol is a nonselective β-adrenoceptor antagonist (beta-blocker, $\beta_1=\beta_2>>>\alpha$) that reduces chronotropic, inotropic, and vasodilatory responses in a dose-dependent manner. However, the correlation that exists between therapeutic effects, the concentration of propranolol in the plasma, and dose is unclear. Propranolol has a half-life of approximately 4 h. In general, propranolol produces an antihypertensive effect possibly by decreasing cardiac output, inhibiting the release of renin by the kidneys, and reducing sympathetic outflow. An additional effect associated with propranolol is its ability to reduce oxygen requirements of the heart by blocking the effects of β-agonists, as well as possessing antiarrhythmic activity [16, 18, 28, 83, 84].

- *Oral Administration* of propranolol should be given in divided doses before meals and at bedtime. The dose of the oral concentrate solution should be diluted in water (or juice, etc.) prior to administration. *Intravenous Administration* requires no dilution, but visual inspection of parenteral products should be made for particulate matter and/or discoloration prior to administration. EKG and central venous pressure during IV administration should not exceed 1 mg/min. In children, propranolol should be infused slowly over a period of 10 min: Inderal Injection Solution (1 mg/mL), Inderal Long-Acting capsules (60, 80, 120, 160 mg), Inderal Tablets (10, 20, 40, 60, 80 mg). Propranolol, as a doping agent, would most likely have a negative effect on skeletal muscle hypertrophy. However, it is favored by marksmen or other athletes that require a steady hand [28, 83].

β_2-Adrenoceptor antagonists such as propranolol (or the more β_2-specific antagonist ICI-118,551) may provide antioxidant protection to the heart by blocking β_2-adrenoceptor agonist–induced oxidative damage (through increased force of contractions) in individuals with congestive heart failure. Additionally, propranolol has been found to provide a measure of protection in ethanol-induced cardiomyopathy, lowering circulating levels of troponin-T-associated ethanol abuse. Thus, treatment with propranolol prevents the ethanol-induced release of troponin-T (through ethanol-induced oxidative damage). Propranolol antagonized the anabolic effects of albuterol and clenbuterol when given at levels of 10 mg/kg body weight twice daily in rats.

Terbutaline (Brethine®, Brethine® SC, Brethaire®, Bricanyl®)

Terbutaline is a β_2-selective adrenoceptor agonists (β_2>>β_1>>>>α) used in the treatment of acute bronchospasm, asthma, chronic obstructive pulmonary disease (COPD), and as a tocolytic agent (†non-FDA-approved indication). The stimulation of β_2-adrenoceptors produces relaxation of bronchial smooth muscle and subsequently increased bronchial airflow. Terbutaline has a more prolonged bronchodilatory effect than either isoproterenol or metaproterenol, but not as long as that of albuterol. Terbutaline has a greater cardiostimulatory effect than albuterol [28].

Treatment with terbutaline or other β_2-adrenoceptor agonists produces receptor downregulation and tolerance to treatment. Furthermore, the continuous use of β_2-adrenoceptor agonists for a period of about 1 year can accelerate a decline in pulmonary function in asthmatics [84]. Additionally, terbutaline produces cardiostimulation, but to a lesser degree than isoproterenol [28].

- *Oral Treatment. Adults and adolescents (>15 years)*: Treatment with 5 mg terbutaline orally 3 times/daily every 6 h (15 mg/day maximum dose). Dosage may be reduced to 2.5 mg orally 3 times/daily if adverse effects occur (7.5 mg/day maximum dose).
- *Children (6–12 years):* Treatment with 0.05 mg terbutaline orally every 8 h. Subsequently, the dosage is slowly increased to 0.15 mg/kg orally every 8 h (5 mg/day maximum). Alternatively, the manufacturer recommends the oral dose to be 2.5 mg 3 times/day (5 mg/day maximum).
- *Subcutaneous Treatment. Adults and adolescents*: Initial treatment is 0.25 mg subcutaneously, repeated in 15–30 min if needed (maximum dose is 0.5 mg in 4 h).
- *Children (6–12 years):* Initially, treat subcutaneously with 0.006–0.01 mg/kg terbutaline (maximum dosage is 0.25 mg). Subsequently, repeat in 15–30 min if needed (4 h delay prior to subsequent treatments).

Biosynthesis of Endogenous β_2-Adrenoceptor Agonists

The rate-limiting enzyme in catecholamine synthesis is tyrosine hydroxylase, a cytosolic enzyme, which catalyzes the formation of L-dopa (3,4-dihydroxy-L-phenylalanine) from the substrates tyrosine and oxygen. Biopterin is the cofactor for tyrosine hydroxylase and may serve as a regulator controlling the velocity of the reaction. Another function of tyrosine hydroxylase is in production of additional tyrosine through the hydroxylation of phenylalanine [85]. However, phenylalanine hydroxylase is the primary enzyme responsible for the hydroxylation of phenylalanine [86]. L-dopa is converted into dopamine through the action of the enzyme dopa decarboxylase, a pyridoxine-dependent enzyme, which removes the carboxyl group from dopa. Dopa decarboxylase, also referred to as aromatic amino acid decarboxylase, can also act on 5-hydroxytryptophan to form serotonin. Dopa decarboxylase is found in both catecholaminergic and serotonergic neurons and nonneuronal tissues (e.g., kidney) throughout the body. Dopamine is then acted on by the enzyme dopamine β-hydroxylase that hydroxylates the β-carbon on the ethylamine side

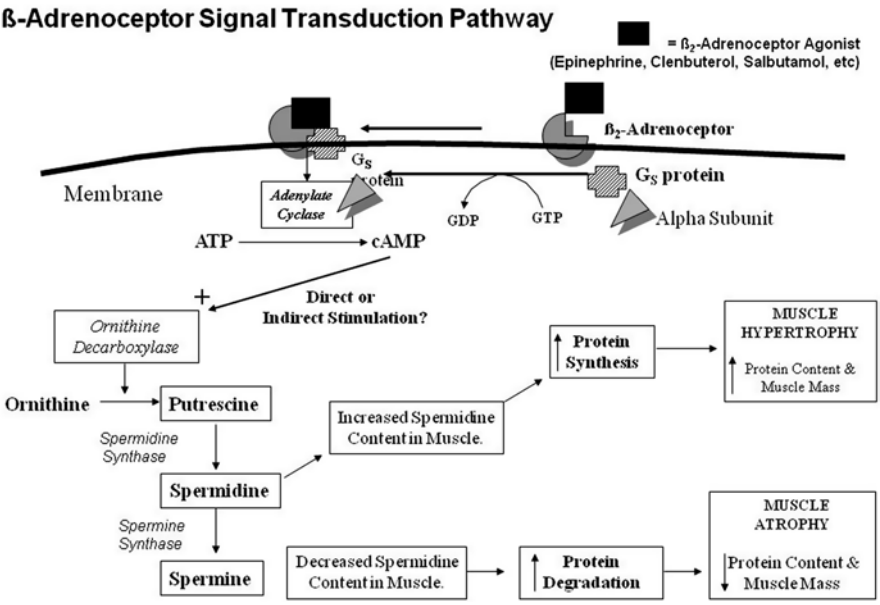


Fig. 15.10 β-Adrenoceptor signal transduction pathway. One possible pathway for β_2-adrenoceptor signal transduction involved with skeletal muscle hypertrophy and atrophy. Note: Spermine may also help resist muscle atrophy by providing a measure of antioxidant protection as it increases with β_2-adrenoceptor stimulation

chain forming norepinephrine. Both dopamine β-hydroxylase and tyrosine hydroxylase are mixed function hydroxylase that use molecular oxygen. However, unlike tyrosine hydroxylase that uses pyridoxine-PO_4, dopamine β-hydroxylase uses ascorbate and Cu^{2+} as cofactors. Also, the highest concentration of dopamine β-hydroxylase is found in vesicles that store catecholamines. Further conversion of norepinephrine to epinephrine takes place in a few neurons of the brain stem that utilize epinephrine as a neural transmitter and in adrenal medullary cells that secrete epinephrine as the primary neurohormone. The soluble enzyme phenylethanolamine N-methyltransferase (PNMT) is the final step in the synthesis of epinephrine where it transfers a methyl group from S-adenosylmethionine to the terminal amine group of norepinephrine. PNMT is regulated by corticosteroids [41, 87].

Mechanism of Action (Fig. 15.10)

Epinephrine acts on both β_1 and β_2-adrenoceptors, stimulating adenylyl cyclase by activating G stimulatory (G_S) protein subunit coupling to the receptor, and subsequently increasing tissue cAMP levels [41, 87, 88]. In turn, cAMP acts as a second messenger to a number of metabolic pathways. One of the most important pathways is the activation of cAMP-dependent protein kinase, which upon

activation phosphorylates a number of key proteins. The enzyme ornithine decarboxylase (ODC), which is activated by cAMP, is the rate-limiting enzyme in the synthetic pathway of polyamines [89–91]. ODC has been identified as a potentially important link in the β-adrenoceptor signal transduction pathway for inducing cardiac and skeletal muscle hypertrophy [63, 78, 92]. Other potential means by which β_2-adrenoceptor agonists produce their anabolic effects are unclear. This class of anabolic agents may be acting directly through the stimulation of protein synthesis or through inhibiting the action of proteolytic enzymes. One other effect that has been associated with the use of β_2-adrenoceptor agonists is that they (in particular clenbuterol) are repartitioning agents, by causing an increase in protein production and reducing fat accumulation. The mechanism of action for these effects is again unclear.

It should be noted that β_2-adrenoceptor agonists appear to be more effective in attenuating disuse-induced skeletal muscle atrophy in predominately fast-twitch (Type II) muscles [e.g., extensor digitorum longus (EDL), plantaris, pectineus] than in predominately slow-twitch (Type I) muscles [e.g., adductor longus (ADL) or soleus]. Effects on mixed fiber-type muscles such as the gastrocnemius are intermediate. In rat exercise models, treatment with β_2-adrenoceptor agonists produced increased muscle mass in all muscles, but their greatest effects were on predominately fast-twitch skeletal muscles rather than slow-twitch [62–64].

Metabolism (Fig. 15.11)

The metabolism of catecholamines to their inactive forms is primarily accomplished by the enzymes monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT). These enzymes are distributed extensively throughout the body with MAO located in the outer membrane of mitochondria and COMT on the outer plasma membranes of nearly all cells. In particular, MAO oxidatively deaminates catecholamines to their respective aldehydes, which are acted on in turn by aldehyde dehydrogenases that convert the aldehydes to their analogous acids. MAO acts on free catecholamines within the nerve terminal and not on those stored within vesicles. However, marked increases in deaminated metabolites can be caused by drugs that interfere with catecholamine storage (e.g., reserpine) or by indirect acting sympathomimetics (e.g., amphetamines). Additionally, MAO is found in the gut and liver to metabolize ingested indirect sympathomimetics (e.g., tyramine and phenylethylamine) found in foods. In patients treated with MAO, inhibitors can potentially be at risk of suffering severe hypertensive crisis when eating foods rich in tyramine. Additionally, as was stated previously in the section under chemistry, a substitution with a methyl group on the α-carbon would block deamination by MAO, as is the case with amphetamine. The enzyme COMT is responsible for acting on extraneuronal catecholamines by transferring a methyl group from a cosubstrate, S-adenosylmethionine, to the hydroxyl group located at position 3 on the phenyl ring [41, 87].

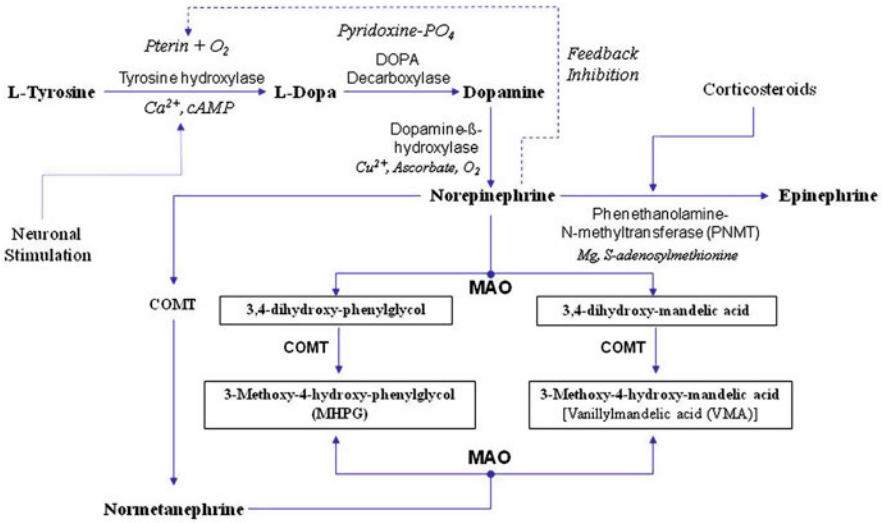


Fig. 15.11 *The biosynthesis of catecholamines* in nerve terminals of catecholaminergic neurons. Tyrosine hydroxylase is the rate limiting in the synthesis of catecholamines and is subject to feedback inhibitory controls by norepinephrine. Corticosteroids induce the synthesis of PNMT in the presence of Mg and S-adenosylmethionine. *Metabolism of catecholamines*. The metabolism of catecholamines is primarily carried out by the enzymes monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT). MAO-A is responsible for metabolizing primarily deamination of norepinephrine and serotonin, while MAO-B is more nonspecific for phenylethylamines. COMT is found on the outer plasma membranes in virtually all cells throughout the body. COMT methylates any catechol group it interacts with

Toxicology: Contraindications and Adverse Reactions

Contraindications

Sympathomimetic drugs are sold as prescription only and/or are considered as drugs of abuse, as in the case of the amphetamines and cocaine. In general, these drugs are categorized as: pregnancy category C, schedule C-II controlled substances (amphetamines, cocaine). They are banned by the NCAA, USOC, and IOC [10, 28]. Clenbuterol, cimaterol, fenoterol, mabuterol, and procaterol are not approved for human use in the USA. Clenbuterol is prohibited for use in food animals (bovine, swine, etc.). However, of all these β_2-adrenoceptor agonists, clenbuterol is the agent most likely to be encountered.

Albuterol

Albuterol is contraindicated in cases of: women who are breast-feeding, cardiac arrhythmias, cardiac disease, children, coronary artery disease, diabetes mellitus, elderly,

hypertension, hyperthyroidism, pheochromocytoma as a result of hypersensitivity to sympathomimetics, pregnancy, seizure disorders (history of seizures), and tachycardia.

Amphetamines (Amphetamine and Methamphetamine)

Amphetamine/methamphetamine are contraindicated in cases of advanced arteriosclerosis, agitated states, during or within 14 days of MAO inhibitors, glaucoma, history of drug abuse, hyperthyroidism, moderate to severe hypertension, symptomatic cardiovascular disease.

Clenbuterol (Equine)

In the USA, clenbuterol is not approved for human use. In horses, it is contraindicated for use in pregnant mares that are near to term, horses suspected of having cardiovascular impairment due to the likelihood of tachycardia, and antagonizes the effects of oxytocin and prostaglandin $F_{2\text{-alpha}}$.

Cocaine

Cocaine is a schedule C-II controlled substance and its use is by prescription only. Cocaine is contraindicated in cases of women who are breast-feeding, cardiac arrhythmias, cardiac disease, cerebrovascular disease, children, coronary artery disease, elderly, hepatic disease, hypertension, infection, pseudocholinesterase deficiency, pregnancy, seizure disorders (history of seizures), thyrotoxicosis, and Tourette's syndrome. Cocaine should not be used in children under 6 years in age.

Dobutamine

Dobutamine is contraindicated in cases of when individuals are experiencing angina, atrial fibrillation, acute myocardial infarction, cardiac arrhythmias, cardiac or coronary disease, children, elderly, hypovolemia, idiopathic hypertrophic subaortic stenosis, neonates, pregnancy, and sulfite hypersensitivity.

Isoproterenol

Isoproterenol is contraindicated in cases when angina, asthma, atrial fibrillation, atrial flutter, breast-feeding, cardiac arrhythmias, cardiac disease, children, coronary artery disease, corticosteroid therapy, diabetes mellitus, digitalis toxicity, elderly, hypertension, hyperthyroidism, hypoxemia, metabolic acidosis, pheochromocytoma, pregnancy, respiratory acidosis, sulfite hypersensitivity, tachycardia, thyroid disease, ventricular fibrillation, and ventricular tachycardia.

Phenylpropanolamine

The use of phenylpropanolamine (PPA) has been discontinued in the USA and is banned by the IOC. PPA is contraindicated in cases of acute myocardial infarction, angina, in women who are breast-feeding, cardiac arrhythmias and disease, cardiomyopathy, children, closed-angle glaucoma, coronary artery disease, diabetes mellitus, elderly, females, glaucoma, heart failure, hypertension, hyperthyroidism, infants, myocardial infarction and heart failure, pregnancy, prostatic hypertrophy, renal impairment and failure, substance abuse, tachycardia, urinary retention.

Propranolol (Inderal®)

The use of β_2-adrenoceptor blockers has been banned by the NCAA, USOC, and the IOC [10, 28]. Propranolol is contraindicated in cases of bronchial asthma, cardiogenic shock, congestive heart failure (except when failure is secondary to tachyarrhythmia treatable with propranolol), and sinus bradycardia. It has been reported that in some patients lacking a history of heart failure, the continued use of β-adrenoceptor antagonists can potentially result in cardiac failure. Furthermore, in cases of congestive heart failure, use of β-adrenoceptor antagonists may be contraindicated because sympathetic stimulation may be essential for supporting circulatory function.

Terbutaline

Terbutaline is contraindicated in cases where women are breast-feeding, cardiac arrhythmias, cardiac and coronary artery diseases, children, diabetes mellitus, elderly, hypertension, hyperthyroidism, pheochromocytoma, pregnancy, seizure disorder, seizures, and tachycardia.

General Adverse Reactions

Adverse effects associated with use of β_2-adrenergic agonists such as albuterol, clenbuterol, and isoproterenol can lead to severe CNS disturbances that include dizziness, headaches, insomnia, nervousness, syncope, tremor, and weakness. Additionally, they can also affect the cardiovascular system by causing angina, bradycardia, excitability, hyperkinesis, hypertension, hypotension, muscle cramps, palpitations, and sinus tachycardia, and ventricular arrhythmias. As a group, β_2-adrenergic agonists can also cause dry mouth, alteration of taste, as well as GI symptoms that include nausea, vomiting, and heartburn. Furthermore, this class of drugs can also have adverse effects on the respiratory system that includes coughing, dyspnea, and pulmonary edema, and bronchospasms. Bronchospasms arise from the action of the "inactive" (+)-*S* enantiomer. Other general adverse effects include dermatitis, diaphoresis, flushing, pallor, rash, pruritus, and urticaria [28, 68].

Specific Adverse Effects of Selected β_2-Adrenoceptor Agonists

Albuterol (Salbutamol™)

Albuterol's adverse reactions are dose dependent and occur more commonly with oral (tablets or syrup) rather than aerosol or inhalation administration. When albuterol is taken *orally*, the most common adverse effects are tremor (10–20%) and anxiety (9–20%). Other adverse effects include those listed in section under general adverse reactions. These reactions can include: angina, angioedema, anxiety, arrhythmia exacerbation, bronchospasm, cough, diaphoresis, diarrhea, dizziness, drowsiness, dyspepsia, epistaxis, excitability, fever, flushing, headache, hoarseness, hostility, hyperglycemia, hyperkinesis, hypertension, hypokalemia, insomnia, irritability, maculopapular rash, muscle cramps, nausea/vomiting, nightmares, palpitations, peripheral vasodilation, pharyngitis, rash (unspecified), restlessness, rhinitis, sinus tachycardia, throat irritation, tremor, urinary retention, and urticaria [28, 83].

When albuterol is administered through *inhalation aerosols*, the most common adverse effects include palpitations, sinus tachycardia, anxiety, tremor, and increased blood pressure that occasionally result in hypertension. Other adverse effects that can be associated with inhalation aerosols include: nausea/vomiting, throat irritation, dyspepsia, insomnia, heachache, epistaxis, cough, dizziness, nightmares, and hostility. Infrequently cases of urticaria, angioedema, maculopapular rash, bronchospasm, hoarseness, and oropharyngeal edema might also be observed with inhalation aerosols. However, the adverse effects associated with the use of the pure (−)-*R* enantiomer, levalbuterol (0.63 or 1.25 mg doses), are nervousness, tremor, and rhinitis. In children (6–11 years old), the adverse effects associated with levalbuterol include accidental injury, asthma (bronchospasm), diarrhea, fever, headache, pharyngitis, rash, and rhinitis. It should be noted that many of the adverse effects associated with the use of albuterol could be attributed to the (+)-*S* enantiomer [66]. More recent studies into the action of the (+)-S enantiomer dispute these findings, where little difference was observed between the racemic and the (−)-*R* enantiomer regarding adverse affects or efficacy, suggesting that the S enantiomer does not adversely affect airway secretions at recommended doses [93, 94]. However, further large multicenter trials are needed to determine the long-term therapeutic advantage and cost-effectiveness of manufacturing the pure enantiomer.

Amphetamines (Amphetamine, Dextroamphetamine, and Methamphetamine)

Although amphetamines are not anabolic agents, they are frequently used as dietary aids or as performance enhancers (increased alertness, etc.). Adverse reactions to amphetamines can include: anorexia, constipation, diarrhea, dizziness, dyskinesia, dysphoria, euphoria, hypertension, impotence, insomnia and over stimulation, palpitations, restlessness, sinus tachycardia, weight loss, and xerostomia [28].

Clenbuterol

When taken in normal dosages (human), clenbuterol is well tolerated. Clenbuterol is used in humans for treating chronic obstructive airway disease at doses of 10–20 g twice daily. In a study conducted with healthy human subjects, no adverse cardiovascular effects were observed and respiratory functions improved.

Clenbuterol is also used to treat horses (tocolysis and respiratory ailments) and cattle (tocolytic agent). Use of clenbuterol can potentially result in CNS disturbances that include headache, insomnia, nervousness, palpitations, restlessness, syncope, distal tremor, and weakness. When taken in high doses or on a chronic basis, adverse effects can include hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, leucocytosis, palpitations, tachypnea-dyspnea, sinus tachycardia, ventricular arrhythmias, and hypertrophy [68, 95]. Additionally, clenbuterol was found to block epinephrine-induced inhibition of insulin-stimulated glucose uptake in rat skeletal muscles. When given in very high doses (carcinogenic study, 25 mg/kg/body weight) to Sprague Dawley rats, no carcinogenicity was found. However, cardiac hypertrophy was observed in a dose-dependent manner.

Acute toxicity has been observed in subjects who ate livers (clenbuterol accumulates in liver) from cattle treated with clenbuterol. Clinical symptoms were distal tremors, headache, moderate hyperglycemia, hypokalemia, leucocytosis, palpitations, and tachypnea-dyspnea. Following 3–5 days. the symptoms disappeared.

Cocaine

Although cocaine is not an anabolic agent, it is frequently use as a recreational drug in combination with androgens and potentially β_2-adrenoceptor agonists. Cocaine is a schedule C-II controlled substance that is addictive. In general, cocaine toxicity can occur in three stages: early stimulation, advanced stimulation, and depression. Higher doses normally lead to progression to more advanced stages of toxicity. Cocaine used in doses of 20 mg can lead to adverse reactions, while doses of 1.2 g are known to be fatal [28].

Adverse reactions to cocaine use can include: abdominal pain, agitation, agnosia, anxiety, apnea, bowel ischemia, cardiac arrest, Cheyne–Stokes respiration, confusion, delirium, diaphoresis, dizziness, emotional lability, exophthalmos, fecal and urinary incontinence, hallucinations (can be auditory, gustatory, olfactory, or visual), headache, hyperreflexia, hypertension, hyperthermia, hyporeflexia, intracranial bleeding, irritability, muscle paralysis, mydriasis, myoglobinuria, nasal congestion, nausea/vomiting, premature labor, psychosis, pulmonary edema, renal tubular obstruction, restlessness, rhabdomyolysis, rhinitis, seizures, septal perforation, serotonin syndrome, sinusitis, spontaneous abortion, tachypnea, and tremor. In addition, repeated bouts of cocaine abuse followed by withdrawal results in stimulating a neuroendocrine stress response and subsequent decreases in cellular immunity [96]. From personnel observations, the impact of cocaine withdrawal following

binge usage resulted in severe immunosuppression of a patient, with neutrophil counts falling to near 0, leaving the patient susceptible to infection.

As a consequence of cocaine use, serious adverse cardiac effects can occur that include: *Early Stage effects* can include hypertension, premature ventricular contractions (PVCs), generalized vasoconstriction, ventricular tachycardia, and sinus bradycardia when used in low doses. *Advanced Stage adverse effects* include cardiac arrhythmias (e.g., ventricular tachycardia and ventricular fibrillation), myocardial ischemia and/or infarction, and ultimately congestive heart failure. *Late Stage depressive cardiovascular effects* include cardiac arrest and circulatory collapse. Concomitant use of cocaine with other CNS stimulants can result in an inordinate degree of anxiety, irritability, seizures, and/or cardiac arrhythmias.

Dobutamine

Adverse effects attributed to the use of dobutamine (β_1- and β_2-adrenergic agonist, where $\beta_1 >> \beta_2$) are similar to other sympathomimetic drugs. These effects are usually transient and unless they become intolerable, medical treatment is not required. Adverse effects normally associated with the use of β-adrenoceptor agonists include: angina, dyspnea, fatigue, headache, hypertension, hypokalemia, hypotension, injection site reaction (local phlebitis), nausea/vomiting, palpitations, paresthesias, phlebitis, premature ventricular contractions (PVCs), and sinus tachycardia. Except for a possible persistent tachycardia, these adverse effects are normally short-lived. In addition, terbutaline can cause metabolic disturbances that include hyperglycemia and hypokalemia, especially at high doses. Infrequently, the use of terbutaline has been reported to cause seizures. However, seizures cease upon the withdrawal of treatment. Infrequently, dobutamine might cause electrolyte disturbances that could result in serious adverse cardiac effects [28].

Isoproterenol

Isoproterenol's adverse reactions are dose dependent. Adverse effects associated with the CNS include: anxiety, diaphoresis, dizziness, headache, insomnia, lightheadedness, mild tremor, restlessness, and weakness. Normally these reactions are transient and do not require medical attention, unless they become prolonged. Chronic use of isoproterenol over long periods can result in tolerance to the drug effect. It is recommended that if this occurs, alternative therapy should be initiated. Additionally, hypersensitivity responses have been reported in individuals with sulfite allergies when they use isoproterenol formulations containing sulfite [28, 83].

Adverse effects associated with the cardiovascular system include: cardiac arrhythmias, heart failure, myocardial infarction, sinus tachycardia, and ventricular arrhythmias (ventricular tachycardia). Also, proarrhythmias can result from drugs that sensitize the myocardium to arrhythmias (e.g., other sympathomimetics or antiarrhythmic agents) or due to a precondition that results from electrolyte imbalances (e.g., hypomagnesemia, hypokalemia, or hyperkalemia). In children who received

intravenous infusions (rates of 0.05–2.7 μg/kg/min) of isoproterenol to treat refractory asthma, clinical deterioration, myocardial infarction (necrosis), congestive heart failure, and death have been reported. Furthermore, factors such as acidosis, hypoxemia, and the coadministration of corticosteroids or methylxanthines (e.g., theophylline, aminophylline, or theobromine) appear to increase the risks of cardiac toxicity.

Other adverse effects associated with oral inhalation of isoproterenol may include bronchial irritation, edema, cough, and oropharyngeal dryness. Isoproterenol when taken either orally or by inhalation can also cause GI disturbances such as nausea and vomiting. On occasion, isoproterenol can cause a reddish discoloration of the saliva when taken either sublingually or by inhalation. The red color does not indicate any harmful effect of the medication or loss of potency, but is the result of oxidation.

Phenylpropanolamine (PPA)

Use of PPA has been discontinued in the USA. Adverse effects associated with the use of PPA can include: angina, exacerbated arrhythmia, diaphoresis, dysuria, hypertension, interstitial nephritis, intracranial bleeding, mydriasis, myocardial infarction, nausea and vomiting, palpitations, premature atrial contractions (PACs), premature ventricular contractions (PVCs), unspecified renal failure, restlessness, rhabdomyolysis, sinus tachycardia, stroke, tachypnea, and xerostomia. In addition, since PPA is a sympathomimetic, it can produce CNS stimulatory effects that can include anorexia, anxiety, dizziness, hallucinations, headache, insomnia, irritability, psychosis, restlessness, and seizures. These effects are commonly associated with excessive use, overdosage, and substance abuse. Furthermore, the elderly appear to have an increased sensitivity to the CNS stimulatory effects of PPA than younger individuals [28, 83].

PPA has often been used as a dietary aid, and the potential for misuse is very high. When PPA is used in higher than recommended doses (overdose) or in combination with a monoamine oxidase inhibitors (MAOI) or caffeine, hypertension or a hypertensive crisis may result. Signs of hypertension could include severe headache, intracranial bleeding, and stroke (nonfatal and fatal). In particular, intracerebral and/or subarachnoid hemorrhage has been well documented with the use of PPA and PPA products (formulations for cough-cold combinations and appetite suppressants). In the Yale Hemorrhagic Stroke Project [28], the FDA was unable to predict who (based on age, race, sex, etc.) was at risk of stroke. However, it was noted that females were significantly at risk.

Propranolol

In general, the adverse effects associated with the use of propranolol are transient and mild, and usually are the result of the drug's therapeutic effects. Bradycardia and hypotension are mild adverse cardiovascular effects associated with propranolol that can be treated with IV atropine if necessary. Adverse cardiovascular effects of a more serious nature effects can include AV block and heart failure. Propranolol

can have adverse effects on the gastrointestinal system by causing diarrhea, nausea, and vomiting. Other adverse reactions can include: alopecia, bronchospasm, diabetes mellitus, exfoliative dermatitis, fatigue, hallucinations, and hyperglycemia. Other adverse reactions include: hypertriglyceridemia, hypoglycemia by interfering with glycogenolysis, hypotension, impotence, libido decrease, myalgia, nightmares, pruritus, musculoskeletal pain, skin hyperpigmentation, and xerosis [28, 83].

Propranolol has been shown to mask the signs of hypoglycemia (e.g., tachycardia, palpitations, and tremors) and can result in a prolonging (or enhancing) of hypoglycemia through interfering with glycogenolysis.

Terbutaline

Adverse effects attributed to the use of terbutaline are similar to other sympathomimetic drugs. These effects are usually transient and unless they become intolerable, medical treatment is not required. Adverse effects normally associated with the use of β-adrenoceptor agonists include: angina, anxiety, arrhythmia, diaphoresis, dizziness, drowsiness, dyspnea, headache, hypokalemia, lethargy, muscle cramps, nausea/vomiting, palpitations, premature ventricular contractions (PVCs), restlessness, seizures, sinus tachycardia, tremor, and xerostomia. Except for a possible persistent tachycardia, these adverse effects are normally short-lived. In addition, terbutaline can cause metabolic disturbances that include hyperglycemia and hypokalemia, especially at high doses. Infrequently, the use of terbutaline has been reported to cause seizures. Once terbutaline has been withdrawn, seizures stop [28].

Mechanisms of Interactions

The Following Classes of Drugs May Interact with β_2-Adrenoceptor Agonists and Other Sympathomimetics When Administering Concurrently

It has been discussed that β_2-adrenoceptor agonists are commonly used in very high concentrations in combination with androgen cocktails. Furthermore, to render greater anabolic effects, β-adrenoceptor agonists may be used in conjunction with human growth hormone, as well as insulin-like growth factor (IGF-1) as well as nutritional supplements [28, 83].

Although the amphetamines and cocaine are sympathomimetic agents, they are not β_2-adrenoceptor agonists. Additionally, they have been used as performance enhancers and are schedule C-II controlled substances that have been banned by both the IOC and USOC.

Androgens

The synergistic effects of clenbuterol and anabolic steroids appear to cause myocardial infarctions, potentially resulting from coronary spasms. In laboratory animals, there is

little information on the anabolic interactions taking between the beta-2-adrenergic agonists clenbuterol and salbutamol and the androgens. Clenbuterol had no effect on blood testosterone levels. However, treatment with dobutamine (β_1-adrenoceptor agonist) caused increases in blood testosterone levels.

Amphetamines

Concomitant use of amphetamines with other sympathomimetics (e.g., β_2-adrenoceptor agonists, cocaine, ephedrine, norepinephrine, and pseudoephedrine) can cause excessive cardiovascular or CNS stimulation. Furthermore, the use of amphetamines in the presence of other sympathomimetics and cardiac glycosides (e.g., digoxin) can result in increased blood pressure, cardiac arrhythmias, and heart rate.

The use of amphetamines with β-adrenoceptor antagonists such as propranolol or ophthalmic β-adrenoceptor antagonist solutions can produce unopposed β-adrenergic activity. Through increased β-adrenergic activity, an increase in blood pressure, bradycardia, or heart block could occur. Other substances that can interact with amphetamines include the following.

Guanethidine

Causes a decrease in guanethidine's antihypertensive effects.

MAOIs

Can cause an increase in the pressor response of amphetamines by causing the release of norepinephrine.

Tricyclic Antidepressants

Concomitant use of tricyclics with amphetamines can decrease the effects of amphetamines.

Urinary Acidifiers

Concomitant use of urinary acidifiers with amphetamines decreases the half-life of amphetamines, thereby shortens the clinical effects.

Urinary Alkalinizers

Concomitant use of urinary alkalinizers with amphetamines increases the half-life of amphetamines, thereby prolonging the clinical effects.

Amphotericin B

The interaction of Amphotericin B with β_2-adrenoceptor agonists such as isoproterenol can increase the risk of developing arrhythmias by causing hypokalemia and hypomagnesemia.

Antihypertensive Agents

There is a potential for decreasing the effectiveness of antihypertensive therapy with concomitant use of β_2-adrenoceptor agonists.

Cardiac Glycosides

The risk of developing cardiac arrhythmias is significantly increased with the concomitant use of β_2-adrenoceptor agonists and cardiac glycosides.

Cocaine

Briefly, the concomitant use of cocaine with other sympathomimetics (e.g., β_2-adrenoceptor agonists, cocaine, ephedrine, norepinephrine, pseudoephedrine) can cause excessive cardiovascular or CNS stimulation. Furthermore, the use of cocaine in the presence of other sympathomimetics and cardiac glycosides (e.g., digoxin) can result in increased blood pressure, cardiac arrhythmias, and heart rate. The use of cocaine concomitantly with tricyclic antidepressants, cardiac glycosides, or levodopa can increase the risk of developing cardiac arrhythmias. The simultaneous use of cocaine with cholinesterase inhibitors can reduce cocaine's metabolism and increase the risk of cocaine toxicity. Because cocaine stimulates a generalized adrenergic response, it can interact with many drugs in a fashion similar to that of β_2-adrenoceptor agonists (e.g., nitrates, MAOIs, halogenated anesthetics).

Corticosteroids

The interaction of corticosteroids with β_2-adrenoceptor agonists such as isoproterenol can increase the risk of developing arrhythmias by causing hypokalemia.

Entacapone

The combined use of drugs metabolized by catechol-O-methyltransferase (COMT) such as isoproterenol and entacapone could result in an increase in heart rates, possibility for arrhythmias, and inordinate changes in blood pressure.

Ergot Alkaloids

The interaction of ergot alkaloids with β_2-adrenoceptor agonists such as isoproterenol can cause peripheral vasoconstriction and increased cardiac output that leads to an increase in blood pressure.

General Anesthetics

The concomitant use of general anesthetics (hydrocarbon derivatives such as cyclopropane, isoflurane, halothane) with β_1- and β_2-adrenoceptor agonists significantly increases the potential for the development of lethal cardiac arrhythmias. This is true for most β-adrenoceptor agonist including albuterol, dobutamine, terbutaline, and especially isoproterenol.

Ginger (*Zingiber officinale*)

Results from in vitro investigations suggest that there is a possible between ginger, *Zingiber officinale*, and β_2-adrenoceptor agonists. This interaction might result in an additive positive inotropic effect. However, no clinical data are available to substantiate this observation.

Guanethidine

The concomitant use of guanethidine and dobutamine could result in a potentiation of dobutamine's pressor, thereby resulting in hypertension and arrhythmias.

Insulin

The interaction of insulin and glucose with β_2-adrenoceptor agonists such as isoproterenol can increase the risk of developing arrhythmias by causing hypokalemia.

Levodopa

Isoproterenol can increase the risk of proarrhythmia, if administered with levodopa.

Loop Diuretics

The interaction of loop diuretics with β_2-adrenoceptor agonists such as isoproterenol can increase the risk of developing arrhythmias by causing hypomagnesemia.

Monoamine Oxidase Inhibitors (MAOIs)

The concomitant use of β_2-adrenoceptor agonists with MAOIs or drugs that possess MAOI activity (e.g., *furazolidone, linezolid, and procarbazine*) can result in severe cardiovascular effects that can result in severe hypotension (*albuterol*) or a prolonging and intensification of the cardiac stimulatory and vasopressor effects associated with isoproterenol (*isoprenaline*). *Terbutaline's* effects on the vascular system have also been reported to increase in the presence of MAOIs. Other MAOIs such as *phenelzine* and *tranylcypromine* possess amphetamine-like activity that results in the release of norepinephrine. The combination of these MAOIs with isoproterenol can exacerbate isoproterenol's β-adrenergic effects and subsequently lead to severe cardio- and cerebrovascular responses. It is recommended that a 14-day washout period be allowed between uses of these drug types.

Nitrates

Treatment with β_2-adrenoceptor agonists can compromise the antianginal effects of nitrates on the myocardium. Increased oxygen demands can be placed on the myocardium with β_2-adrenoceptor agonists such as albuterol, clenbuterol, isoproterenol, and terbutaline. Using β_2-adrenoceptor agonists in patients requiring antianginal therapy can counteract the therapeutic activity of nitrates.

Penicillins

The interaction of some penicillins (e.g., as piperacillin or mezlocillin when administered in high doses) with β_2-adrenoceptor agonists such as isoproterenol can increase the risk of developing arrhythmias by causing hypokalemia.

Sympathomimetics

In general, the use of β_2-adrenoceptor agonists along with other sympathomimetics or CNS stimulants can result in the release of endogenous catecholamines and produce additive effects that can result in CNS or cardiovascular toxicity. The use of β-adrenoceptor agonists with cocaine can intensify cocaine's effects.

Theophylline, Aminophylline

Although clinically methylxanthines and β_2-adrenoceptor agonists are routinely used together, it should be noted that there is an increase risk of additive CNS stimulation, with sensations of tremor or nervousness. Additionally, the interaction of β_2-adrenoceptor agonists with methylxanthine derivatives such as caffeine, theophylline,

aminophylline, or theobromine could potentially lead to an increase in adverse reactions including myocardial infarction, congestive heart failure, and death.

Thiazide Diuretics

The interaction of some thiazide diuretics with β_2-adrenoceptor agonists such as isoproterenol can increase the risk of developing arrhythmias by causing hypokalemia.

Thyroid Hormones

The concomitant use of β_2-adrenoceptor agonists with thyroid hormones can result in an intensification of the effect of either drug on the cardiovascular system. The combined use of these drugs could result in a further risk of coronary insufficiency in patients suffering from coronary artery disease.

Tricyclic Antidepressants and Maprotiline

Maprotiline, a tetracyclic antidepressant, inhibits the reuptake of norepinephrine at the neuronal membrane. Consequently, with the higher levels of norepinephrine, there would be an exacerbation of β-adrenergic agonist activity that could lead to peripheral vasoconstriction and a subsequent increase in blood pressure, potentially inducing hyperpyrexia.

Cyclofenil

Cyclofenil, though not an anabolic/androgenic steroid, acts as an antiestrogen and increases testosterone production. It is a weak/mild estrogen receptor antagonist [56, 97].

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

When the athlete is trying to obtain a harder appearance, cylcofenil is either used during steroid treatment, after the treatment, before competitions with doping tests. The dosage used lies between 400 and 600 mg/day, and below this, the results are poor. It takes a period of 1 week to begin to see effects. Athletes report strength gains, an increase in energy, and faster regeneration. Cyclofenil is not readily available, but can be found in other countries under the trade names listed in Table 15.10.

Table 15.10 Trade names for cyclofenil

Trade name	Dose available	Manufacturer	Country
Fertodur (O.C.)	200 mg tab.	Schering	D, CH, I
Fertodur	200 mg tab.	Schering	PT, GR, TK, M
Neoclym	200 mg tab.	Poli	I
Ondogyne (O.C.)	400 mg tab.	Roussel	F
Rehibin	100 mg tab.	Serono	GB
Sexovid	100 mg tab.	Teikiku zoki	J
Sexovid (O.C.)	100 mg tab.	Leo	ES

O.C. over the counter, *CH* China, *D* Germany, *ES* Spain, *F* France, *GB* Great Britain, *GR* Greece, *J* Japan, *I* Italy, *M* Mexico, *PT* Portugal, *TK* Turkey

Mechanism of Action

Cyclofenil weakly interacts with estrogen receptors, thus antagonizing estrogen's ability to bind to the receptor.

Toxicology: Contraindications and Adverse Reactions

Contraindications

It is ineffective among women.

Adverse Reactions

The following adverse reactions have been reported during use: light acne, hot flashes. When cyclofenil is discontinued, some athletes report a depressed mood and a slight decrease in physical strength. In addition, those who take cyclofenil as an antiestrogen during steroid treatment could experience a rebound effect when the compound is discontinued.

Mechanisms of Interactions

Cyclofenil is used in combination with steroid treatment to obtain a harder appearance. This combination maintains a low estrogen level with lower water retention and less gynecomastia.

Human Growth Hormone

Human growth hormone *(Somatotropin; Genotropin®, Humatrope®, Norditropin®, Nutropin®, Saizen®, Serostim®, Tev-Tropin™, Biotropin®, Nutropin Depot™, Nutropin® AQ)* is secreted by the pituitary gland and is a heterogeneous mixture of

peptides. It stimulates normal skeletal, connective tissue, muscle and organ growth in children and adolescents [28].

Human growth hormone has been purified and is produced by recombinant DNA technology. It is produced from either a mammalian cell line (mouse C127) or *Escherichia coli*. Its amino acid sequence and structure are identical to the dominant form of human pituitary growth hormone. Prior to the mid-1980s, growth hormone was obtained from human cadavers. Today, several somatotropin products are available in either normal or long-acting extended-release forms.

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

In both children and adults, somatotropin or its analogs are administered as injectables to treat various growth failures due to growth hormone deficiency, chronic renal disease, Prader–Willi syndrome or Turners's syndrome, and cachexia or AIDS wasting.

Several somatotropin products are available (see above) which are normal or long-acting extended-release forms (i.e., Nutropin Depot™). These extended-release forms involve insertion of micronized particles of somatotropin into microspheres.

Somatotropin is administered by either intramuscular or subcutaneous injection. In normal males, the mean half-life of intravenous somatotropin is 0.6 h, whereas via subcutaneous or intramuscular routes, the half-lives are 1.75 and 3.4 h, respectively. Slower absorption of the drug after subcutaneous or intramuscular administration is responsible for the longer half-lives. Approximately 20% of circulating somatotropin is bound to growth hormone–binding protein. Bioavailability after subcutaneous administration ranges between 70% and 90%. Little excretion of the compound occurs via urine [23].

The depot form of the drug has a bioavailability that ranges from 30% to 55% depending on the dosing regimen. Once released from the microspheres, the kinetics is the same as somatotropin formulated for daily administration. Serum growth hormone levels above 1 μg/L persist for 11–14 days following single doses of 0.75–1.5 mg/kg [28].

The pharmacokinetics is similar in children and adults and not affected by gender. In individuals with renal or hepatic insufficiency, there is a decreased clearance of the drug.

For Treatment of Growth Failure or Growth Hormone Deficiency

Children would typically receive 0.16–0.24 mg/kg/week subcutaneously divided into seven equal daily injections. For adults, the dosage would be a maximum of 0.006 mg/kg/daily subcutaneously. For depot forms, the dosage for children typically would be 1.5 mg/kg subcutaneously on the same day each month or 0.75 mg/kg

twice each month on the same 2 days (i.e., days 1 and 15). For patients over 45 kg, twice-per-month dosing is recommended. Dosage and administration would be adjusted for individual patients.

For Treatment of AIDS Wasting

Daily bedtime subcutaneous injections of Serostim for adults are given as follows: 6 mg for individuals greater than 55 kg body weight, 5 mg for 45–55 kg, 4 mg for 35–45 kg, and 0.1 mg/kg for less than 35 kg.

In Bodybuilding

"HGH enhancers" are used to raise human growth hormone levels. These over-the-counter supplements can contain cow's colostrum (rich in growth factors, i.e., growth hormone and IGF-1, immune factors, etc.) or an herbal extract of *Tribulus terrestris* (which stimulates production of luteinizing hormone, testosterone, follicle-stimulating hormone, and estradiol) [28].

In addition, under conditions such as acromegaly where human growth hormone levels are elevated, somatostatin analogs (inhibitors of growth hormone release) such as octreotide (i.e., Sandostatin or Sandostatin Lar Depot) are used.

Biosynthesis of Endogenous Human Growth Hormone

Human growth hormone is secreted from the pituitary gland and is a heterogeneous mixture of peptides. The principal form is a 191 amino acid polypeptide with a molecular mass of 22 kDa. Growth hormone secretion is pulsatile and occurs in discrete bursts. This release is enhanced by growth hormone–releasing hormone (GHRH) and reduced by somatostatin, both of which bind to receptors. In addition, stimulators of growth hormone release include dopamine, serotonin, alpha-adrenergic agonists, and ghrelin, whereas inhibitory factors include beta-adrenergic agonists, insulin-like growth factor-1, and growth hormone.

Mechanism of Action

Pituitary growth hormone directly stimulates the production of somatomedins or insulin-like growth factors (IGFs) in the liver and other tissues. It increases triglyceride hydrolysis in adipose tissue and hepatic glucose output. These direct actions are potentiated by glucocorticoids and oppose the actions of insulin on fat and carbohydrate metabolism. The anabolic and growth-promoting effects of growth hormone are mediated through IGFs [98]. These include increases in the production of skeletal growth (growth and metabolism of the epiphyseal plates), the number and size of skeletal muscle cells, and the red cell mass [28, 37, 98]. In addition, the metabolism of proteins, carbohydrates, and lipids; mineral retention; and the synthesis

of chondroitin sulfate and collagen in connective tissue are stimulated. These indirect effects are insulin-like and opposed by glucocorticoids. Overall, they stimulate normal skeletal, connective tissue, and muscle and organ growth in children and adolescents.

Metabolism

Growth hormone is catabolized in the liver and kidneys.

Toxicology: Contraindications and Adverse Reactions [28]

Contraindications

Somatotropin is contraindicated in patients who are pregnant or breast-feeding. In elderly or neonatal patients, somatotrophin treatment is not recommended.

Somatotrophin is not recommended if they are undergoing chemotherapy, radiation therapy, or surgery or if they have experienced trauma.

It should not be used in patients with the following conditions: benzyl alcohol hypersensitivity, cresol hypersensitivity, diabetes mellitus, epiphyseal closure, glycerin hypersensitivity, hypothyroidism, increased intracranial pressure, neoplastic disease, otitis media, acute respiratory failure, and scoliosis.

Adverse Reactions

The following adverse reactions have been reported: antibody formation, arthralgia, bleeding, carpal tunnel syndrome, fluid retention, glycosuria, gynecomastia, headache, hematuria, hyperglycemia, hypothyroidism, increased intracranial pressure, injection site reaction, myalgia, nausea/vomiting, pancreatitis, paresthesias, peripheral edema, unspecified rash, secondary malignancy, seizures, skin hyperpigmentation and weakness.

Mechanisms of Interactions

The following classes of drug may interact with human growth hormone (somatotropin) when administered concurrently.

Corticosteroids (i.e., Cyclosporine)

Corticosteroids can inhibit the growth-promoting effects of somatotropin; thus, the corticosteroid dosage should be carefully adjusted.

Sex Steroids (i.e., Testosterone, Estrogen)

Endogenous testosterone is a male sex hormone ($C_{19}H_{28}O_2$) that is secreted by primarily by the testes. Its functions include the stimulation and the development of male sex organs, secondary sexual traits and sperm. Exogenous (pharmacological) usage of testosterone in medicine is primarily for treatment of testosterone deficiency, etc. IUPAC Name: (8R,9S,10R,13S,14S,17S)- 17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one, CAS Number: 58-22-0.

Endogenous estrogens are female sex hormones that include 17ß-estrodiol ($C_{20}H_{24}O_2$), (17α)-estrodiol and esterone as well as several others. Of the various estrogens, 17ß-Estrodiol is the one most commonly measured. In women, endogenous estrogens are important in promoting the development of female secondary sexual characteristics (breasts, endometrium thickening, and regulation of menstrual cycle). In males the estrogens are essential for maintaining a healthy libido and in regulating the maturation of sperm. The estrogens are used pharmacologically as oral contraceptives and as replacement therapy in postmenopausal women. 17ß-estrodiol: IUPAC Name: (17α)-estra-1,3,5(10)-triene-3,17-diol, CAS Number: 77538-56-8.

Cytochrome P-450 Pathway

Somatotropin stimulates the activity of cytochrome-mediated metabolism of antipyrine and other drugs.

Gonadotropin-Releasing Hormone

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

There are several forms of synthetic gonadotropin-releasing factors: sermorelin (Geref, a synthetic, parenteral growth hormone–releasing hormone) and gonadorelin (Factrel, a synthetic luteinizing hormone–releasing hormone) given by injection and implantable form leuprolide acetate, a synthetic luteinizing hormone–releasing hormone (Viadur) [23].

Factrel is used to diagnose gonadotropin deficiency. It is given to adults and children over 12 years of age at a dose of 100 μg either subcutaneously or intravenously. In younger children, the dose is 100 μg intravenously.

Geref is used to treat growth hormone deficiency as well as diagnose growth hormone secretion by the pituitary gland. To treat growth hormone deficiency in children, a subcutaneous dose of 0.03 mg/kg (30 μg/kg) is given once daily at

bedtime. Once the epiphyses are fused, discontinue treatment. For diagnosing growth hormone deficiency, adults are given 1 μg/kg in a single intravenous dose following an overnight fast.

Viadur is 12-month implant (120 μg/day) that continuously delivers leuprolide acetate for the treatment of prostate cancer. After an initial stimulation, gonadotropin secretion is inhibited, leading to decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. These decreases occur after 2–4 weeks of administration.

Nafarelin is a synthetic analogue of endogenous gonadotropin-releasing hormone (GnRH) with 200 times the potency. It is used to treat precocious puberty of central origin and endometriosis [28]. In addition, nafarelin is used to treat women with uterine leiomyoma or hirsutism and to shrink prostatic tissue in men with BPH. It is also used in in vitro fertilization. Nafarelin is administered intranasally [28] and acts by stimulating the release of LH and FSH from the anterior pituitary. However, over time this action is attenuated.

Treatment with nafarelin results in decreases in serum estradiol levels in women and spermatogenesis in men. The recommended doses of nafarelin are 400 μg/day for treating symptoms associated with endometriosis. Nafarelin has an overall efficacy equivalent to that of other GnRH-agonists [99].

Mechanism of Action

The synthetic hormone stimulates release of the gonadotropins at the level of the pituitary gland.

Toxicology: Contraindications and Adverse Reactions

Contraindications

Use of gonadotropin-releasing factors is not recommended in pregnant and nursing mothers. Nafarelin is contraindicated in pregnant or lactating females, undiagnosed abnormal vaginal bleeding, or in individuals that are hypersensitive to GnRH or GnRH-agonists.

Adverse Reactions

For gonadotropin-releasing factors, the following adverse reactions have been reported: abdominal discomfort, flushing, headache, lightheadedness, nausea/vomiting, swelling, and pain at the injection site. For nafarelin, the adverse reactions are more extensive than that observed in the gonadotropin-releasing factors. These include: anxiety, breast pain and edema, dizziness, depression, decreases in bone

density, hot flashes, headaches, impotence, nasal irritation, vaginal dryness, nervousness, changes in mood or libido, insomnia, vaginal bleeding (including vaginal irritation, odor, pruritus, infection, or pain), hypertrophy of female genitalia, vaginitis, dysmenorrhea, pyrexia, weight gain, fatigue, acute generalized hypersensitivity reaction.

Mechanisms of Interactions

No significant drug interactions have been noted with nafarelin [28]. However, the following drugs may interact with the releasing hormones when administered concurrently:

Androgens, Estrogens, Glucocorticoids, and Progestins

They affect secretion of gonadotropins.

Digoxin and Oral Contraceptives

Gonadotropin concentrations are suppressed.

Levodopa and Spironolactone

Gonadotropin concentrations can be transiently elevated.

Phenothiazines and Dopamine Antagonists

The response to gonadotropins can be blunted by increased prolactin levels.

Insulin-Like Growth Factor-1 (IGF-1)

Insulin-like growth factor-1 (IGF-1), also known as somatomedin-C, functions as the principal mediator of the action of human growth hormone. IGF-1 has a single chain, 70 amino acid polypeptide that has a 50% homology with insulin. IGFs mediate the anabolic and growth-promoting effects of growth hormone, including increases in the production of skeletal growth (growth and metabolism of the epiphyseal plates), the number and size of skeletal muscle cells and the red cell mass. It is believed that reestablishment of lost neuromuscular contacts, due to nerve degeneration, is facilitated by IGF-1 [28, 98].

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

There is a recombinant form of human IGF-1, mecasermin (Myotrophin, Cephalon/Chiron), which is under review for FDA approval for use to slow down the progression of muscle paralysis associated with amyotrophic lateral sclerosis. In addition, there is a new clinical trial scheduled to start winter 2002. In the phase III trial, a single daily dose of mecasermin is 0.05 and 0.1 mg/kg given subcutaneously was suggested.

Since IGF increases lean body mass, reduces fat, builds bone, muscle and nerves, it is popular with bodybuilders. It is a major ingredient in many HGH enhancers. In addition, recombinant IGF-1 is also sold as an oral spray (i.e., IGF-1, Peachtree Health Products, FL) and in tablet form (i.e., Homeopathic IGF-1) [100]. The spray is applied under the tongue three times per day, at least 30 min before or after meals. The tablet is taken once per day, at least 30–90 min after eating.

Biosynthesis of IGF-1

There are two insulin-like growth factors – IGF-1 and IGF-2. They are polypeptides with molecular masses of 7,500 Da and are homologous to proinsulin. IGF-2 has more insulin-like activity than IGF-1, while IGF-1 is more growth hormone dependent and is more potent as a growth factor.

IGF-1 is synthesized by many tissues (including the CNS and muscle), but the liver is the major source of circulating IGF-1. The extrahepatic synthesis and secretion of IGFs is growth hormone dependent, but these IGFs are believed to act locally as paracrine modulators. IGF synthesis is also regulated by thyroid hormone and insulin. Circulating IGFs are bound to a family of binding proteins that act as transport proteins and also modulate the actions of IGFs on target tissues.

Mechanism of Action

IGF-1 acts through an IGF-1 receptor, which is structurally related to the insulin receptor. It has intrinsic tyrosine kinase activity, which mediates the hormonal signal. IGF-1 receptors are found in a variety of tissues including the CNS, peripheral nerves, and muscle.

Toxicology: Contraindications and Adverse Reactions

Contraindications

No contraindications are reported.

Adverse Reactions

The following adverse reactions have been reported: injection site reaction, diaphoresis, knee pain, and changes in hair growth or texture were seen in phase III.

Mechanisms of Interactions

Bodybuilders recommend concurrent administration of IGF-1 with multi-minerals to obtain better results.

Clomiphene (Clomid®, Serophene®) [28]

Clomiphene citrate (2-[p-(2-chloro-1,2-diphenylvinyl)phenoxy] triethylamine citrate) is an orally administered, nonsteroidal, ovulatory stimulant with a molecular weight of 598.09 g/mol. Clomiphene is recommended for the induction of pregnancy in patients with polycystic ovary syndrome, amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology.

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

Clomphene is available in 50-mg tablets. Treatment should begin with a dose of 50 mg daily for 5 days. If ovulation does not appear to occur after the first course of therapy, the dose should be increased to 100 mg once per day for 5 days. This course may be started as early as 30 days after the previous one after precautions are taken to exclude the presence of pregnancy. The maximum daily dose is 100 mg. If ovulation does not occur, further treatment is not recommended. Coitus should be timed to coincide with the expected time of ovulation. In patients with unusual sensitivity to pituitary gonadotropin, such as those with polycystic ovary syndrome, the 50-mg dose is particularly recommended.

Mechanism of Action

Clomiphene interacts with estrogen-receptor-containing tissues, including the hypothalamus, pituitary, ovary, endometrium, vagina, and cervix. It may also compete with estrogen for estrogen-receptor-binding sites and may delay replenishment of intracellular estrogen receptors. It blocks the normal negative feedback of circulating estradiol preventing the estrogen-mediated decrease in output of gonadotropin-

releasing hormone. Clomiphene treatment results in an increased release of pituitary gonadotropins, initiating steroidogenesis and folliculogenesis. These cause growth of the ovarian follicle and raise circulating estradiol levels. Clomiphene may allow several oocytes to reach maturity. After ovulation, plasma progesterone and estradiol levels rise and fall during the normal ovulatory cycle and prepare the endometrium for implantation.

It has been suggested that both clomiphene's estrogenic and antiestrogenic properties participate in initiation of ovulation, but the estrogenic effects of clomiphene are secondary to the primary effects on hypothalamic-pituitary-ovarian function. Clomiphene has no apparent androgenic, antiandrogenic, or progestational effects, nor does it affect pituitary-thyroid or pituitary-adrenal function. After clomiphene therapy discontinuation, there is usually no continued pharmacological effect on subsequent menstrual cycles. However, in some females, spontaneous ovulation has continued. It should be noted that since clomiphene is a hormone-like substance, its use is banned from athletic competition by the IOC, NCAA, and the USOC [10, 28]. Because of its antiestrogenic properties, clomiphene could potentially be used to enhance the effectiveness of androgens by blocking their secondary estrogenic effects.

Metabolism

Orally administered clomiphene is readily absorbed and primarily excreted via feces (42%) and a smaller portion via urine (8%). The half-life of clomiphene is 5 days; however, it has been reported in the feces 6 weeks after administration.

It should be noted that clomiphene is a combination of racemic isomers, enclomiphene and zuclomiphene, whose pharmacokinetic and pharmacodynamic parameters have not been elucidated. Zuclomiphene is thought to be the more estrogenic isomer. Clomiphene appears to undergo hepatic metabolism. Both unchanged drug and its metabolites are excreted in the feces via the bile. There may be stereospecific enterohepatic recycling or sequestering. The zuclomiphene isomer appears to accumulate over several cycles of treatment; however, the combined maximum plasma levels of enclomiphene and zuclomiphene do not appear to exceed 100 mmol/L.

Toxicology: Contraindications and Adverse Reactions [28]

Contraindications

Clomiphene is not recommended in patients without an intact hypothalamic-pituitary tract and ovarian response (i.e., untreated adrenal insufficiency, pituitary insufficiency or primary pituitary failure, pituitary adenomas or other pituitary tumor, primary ovarian failure, or untreated thyroid disease), since these patients will not respond to treatment.

In females with diabetes mellitus, hirsutism (or hyperandrogenism), hyperinsulinemia, obesity, or lowered endogenous estrogen levels, there may be a reduced response to clomiphene.
Clomiphene is contraindicated in patients with abnormal or dysfunctional uterine bleeding of undetermined origin, ovarian cancer or endometrial cancer, endometriosis, ovarian enlargements or preexisting ovarian cysts not due to polycystic ovarian syndrome.
Clomiphene should not be used in women after conception has occurred.
Clomiphene is not recommended in patients with hepatic disease or dysfunction, since the reduced clearance of the drug will result in higher plasma concentrations and increased risk of certain side effects. Liver function should be evaluated in all patients prior to the start of treatment.
Patients should be advised to avoid drinking alcoholic beverages or tobacco smoking during treatment, as both will decrease its effectiveness.
In patients with active thrombophlebitis or other active thromboembolic disease, clomiphene should be used very cautiously.
Additional contraindications are abdominal pain, breast cancer, breast-feeding, major depression or psychosis, driving or operating machinery, testicular failure, visual disturbance, and vomiting.

Adverse Reactions

The following adverse reactions have been reported: abdominal pain, alopecia, anxiety, appetite stimulation, ascites, blurred vision, cervical mucus thickening, diarrhea, diplopia, dizziness, dyspnea, elevated hepatic enzymes, erythema multiforme, fatigue, headache, hepatitis, hot flashes, hypotension, increased urinary frequency, insomnia, mastalgia, menstrual irregularity, mittelschmerz, nausea and vomiting, oliguria, ovarian enlargement, ovarian hyperstimulation syndrome (OHSS), pelvic pain, photophobia, pleural effusion, pruritus, psychosis, pulmonary edema, pulmonary embolism, restlessness, scotomata, secondary malignancy, teratogenesis, thromboembolism, thrombosis, urticaria, visual impairment, and weight gain.

Mechanisms of Interactions [43]

The following drugs and classes of drug may interact with clomiphene when administered concurrently:

Black Cohosh (*Cimicifuga racemosa*)

This drug may suppress production of luteinizing hormone and thus antagonize clomiphene treatment.

Androgens

Hyperandrogenism and infertility have been associated with increased levels of the hormone prasterone, dehydroepiandrosterone, and DHEA. Thus, they may antagonize clomiphene treatment.

Soy Isoflavones

There may be competition at the estrogen receptor, thus reducing effectiveness of the treatment.

Tamoxifen (Nolvadex®)

Tamoxifen is a nonsteroidal antiestrogen agent in a class of drugs called selective estrogen receptor modulators. Tamoxifen's structure is based on the same nucleus as diethylstilbestrol, but its additional side chain (transisomer) imparts antiestrogenic activity. Tamoxifen is chemically related to another antiestrogen, clomiphene.

Tamoxifen is a primary therapy for metastatic breast cancer in both men and postmenopausal women. In premenopausal women with metastatic breast cancer, it is an alternative to ovarian ablation. Tamoxifen is more effective for patients with estrogen receptor–positive disease. It is also indicated as adjuvant therapy in postmenopausal women with node-positive and node-negative breast cancer following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. Other potential benefits of tamoxifen include lowered serum cholesterol concentrations, reduced incidence of myocardial infarctions, and increased bone mineral density [28].

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

Tamoxifen is available as tamoxifen citrate (NOLVADEX®, AstraZeneca) in 10-mg and 20-mg tablets. In patients that have breast cancer, a daily dose is 20–40 mg per day is recommended, when greater than 20 mg/day, the dose is divided into two (morning and evening). Similarly, in patients with ductal carcinoma in situ or for the reduction in the incidence of breast cancer in high-risk women, the recommended daily dose is 20 mg/day given over a period of 5 years [28].

Dosage adjustment in patients with renal dysfunction is unnecessary, but patients with biliary stasis may need a lower dose.

Orally administered tamoxifen is rapidly absorbed with a peak plasma concentration after 4–5 h. Bioavailability is comparable between the 10-mg tablet twice

daily and a single 20-mg daily dose. Its main cytochrome P-450 metabolite, desmethyl tamoxifen, is biologically similar to tamoxifen. After repeated doses, tamoxifen accumulates and reaches steady state in the plasma in 4 weeks, while desmethyl tamoxifen reaches steady state in 8 weeks. Tamoxifen has an initial half-life of 7–14 h and an extended secondary phase of 4–7 days, while the metabolite has one of approximately 14 days. It should be noted that tamoxifen is banned from use (males) in athletic competition by the IOC, USOC, and the NCAA [10, 28].

Mechanism of Action

Tamoxifen is a competitive inhibitor of estradiol binding at the estrogen receptor. It induces a change in the three-dimensional shape of the receptor and inhibits its binding to the estrogen-responsive element on DNA. Tamoxifen has mixed estrogen antagonist and agonist properties. In bone, it stimulates estrogen receptors and may prevent postmenopausal osteoporosis, while in breast tissue, it has antiestrogenic effects. Additionally, cell cycling is slowed by tamoxifen's activity in the nucleus. Tamoxifen's interaction with nuclear chromatin blocks or alters the expression of estrogen-dependent genes (RNA transcription) and results in reduced DNA polymerase activity, impaired thymidine utilization, blockade of estradiol uptake, and decreased estrogen response.

Tamoxifen decreases insulin-like growth factor type 1, which stimulates cancer cell growth and development, and stimulates the secretion of transforming growth factor-beta associated with inhibiting the activity of breast cancer cells.

Metabolism

Tamoxifen distributes widely throughout the body and is extensively metabolized in the liver by the cytochrome P-450 system. In plasma, N-desmethyl tamoxifen is the main metabolite and is biologically similar to tamoxifen. Tamoxifen undergoes some enterohepatic circulation. While excretion of both the unchanged drug and its metabolites is primarily in the feces, conjugated parent compound and metabolites make up more than 70% of the total excreted [28].

Toxicology: Contraindications and Adverse Reactions

Contraindications

Tamoxifen is contraindicated in patients who are pregnant or breast-feeding. In children, the safety and effectiveness has not been determined.

Anticoagulats

Tamoxifen treatment is contraindicated in patients requiring anticoagulation therapy and those with a history of thromboembolic disease.

Endometrial Cancer

It should not be used in patients with endometrial cancer or endometrial changes including hyperplasia and polyps.

Intramuscular Injections

Intramuscular injections should not be given during tamoxifen treatment to avoid bleeding, bruising, or hematomas.

It Should Be Used with Caution in Patients with the Following Conditions

Preexisting bone marrow suppression (i.e., neutropenia, leukopenia, or thrombocytopenia), abnormal gynecological symptoms (i.e., menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, pelvic pain, or pressure), visual disturbance (i.e., cataracts), lipoprotein abnormalities (i.e., hypercholesterolemia, hyperlipoproteinemia), or hypercalcemia.

Adverse Reactions

Adverse reactions to tamoxifen treatment are usually mild and transient.

Menopausal symptoms (i.e., hot flashes, night sweats, nausea/vomiting) include amenorrhea, dysmenorrhea, menstrual irregularity, vaginal bleeding, vaginal discharge, and vaginal irritation (dryness) have been reported, but do not require discontinuance of treatment.

Endometrial and uterine changes (i.e., endometrial hyperplasia, polyps, endometriosis, uterine fibroids, ovarian cysts) may occur during treatment. Increased incidence of uterine and endometrial cancer may also occur.

Early Pregnancy. In women exposed to tamoxifen during early pregnancy, teratogenesis, abnormal reproductive anatomy, fetal death, spontaneous abortions, vaginal bleeding, and DES-like syndrome have been reported.

While bone marrow suppression is rare, anemia, leukopenia, neutropenia, and thrombocytopenia have been reported.

Thromboembolism (i.e., pulmonary embolism, deep vein thrombosis, stroke) has been reported as significantly increased with tamoxifen treatment.

Ocular effects (i.e., cataracts, corneal deposits, corneal opacification, optic neuritis, retinopathy, and visual impairment) have been reported.

During initial tamoxifen treatment for metastatic breast cancer, bone pain, tumor pain, and/or hypercalcemia can occur. Secondary malignancies have been reported.

Elevated hepatic enzymes and hyperbilirubinemia may occur and could indicate severe hepatoxicity. Rare effects, but possibly fatal, are cholestasis, hepatitis, hepatic necrosis, and fatty changes in the liver. Also rare are hyperlipidemia and pancreatitis.

Occasionally, males treated for breast cancer report a decrease in libido and impotence.
Additional adverse reactions include: alopecia, anaphylactoid reactions (i.e., angioedema, erythemia multiforme, Stevens–Johnson syndrome and pemphigus-like, bullous rash), cough, depression, edema, fatigue, rash (unspecified), and weight loss.

Mechanisms of Interactions

The following drugs and classes of drug may interact with tamoxifen when administered concurrently:

Anticoagulants

There is increased incidence of abnormal bleeding.

Antineoplastic Agents and Other Chemotherapy Agents

Antineoplastic agents and other chemotherapy agents (i.e., cyclophosphamide, ifosfamide, and the non-synthetic chemotherapy agents: anthracyclines, docetaxel, etoposide, VP-16, paclitaxel, vinca alkaloids): There is increased risk of a thromboembolic event. Tamoxifen inhibits cytochrome P-450 mixed function oxidases and blocks the multidrug resistance glycoprotein that is part of the mechanism of resistance to naturally occurring (non-synthetic) chemotherapy agents [28]. To establish whether this desirable effect is clinically significant, trials have been conducted in tumor-bearing dogs that suggest the use of tamoxifen and similar agents may be effective in countering multidrug resistance to chemotheraputic agents [101, 102]. However, tamoxifen may interfere with the activation of other chemotherapeutic agents such as cyclophosphamide and ifosfamide through the inhibition of the mixed function oxidases.

Metabolism Inhibitors

Inhibitors of tamoxifen metabolism include antiretroviral protease inhibitors, cyclosporine, delavirdine, efavirenez, erythromycin, imatinib, nifedipine, STI-571 and diltiazem: These inhibit metabolism of tamoxifen by inhibiting the cytochrome P-450 3A4 isozyme.

Metabolism Inducers

Carbamazepine, barbiturates, bexarotene, bosentan, ethosuximide, fosphenytoin, nevirapine, phenytoin, and troglitazone: These induce the metabolism of tamoxifen by stimulating the cytochrome P-450 3A4 isozyme.

Benzodiazepines

These induce or compete with tamoxifen metabolism.

Estrogens and Oral Contraceptives

These are pharmacological opposites to tamoxifen

Bromocriptine

This will increase serum concentrations of tamoxifen and desmethyl tamoxifen.

Rifabutin, Rifampin, and Rifapentine

Reduce the half-life and maximum concentration of tamoxifen in the body. This could reduce tamoxifen's effectiveness.

Soy Isoflavones

Compete with tamoxifen at the estrogen receptor.

Melatonin

Enhances tamoxifen's effects.

Phytoestrogen Compounds

Phytoestrogen compounds [i.e., Black Cohosh (*Cimicifuga racemosa*)] may potentiate or interfere with tamoxifen's actions at the estrogen receptor.

Aromatase Inhibitors

Inhibitors of the aromatase enzyme system block the conversion of androgens to estrogens. The growth of many breast cancers is estrogen receptor mediated and, thus, can be stimulated by estrogen. In postmenopausal women, the principal source of circulating estrogen (primarily estradiol) is conversion of adrenally generated androstenedione to estrone by aromatase in peripheral tissues, such as

adipose tissue, with further conversion of estrone to estradiol. By blocking estrogen production, estrogen-sensitive tumors can be reduced in size and their progression delayed in some women. This class of drugs are permitted by the NCAA, but banned by the IOC and USOC [6, 23]. Furthermore, use of aromatase inhibitors in men is forbidden because it would potentially present an unfair advantage by reducing levels of estrogen and subsequently prolonging testosterone bioavailability. One example of the aromatase inhibitor activity in boys is the delaying of epiphyseal fusion, thereby promoting an increase in height. However, more studies are required to fully establish the indirect anabolic nature of aromatase inhibitors as a group. Nevertheless, although there is not a large pool of information concerning the use of aromatase inhibitors as doping agents, the potential for their abuse as part of a current or future anabolic cocktail is great [28, 103].

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

This class of drugs is steroidal and nonsteroidal inhibitors of the aromatase enzyme system. Drugs of this class are used as the first-line treatment of locally advanced metastatic breast cancer (hormone receptor positive or hormone receptor unknown) in postmenopausal women. Aromatase inhibitors are also used for treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen treatment.

Anastrozole

Anastrozole (Arimidex®, AstraZeneca) is orally administered in 1-mg tablet form. Absorption is not affected by food. For first-line therapy, it is taken once per day. Treatment continues until tumor progression is evident. For second-line therapy, Arimidex is administered as a single 1-mg tablet once per day. For patients with mild/moderate hepatic impairment, no dose change is recommended. However, patients should be monitored for side effects. Arimidex has not been studied in patients with severe hepatic impairment. No dose changes are necessary for patients either with renal impairment or in elderly patients [28].

Anastrozole, the parent drug, is the primary inhibitor of aromatase activity. The major circulating metabolite, triazole, has no pharmacological activity. From an oral dose, anastrozole is well absorbed into the systemic circulation and is primarily excreted in the feces (85%) after hepatic metabolism and to a lesser extent in the urine (11%). The terminal elimination half-life is approximately 50 h in postmenopausal women. When taken for 7 days once per day, plasma concentrations approach steady-state levels, which are 3- to 4-fold higher than levels observed after a single dose of Arimidex. Plasma proteins bind 40% of the circulating anastrozole.

When given at a dose of 1 mg or greater daily, estradiol was suppressed to the lower limit of detection (3.7 pg/L). Within 24 h, estradiol was reduced 70%, while after 14 days, an 80% reduction was attained.

Anastrozole was not found to affect levels of cortisol, aldosterone, or thyroid-stimulating hormone. It does not possess direct progestogenic, androgenic, or estrogenic activity, but does affect circulating levels of progesterone, androgens, and estrogens.

Letrozole

Letrozole (Femara®, Novartis) is available in a one 2.5-mg tablet administered orally. For adults and elderly patients, the 2.5-mg tablet is given once per day. Treatment should continue until tumor progression is evident. No adjustment in dosage is required for patients with renal impairment, if their creatinine clearance is greater than or equal to 10 mL/min. In patients with-mild-to moderate hepatic impairment, no dosage change is necessary. However, in patients with severe hepatic impairment, caution should be exercised in dosing [28].

Letrozole is rapidly and completely absorbed from the gastrointestinal tract and unaffected by food. It is metabolized slowly to an inactive metabolite, a glucuronide conjugate, which is excreted renally. The terminal elimination half-life is 2 days. After daily dosing at 2.5 mg, the steady-state plasma level is reached in 2–6 weeks and is 1.5–2 times higher than a single dose administration. Letrozole is weakly protein bound.

In postmenopausal women with advanced breast cancer, daily doses of 0.5–5 mg resulted in estrogen suppression below the limits of detection. There is no impairment of adrenal steroidogenesis, androgens, or thyroid-stimulating hormone.

Exemestane

Exemestane (Aromasin®, Pharmacia and Upjohn Co.) is available in 25-mg tablets. It is used in the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. For adults and the elderly, one 25-mg tablet is taken by mouth once a day after meals. This dosage is the maximum daily dose; higher doses are tolerated, but do not increase estrogen suppression. Treatment is continued until tumor progression is evident. No safe and effective use has been established for children and adolescents. In patients with hepatic impairment or renal impairment, the dosage does not need to be changed.

Exemestane is rapidly absorbed with a T_{max} of 1.2 h and a bioavailability of 42%. It is extensively distributed into tissues. Exemestane is bound to plasma proteins (90%). Maximal aromatase suppression occurs at doses of 10–25 mg. Maximum suppression of circulating estrogens occurs 2–3 days after the start of treatment (25 mg/day by mouth) and persists for 4–5 days [28].

- Exemestane has no effect on synthesis of steroids, androgens, luteinizing hormone, and follicle-stimulating hormone.

Aminoglutethimide

Aminoglutethimide (Cytadren®, Novartis) is an oral adrenal steroid inhibitor. It is used for the suppression of adrenal function in Cushing's syndrome. Although not FDA-labeled, it has been used in the treatment of breast carcinoma and prostate carcinoma. Aminoglutethimide is available as a 250-mg tablet. For treatment of Cushing's syndrome, adults receive an initial dose of 250 mg by mouth twice to three times a day for approximately 2 weeks. The maintenance dose is 250 mg by mouth every 6 h, if necessary, this dose can be increased to a maximum of 2 g per day. In children, safety and efficacy has not been established. For treatment of breast or prostatic cancer, adults receive an initial dose of 250 mg by mouth twice to three times a day for 2 weeks in combination with 40 mg/day of hydrocortisone (10 mg in the morning and at 5 PM, 20 mg at bedtime). The maintenance dose is 250 mg by mouth every 6 h in combination with hydrocortisone (40 mg as described above) [28].

Vorozole

Vorozole (Rivizor®, Johnson & Johnson; Janssen Pharmaceutica) is classified as an aromatase inhibitor. It was studied as an agent for managing advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy. However, the data from phase III clinical testing did not show a significant benefit, so it was withdrawn from consideration. No dosage information is available. Vorozole is roughly 1,000-fold more potent than aminoglutethimide as an aromatase inhibitor.

Mechanism of Action

These aromatase inhibitors act by suppressing production of estrogen in the adrenal, peripheral tissues, and in the cancer tissue itself. Anastrozole and letrozole are potent and selective nonsteroidal inhibitors of aromatase. They act by competitively binding to the heme of the cytochrome P450 subunit of the enzyme.

Exemestane is an irreversible, steroidal aromatase inhibitor. Since it is structurally related to androstenedione, it functions as false substrate for aromatase. It is converted into an intermediate that binds irreversibly to the active site of aromatase causing its inactivation, also known as "suicide inhibition" [28].

Aminoglutethimide inhibits the enzymatic conversion of cholesterol to pregnenolone, thereby reducing the synthesis of glucocorticoids, mineralocorticoids, estrogens, and androgens. There is a compensatory increase in secretion of adrenocorticotropic hormone (ACTH) by the pituitary, requiring glucocorticoid administration to maintain the effects of aminoglutethimide. Aminoglutethimide also inhibits estrogen production from androgens in peripheral tissues by blocking the aromatase enzyme.

Metabolism [103, 104]

Anastrozole

Anastrozole is extensively metabolized in the liver and excreted as metabolites. The known metabolites are triazole, a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide of anastrozole itself. The major route of elimination is via the feces, while renal elimination represents a minor fraction.

Letrozole

Letrozole is metabolized to a pharmacologically inactive carbinol metabolite that is excreted renally as a glucuronide conjugate in the urine.

Exemestane

Exemestane is extensively metabolized via oxidation of the methylene group and reduction of the 17-keto group with subsequent formation of many secondary metabolites. The principle isozyme is cytochrome P450 (CYP) 3A4. The metabolites are inactive or inhibit aromatase to a lesser degree than the parent drug. The 17-dihydrometabolite may have androgenic activity.

Aminoglutethimide (AG)

In a study conducted by Alshowaier et al. [105], they determined the pharmacokinetics of both enantiomers (*R-AG and S-AG, dose 500 mg racemic AG, serial plasma and urine samples collected over 48 h*) and their acetyl metabolites (R-AcAG and S-AcAG) in breast cancer patients. Half-lives were similar for both enantiomers, but the plasma concentration (analysis by HPLC/UV detection) of the R enantiomer was 1.5 times higher than the S-AG, and the pharmacokinetic profile for both AG enantiomers followed a one-compartment open model. Of the 500-mg dose, 41% was excreted in the urine as the parent compound (15% R-AG and 26% S-AG) and 5.1% as the acetylated metabolites (2.9% R-AcAG and 2.2% S-AcAG). They also found that the renal clearance of the S-AG was 2.3-fold greater than the R enantiomer [105]. However, the R-AG enantiomer was found to be significantly more potent than S-AG. The investigators concluded that the primary factor contributing to the potency of racemic AG was primarily due to the R enantiomer rather than its pharmacokinetic differences.

Vorozole

Vorozole, a triazol derivative, is a new third-generation aromatase inhibitor. Animal studies conducted by Lidstrom et al. [103] in rhesus monkeys showed that the

biodistribution of radiolabeled vorozole [(N-methyl-11 C) Vorozole] was high in the liver and reached a constant level (20%) of the injected dose after 10 min. Additionally, labeled vorozole showed high specific binding to aromatase-rich tissue, while binding to other tissues was lower and less specific. The dissociation constant (Kd) for vorozole was 17 nM [103].

In studies conducted by Gross [106] using an in vitro model for cytochrome p450 aromatase, it was shown that the IC_{50} against aromatase was 0.44 nM (cultured rat ovarian granulose cells) and 1.38 nM (human placental aromatase). Vorozole was shown to be selective for aromatase and did not affect other cytochrome P450-dependent reactions. Furthermore, vorozole did not exhibit any agonistic or antagonistic activity toward steroid (estrogen, progestin, androgen, or glucocorticoid) receptors.

Treatment with vorozole produced a dose-dependent decrease in aromatase activity and circulating levels of estrogens. Furthermore, tissue levels of estrone and estradiol decreased by 64% and 80%, respectively. Clearance values of vorozole were constant in all age groups up to 50 years. In age groups greater than 50 years, clearance rates decreased at a rate of 0.047 l/h/year. Following a single dose, clearance values were lower in breast cancer patients (4.8 l/h) than in healthy male and female volunteers (8.6 l/h). Additionally, drug clearance was independent of demographic variables related to body size (total body weight, body surface area, lean body mass), whereas the apparent distributional flow (Q) and central volumes of distribution (Vc) were proportional to the total body weight (0.17 l/h/kg and 0.43 l/kg, respectively). The peripheral volume of distribution (Vp) was found also found to be proportional to total body weight and was higher in women than in men (0.64 and 0.40 l/kg, respectively). They found that neither race nor duration of therapy (0.5–28 months) was a factor with respect to drug effect. They concluded that although there was a relatively high degree of residual interpatient variability in vorozole clearance, it was unlikely that age was of any clinical significance [106].

Toxicology: Contraindications and Adverse Reactions [28]

Contraindications

Anastrozole

Anastrozole is to be used with caution in patients with hepatic cirrhosis or mild-to-moderate hepatic impairment. It has not been tested in patients with severe hepatic impairment. Anastrozole is contraindicated in premenopausal females and in patients who are pregnant or breast-feeding. It causes pregnancy loss and fetal harm, but is not teratogenic. Also, it may be excreted into the breast milk.

Letrozole

Letrozole is contraindicated in patients hypersensitive to letrozole or its recipients. Letrozole may cause fetal harm when administered to pregnant women. It is embryotoxic and fetotoxic and may be teratogenic. Letrozole should not be administered to women who are breast-feeding as it may be excreted into breast milk.

Exemestane

Exemestane should not be given to premenopausal females and in patients who are pregnant or breast-feeding. In animal studies, exemestane caused fetal abnormalities and death in fetuses as well as causing other complications in the breast milk. The safety and efficacy of exemestane in children have not been established.

Aminoglutethimide

In patients under stress (i.e., surgery, trauma or acute illness), beaware of the possibility of cortical hypofunction.

Vorozole

Contraindications are unclear.

Adverse Reactions [28]

The following adverse reactions have been reporte.

Anastrozole

The major adverse effects were hot flashes, gastrointestinal disturbance (i.e., diarrhea, abdominal pain, constipation, nausea/vomiting, and dry mouth), vaginal bleeding, thromboembolism and nervous effects (i.e., anxiety, confusion, depression, dizziness, headache, hypertonia, insomnia, and paresthesias). Less frequent effects are asthenia, back pain, bone pain, pelvic pain, arthralgia, dyspnea, hypertension, increased cough, pharyngitis, rash (unspecified), vasodilation, and edema.

Letrozole

The most frequent adverse reactions are bone pain, back pain, hot flashes, nausea, arthralgia, and dyspnea. Other less frequent effects were peripheral thromboembolic

events (i.e., venous thrombosis, thromboplebitis, portal vein thrombosis, and pulmonary embolism), cardiovascular events (i.e., angina, myocardial infarction, myocardial ischemia, and coronary heart disease), and cerebrovascular events (i.e., transient ischemic attacks, thrombotic, or hemorrhagic strokes).

Exemestane

The most common adverse effects include hot flashes, fatigue, pain (unspecified), depression, insomnia, anxiety, dyspnea, dizziness, headache, and weight gain. Common gastrointestinal effects include nausea/vomiting, abdominal pain, anorexia, constipation, and diarrhea. Less frequent adverse effects include arthralgia, alopecia, confusion, dyspepsia, respiratory infections, and urinary tract infections.

Aminoglutethimide

Adverse reactions include drowsiness, morbilliform skin rash, nausea/vomiting, anorexia, adrenal insufficiency, hypothyroidism, masculinization, hirsutism, headache, dizziness, hypotension, pruritus, myalgia, and fever.

Vorozole

Adverse reactions are unclear.

Mechanisms of Interactions

The following classes of drug may interact with aromatase inhibitors when administered concurrently [28].

Estrogen-Containing Products

Estrogen-containing products (including oral contraceptives, androstenedione, prasterone, dehydroepiandrosterone): These products will interfere with the pharmacological actions of aromatase inhibitors.

Inducers of Cytochrome P450 3A4 and Hepatic Microsomal Inducers

Cytochrome P450 3A4 inducers will cause a decrease in plasma levels of exemestane, while oral anticoagulants, theophylline, digitoxin, medroxyprogesterone result in

decreased pharmacologic effects due to increased hepatic microsomal enzymes by aminoglutethimide.

Dexamethasone

Aminoglutethimide accelerates its metabolism.

Warfarin

Aminoglutethimide diminishes its effects.

Ethanol

It can potentiate the effects of aminoglutethimide.

Erythropoietin

Erythropoietin-Stimulating Agents (ESAs) is the generic term used for drugs that stimulate red blood cell production, resulting in a greater oxygen-carrying capacity. It is the hemoglobin contained in the red blood cells (RBC) that is responsible for binding the oxygen, and it is the hemoglobin-bound oxygen that plays a critical role in athletic performance, and agents that enhance oxygen delivery to tissues increase aerobic power [107]. These drugs were approved in the late 1980s or early 1990s and consisted of recombinant human erythropoietins, which are also referred to as EPOs, rhEPOs or epoetins. In general, ESAs are short-acting drugs (usually given thrice weekly) and are used to treat anemia, while a longer-acting form darbepoetin alfa (an NESP, i.e. Novel Erythropoietin-Stimulating Protein) is given in weekly doses [108, 109].

Erythropoietin (EPO) is a glycoprotein hormone/cytokine that is produced by the peritubular capillary endothelial cells in the kidney. EPO production is stimulated by low blood oxygen tension where it in turn stimulates red blood cell production (erythropoiesis) in the bone marrow. In addition to stimulating erythrocyte production, EPO is also involved in the wound healing process [110] and responding to neuronal injury in the brain [111]. Recombinant isoforms of erythropoietin, epoetin alfa and darbepoetin alfa, have been developed, with FDA approval, for treatment of anemia in zidovudine-treated HIV patients, chronic renal failure patients, and in patients receiving cancer chemotherapy. Furthermore, EPO isoforms have been FDA approved to reduce the need for allogeneic blood transfusions in surgery patients.

Endogenous and recombinant isoforms of EPO have been shown to have different glycosylation patterns [112–114], thereby providing a means by which to potentially

identify the illicit use of EPO isoforms by athletes. Because of the ability of EPO to induce erythropoiesis, EPO has been used as a doping agent in endurance sports. These events include cycling, rowing, distance running, cross-country skiing, biathlon, and triathlons. The 2002 Winter Olympic Games in Salt Lake City marks the first time that an isoform of EPO (darbepoetin alfa) was identified in blood and urine samples of the competing athletes [115]. Since then, epoetin alfa and other isoforms were banned drugs by WADA, the NCAA, IOC, and USOC.

The assay for detecting EPO isoforms in concentrated urine is based on a "double-blotting" technique specially designed to overcome problems associated with non-specific binding of secondary antibodies in immunoblotting. It had been previously observed that using IB protocols in testing for EPO isoforms resulted in strong non-specific binding of secondary antibodies to urinary proteins. However, by using the double-blotting technique, the risk of nonspecific binding of the secondary antibodies to urinary proteins is eliminated [116]. However, since 2006, considerable debate has arisen regarding the validity of the adopted WADA testing procedures for EPO after post-exercise sampling of urine [114, 117]. It has been suggested that the adopted monoclonal anti-EPO antibodies are not monospecific in the protein-rich urine [114, 117]. Obviously, further testing and validation procedures will need to be conducted to resolve this issue.

Pharmacology and Kinetics

Drug Usage: Preparations and Routes of Administration

Epoetin Alfa (Epogen®, Procrit®; Procrit, Ortho Biotech)

Epoetin alfa is a recombinant form of the renal hormone erythropoietin, produced by Chinese hamster ovarian cells with the erythropoietin gene inserted. Native erythropoietin is a glycosylated protein with a molecular weight of about 36,000 Da. The recombinant form is biologically and immunologically indistinguishable from the native form with a molecular weight of 30,400 Da. Epoetin alfa is available as an injectable in solutions of 2,000, 3,000, 4,000, 10,000, 20,000, and 40,000 Units/mL. For the treatment of anemia in patients with chronic renal failure (both those on dialysis and those dialysis-free): In adults and adolescents over 16 years of age, the initial dose is 50–100 Units/kg given either intravenously (IV) or subcutaneously (SC) three times per week. After 2 weeks of therapy, the hematocrit should rise more than four points. If the hematocrit does not increase by 5–6 points after 8 weeks, then the dose needs to be increased. Clinically significant changes in hematocrit may take 2–6 weeks to occur. Dosage changes should not be made more frequently than once per month. The dosage must be individualized to maintain the hematocrit within the suggested target range (30–36%). If after a dosage adjustment the hematocrit does not improve, iron stores must be reevaluated. The median maintenance dose is 75 Units/kg IV/SC three times per week (range: 12.5–525 Units/kg).

In adult chronic renal failure patients not on dialysis, divided doses of 75–150 Units/kg/week are given by IV/SC [28, 83].

In adolescents younger than 16 years old, children and infants with more than 1 month on dialysis, the initial dosage is 50 Units/kg given IV/SC three times per week. For pediatric hemodialysis patients, the median maintenance dose was 167 Units/kg/week (range: 49–447 Units/kg/week). For peritoneal dialysis patients, the median maintenance dose was 76 Units/kg/week (range: 24–323 Units/kg/week).

In adolescents younger than 16 years old, children and infants with more than 1 month not on dialysis, 50–250 Units/kg IV/SC three times per week. The maintenance dosage must be individualized to keep the hematocrit within the suggested target range (30–36%).

- *For the treatment of zidovudine-induced anemia in HIV-infected patients* (with erythropoietin levels less than 500 mUnits/mL who receive zidovudine at a dose of less than or equal to 4,200 mg/week): For adults, an initial dose of 100 Units/kg IV/SC is given three times per week. Hematocrit should be monitored weekly during the first 8 weeks. The dose may be increased by 50–100 Units/kg, up to a maximum of 300 Units/kg, if the response is poor after 8 weeks. Every 4–8 weeks, the hematocrit should be evaluated and the dose adjusted accordingly. If a patient at the maximum dose does not respond, then higher doses will probably not be effective. Once the desired hematocrit (30–36%) is obtained, the dose should be adjusted to maintain this level.

  For adolescents, children, and infants 8 months old or older (not FDA approved), a dose of 50–400 Units/kg IV/SC 2–3 times per week should be given [28, 83].
- *For the treatment of anemia in patients with non-myeloid malignancies* [where the anemia is due to at least 2 months of concomitantly administered chemotherapy (erythropoietin levels above 200 mUnits/mL)]: In adults, an initial dose of 150 Units/kg subcutaneously three times per week. The dosage may be increased to 300 Units/kg three times per week if the response is poor. If they still respond poorly at this maximum dose, it is unlikely that they will respond to higher doses. The dose should be adjusted to maintain a hematocrit of 30–36%. For adolescents, children, and infants older than 6 months (not FDA approved), dosages of 25–300 Units/kg IV/SC three to seven times per week can be given.
- *To reduce the need for allogenic blood transfusions in anemic patients (hemoglobin levels between 10 and 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery*: 10 days before surgery, on the day of surgery, and for 4 days after surgery, adults are given a dosage of 300 IU/kg/day subcutaneously. An alternative to this regimen is 600 IU/kg subcutaneously once weekly, 21, 14, and 7 days before surgery plus one dose on the day of surgery. During this therapy, all patients should receive adequate iron supplementation. Please note that this therapy is for patients at high risk for perioperative transfusions where significant, blood loss is anticipated, and not for anemic patients who are willing to donate their blood.
- *For the treatment of anemia of prematurity (not FDA approved) combined with iron supplementation*: In premature neonates, a dosage of 25–100 Units/kg

subcutaneously three times per week is given. Alternative regimens include 100 Units/kg SC 5 times per week or 200 Units/kg SC every other day for 10 days.

- *For the treatment of anemia associated with myelodysplastic syndrome (MDS) (not FDA approved):* In *adults*, a dosage of 150–300 mL/kg subcutaneously three times per week is given.
- *For the treatment of orthostatic hypotension (not FDA approved) associated with primary autonomic failure:* For adults, a dosage of 25–50 U/kg subcutaneously three times per week was given. For all of the above treatments, patients with either hepatic or renal impairments did not appear to require an adjustment of the dosages.

Epoetin alfa is administered by intravenous or subcutaneous injection. Peak plasma concentrations occur between 5 h and 24 h after subcutaneous injection; this route gives a more sustained response. The circulating half-life is 4–13 h with detectable levels maintained for at least 24 h. The intravenous route results in a rapid rise in plasma concentration. Between 50 mL/kg and 300 mL/kg, given three times per week, there is a dose-dependent response; above 300 mL/kg, there is no significant increase in response. The pharmacokinetics profile of epoetin alfa in children and adolescents appears to be similar to that of adults.

Darbepoetin Alfa

Darbepoetin alfa is a second-generation recombinant form of the renal hormone erythropoietin, produced by Chinese hamster ovarian cells with the erythropoietin gene inserted. The recombinant form is biologically and immunologically indistinguishable from the native form with a molecular weight of 30,400 Da.

Darbepoetin alfa is available as an injectable in solutions of 25, 40, 60, and 200 μg/mL [28, 83].

- *For the treatment of anemia in patients wi th chronic renal failure (both on dialysis and dialysis-free) who are not currently receiving epoetin alfa:* In *adults*, an initial dose of 0.45 μg/kg IV/SC once per week. The dose must be adjusted to obtain and maintain the desired effect. In hemodialysis patients, the median maintenance dose is 0.41 μg/kg SC/IV once weekly (range: 0.26–0.65 μg/kg once weekly).
- *For anemia in patients with chronic renal failure* (both on dialysis and dialysis-free) who are receiving epoetin alfa at doses of <2,500; 5,000–10,000; and 34,000–89,999 units/week, equivalent doses of darbepoetin would be 6.25, 25, and 100 μg/week.
- *For anemia in patients with non-myeloid malignancies (not FDA approved):* In a study of *adult* anemia patients not receiving chemotherapy, patients responded to doses of 1, 2.25, and 4.5 μg/kg IV/SC once per week for 12 weeks. In a second study, patients received chemotherapy 0.5, 1.5, or 2.25 μg/kg IV/SC once per week.

For all of the above treatments, patients with either hepatic or renal impairments did not appear to require an adjustment of the dosages. Darbepoetin alfa can be

administered either intravenously or subcutaneously. With the subcutaneous route, the response is more sustained and the peak plasma concentrations occur between 24 h and 72 h after administration. The IV route produces a more rapid peak plasma concentration. Dose-dependent responses occur at doses up to 0.45 μg/kg/week. The pharmacokinetic profile of darbepoetin alfa in children and adolescents has not been assessed.

Mechanism of Action

Erythropoietin, a glycoprotein, stimulates the division and differentiation of committed erythroid progenitor cells in the bone marrow to produce red blood cells. Epoetin alfa has the same biological activity as native compound. In adults, the majority of erythropoietin is produced in the kidney and the rest by the liver. During fetal development, the liver is the primary source of erythropoietin, and at birth production is transferred to the kidney. The cells that produced erythropoietin are interstitial cells of the inner cortex that are close to the proximal tubules. As the hematocrit decreases, reducing tissue oxygenation, more cells are recruited to produce erythropoietin. This production can increase by 100- to 1,000-fold. In patients with chronic renal failure, this production is impaired leading to anemia.

Metabolism

The metabolism and elimination of erythropoietin and the two recombinant compounds (epoetin alfa and darbepoetin alfa) are not completely known. The glycosylation of erythropoietin prevents it from being cleared rapidly from the blood. Non-glycosylated compound has a half-life in vivo of a few minutes. It is not removed by hemodialysis. About 10% of the dose appears to be excreted in the urine [28, 83].

Toxicology: Contraindications and Adverse Reactions [28, 83]

Contraindications

Contraindications for epoetin alfa and darbepoetin alfa are identical.

Uncontrolled Hypertension or Allergic Conditions

These therapies should not be used in patients with uncontrolled hypertension, or who are allergic to hamster protein, albumin, or benzyl alcohol. There is an increased risk of thrombotic events (including myocardial infarction, seizures, stroke, or death).

Hemodialysis

In hemodialysis patients, there may be a need for anticoagulation therapy during treatment.

Porphyria

This therapy is contraindicated in patients with porphyria. Patients may develop functional or absolute iron deficiency. It is not indicated in patients with iron-deficiency anemia or anemias due to acute or chronic blood loss. Emphasis on dietary and dialysis requirements is important. Some patients have been reported to develop hyperkalemia.

Breast-Feeding

These therapies are contraindicated for pregnant patients or those who are breast-feeding.

Contraindicated Drug Combinations

Combinations of drugs (i.e., androgens, darbepoetin alfa, epoetin alfa) that stimulate erythropoiesis with epoetin alfa should be avoided.

Interference by the Following Conditions Has Been Reported

Acute or chronic infection or inflammation, aluminum overload, cystic fibrosis, erythrocyte enzyme deficiency, folate deficiency, hematological disease (e.g., thalassemia, refractory anemia, or other myelodysplastic disorder), hyperparathyroidism, hypersplenism, occult blood loss, osteitis fibrosa cystica, or vitamin B12 deficiency.

Adverse Reactions

The following adverse reactions have been reported for both compounds. The adverse effects include: arthralgia, asthenia, bronchospasm, chest pain (unspecified), cough, diarrhea, dizziness, edema, encephalopathy, erythema, fatigue, fever, headache, hypertension, infection, injection site reaction, myalgia, myocardial infarction, nausea/vomiting, paresthesias, phlebitis, pruritus, rash (unspecified), seizures, thromboembolism, thrombosis, urticaria, and weakness.

Mechanisms of Interactions

The following classes of drug may interact with erythropoietin analogs when administered concurrently:

Androgens

Since androgens stimulate erythropoiesis, concurrent administration can increase the patient's response to these therapies, reducing dosage required. This combination of drugs should be avoided if possible.

Darbepoetin Alfa, Epoetin Alfa

The combination of the two erythropoiesis stimulators should be avoided.

Desmopressin

Reduced bleeding time from desmopressin usage results in patients with end-stage renal disease.

Probenicid, Amphotericin B

Inhibit secretion of endogenous erythropoietin.

Iron Supplements

Iron stores in the body must be replete. Inadequate stores will reduce the response to these therapies.

Toxicology: Contraindications [28]

Contraindications

In 2008, the FDA putout advisories recommending the ESAs should not be used in patients with metastatic breast cancer, head and neck cancer, or the treatment of cancers that could potentially be cured. Patients treated with ESAs who have cancer (breast, head and neck, or non-small cell lung cancer, lymphoid malignancies, and

cervical cancer) demonstrated shortened overall survival and/or time to tumor progression. These observations led the FDA to rule that ESAs are contraindicated for use in patients receiving myelosuppressive curative treatment.

Epoetin Alfa

From a trial where epoetin alfa was used in high doses (40,000 units daily for 3 days) for the treatment of ischemic stroke, results indicated higher death rates than placebo control groups (16% versus 9%). Death from intracranial hemorrhage was 4% in the epoetin alfa group and 1% for the placebo group.

ESAs (2008 Report)

For patients suffering from renal failure, the FDA posted warnings of increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence when ESAs are administered to target higher versus lower hemoglobin levels (13.5 versus 11.3 g/dL; 14 versus 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 g/dL to 12 g/dL. The FDA is waiting for additional result to further modify the warning.

Continuous Erythropoietin Receptor Activator (CERA)

CERA (R-744, Mircera) was developed by Hoffman La Roche and is a third-generation ESA intended for use to treat anemia arising from chronic kidney disease, thereby stabilizing hemoglobin content [118]. CERA, which refers to a subclass of drugs, is a continuous erythropoietin receptor activator that is made up of a single methoxy-polyethylene glycol polymer (approximately 30,000 Da). The inclusion of the glycol polymer causes CERA to have a prolonged half-life of approximately 130 h [119]. Physiologically, receptors for erythropoietin have been found throughout the body, including the brain and skeletal muscle [120–124], suggesting that treatment with ESAs (EPO, CERA, etc.) elevates hemoglobin as well as the other globin proteins (myoglobin and neuroglobin). In addition, there would be concomitant increases in transferrin content, antioxidant protection and enhanced levels of neuroprotection. Furthermore, myoglobin levels in skeletal muscle would also be increased significantly [125]. In atrophied skeletal muscle, total protein and myoglobin content decreases [126], thereby reducing muscle strength and endurance [120, 126–128]. However, with elevated myoglobin content because of ESA-usage, muscles would maintain higher oxygen content than would normally be present and thereby the individual would be more resistant to muscle fatigue (i.e., greater endurance) and a significant competitive edge [118–123, 125, 128].

Comparative EPO receptor binding properties of epoetin-beta and CERA were conducted using soluble recombinant EPO receptors. Results from these studies demonstrated that the equilibrium dissociation constants of CERA and epoetin-beta were 140 and 2.9 nmol/L, respectively [122, 123]. Additionally, CERA had approximately a 50- to 100-fold lower affinity for EPO receptor binding sites than that of epoetin-beta [150], potentially through a slower association with the receptor [122, 123]. Thus, it was concluded that the observed differences in receptor binding properties of CERA may account for the continuous stimulation of EPO. Furthermore, the combination of slow systemic clearance and prolonged half-life may account for the monthly administrations [151].

CERA was developed for maintaining hemoglobin levels in patients suffering from chronic kidney disease [118]. Unlike other ESAs, treatment with CERA is on a monthly schedule rather than weekly or biweekly. The drug is currently undergoing phase III testing in Europe.

Human Chorionic Gonadotropin (hCG)

Human chorionic gonadotropin (hCG) is a polypeptide hormone heterodimer that is comprised of a common α-subunit noncovalently bound to a β-subunit. The recombinant form of hCG (r-hCG) is called choriogonadotropin alfa. In females, hCG is normally secreted from the fetal portion of the placenta during pregnancy. Additionally, hCG serves an important function in the male fetus by inducing sexual differentiation by stimulating fetal testosterone synthesis in the testicular leydig cells [127]. In adult humans (both males and females), hCG is also produced in low concentrations by the pituitary [124, 127].

Functionally, hCG-is a gonad stimulating hormone. Pharmacologically, hCG acts similar to luteinizing hormone (LH) and can be used as an LH substitute [124]. In males, hCG has been used to treat cryptorchidism since 1931 and hypogonadism [124]. However, in the 1970s, gonadotropin-releasing hormone (GnRH) analogues became a treatment option [124]. In females, hCG is used in protocols for treating controlled ovarian hyperstimulation for infertility.

In competitive sports, the use of hCG has been banned. It has been reported that hCG has been used by some professional and armature athletes to prevent testicular atrophy resulting from the abuse of anabolic androgenic steroids as well as stimulating testosterone production. Levels of hCG can be measured in urine and serum [129, 130].

Detection and Laboratory Test Interferences

This is a brief overview of analytical approaches to detecting anabolic/androgenic steroids in various biological samples [13].

Biosamples

The presence of androgens can be detected in samples such as whole blood, plasma, and urine. Other matrices (tissues) for analysis of anabolic steroids can include bone, hair, liver, cardiac and skeletal muscles, saliva, and sweat of humans or laboratory animals (rats, mice, etc.).

Urine

Urine provides an ideal matrix for the qualitative and quantitative determination of androgens by providing large volumes and relatively high concentrations of the parent compound and metabolites for analysis. Additionally, early researchers used human male urine to isolate and purify androgen crystals. From these crystals, they were able to eventually identify and characterize individual hormones and their metabolites, as well as establish their androgenic and anabolic properties. Historically, the identity of testosterone, the prototypical anabolic steroid, was first established from crystals isolated from volumes (~15 L) of human male urine. Testosterone was the most potent endogenous anabolic and androgenic steroid known at that time. Subsequent work showed that dihydrotestosterone (DHT), the active form of testosterone in tissue, was actually more potent than testosterone while having the same affinity for the androgen receptor [13].

On a functional level, urinary androgens reflect an incomplete but relevant indication of endocrine secretory activity. However, care must be taken when attempting to interpret urine androgen values since multiple sources for androgenic properties or androgenic/anabolic effects on excretion are involved. Additionally, caution must be used with respect to interpreting the qualitative and quantitative results for urinary androgen metabolites because: (1) active parent molecules are metabolized through multiple pathways, (2) drugs can alter androgen metabolism, and (3) foods and food supplements can alter androgen metabolism. Other problems associated with urinary androgen assays include the time it takes for collecting 24-h urine samples.

The ratio of concentrations for testosterone glucuronide to epitestosterone glucuronide (T/E ratio) in urine is the most frequently used method for establishing testosterone abuse in athletes [131]. Results showing T/E ratios >6 have been considered proof of past abuse of testosterone. However, questions have been raised regarding the validity of using T/E ratios alone as a marker of testosterone abuse in urine doping analysis since naturally occurring ratios >6 have been reported. Additionally, one must consider the question whether great athletes have higher than average testosterone levels, thereby giving rise to these higher T/E ratios. Thus, in light of these problems, the possibility of reporting false-positives becomes a great concern. To address this problem, alternative methods for determining testosterone abuse have been addressed including urinary testosterone/luteinizing hormone ratio, hair analysis, HPLC/MS, and GC/combustion-isotope-ratio mass spectrometry.

In studies conducted by Kjeld et al. [132, 133], they showed that urinary unconjugated testosterone, DHT, estradiol, and progesterone levels changed under various

storage conditions (temperature, presence of enzyme inhibitors, bacteriostatic agents, and various salts). Unconjugated testosterone levels did not change when samples were stored at temperatures of −20°C. When samples were stored at 4°C, they remained stable for up to 5 days. However, when samples were stored at 18°C, testosterone levels were found to increase by an average of 100% over 2–3 days, while DHT levels increased by approximately 200%. When the samples were stored at 37°C, the rate of increase for testosterone was 2–3 times faster than when stored at 18°C. In addition, the rate of increase of unconjugated androgens can be altered by the addition of enzyme inhibitors, bacteriostatic agents, and various salts. Changes in sample pH were found to impact levels of unconjugated androgens. At pH 8.6, there was no significant effect, but at pH 2, levels of free androgens were found to increase by approximately fourfold over a period of 10 min. Similar results were observed for estradiol and progesterone. Thus, storing urine samples at −20°C will help preserve their profile with respect to free to glucuronidated doping agents as well as the quality of the parent drug. This is true for the androgens, estrogens, as well as other drugs (β-adrenoceptor agonists/antagonists, cocaine, amphetamines, etc.). *However, when analyzing urine samples for the presence of doping agents, the total drug concentration is of primary interest.* Nevertheless, proper storage will help ensure high-quality samples that may be used for multiple testing if the occasion arises. Furthermore, if a sample is frequently used, smaller aliquots should taken and stored to prevent freeze–thaw damage. Samples should never be refrozen following thawing. Thus, when in doubt about the stability of the compound to be analyzed, the specimen should be frozen at −20°C or less. In addition, if the specimen is a protein or peptide hormone, the specimen should be frozen and stored at −70°C or less. It is important to note that the specimens should be stored at a constant temperature; therefore, self-defrosting freezers should be avoided if possible. This is especially true for protein hormones and growth factors [13].

Independent of the type of analysis, another problem frequently encountered with urine samples is bacterial contamination. Bacterial growth in urine can be prevented by the addition of a general bacterial static agent such as 1% boric acid, chloroform, or toluene.

Whole Blood, Plasma, and Saliva

The collection of urine over a 24-h period can be inconvenient for the individual and often problems with renal function may contribute to erroneous results. In contrast, the collection of plasma, its transport, and analysis are much more convenient for all concerned [13].

In general, it is accepted that analysis of biological samples constitutes an ideal and objective means for establishing the use of doping agents (or other drugs). Analyses are usually preformed on urine samples by immunoassay screens, followed by GC/MS conformation of positive specimens. However, with the advent of more sensitive techniques (e.g., ELSIA), analysis of plasma for specific drugs is replacing many of the urine assays. Additionally, plasma (or serum) is ideal for pharmacokinetic

studies where repeated sampling is required over a short period of time. An example of sampling times for bioavailability would be: 15 min before bolus IV dose of drug (time 0), followed by post-dosage times of 5, 10, 15, 30 min, 1, 2, 3, …, out to 72 h or greater. However, it should be noted that plasma sampling is representative of only that time in which it was drawn due to the rapid fluctuations that occur in hormone levels or changes in the bioavailability of doping agents following irregular dosing with various anabolic cocktails.

The use of other biological specimens such as saliva and hair (see Sect. 11.6.1.3) for the analysis of anabolic steroids and other drugs of abuse has been met with varying degrees of success. From the work conducted by Rantonen et al. [134], they showed that a good correlation existed between plasma and saliva cortisol ($r = 0.47$, $p < 0.001$) and human growth hormone (hGH, $r = 0.59$, $p < 0.001$) levels in pediatric cases. However, they also found that hGH levels in the saliva was approximately 1,000-fold less than that observed in the plasma [134].

Earlier studies conducted by Vapaatalo et al. [135] found that when using TLC for screening saliva in test subjects for the drugs amphepramone, amphetamine, ephedrine and prolintane, they were only able to detect ephedrine on a consistent basis [135]. In contrast, urine analysis showed that all drugs and/or their metabolites were present in the urine. Thus, they concluded that screening the saliva for doping agents was inferior to urine. However, in years since Vapaatalo's study, technological advances in instruments and analytical techniques allowed for screening the saliva for drugs of abuse, therapeutic drugs, and nonpeptide hormones. Hofman [136] showed that there was generally a good correlation existing between plasma and saliva drug levels. However, because of diurnal and monthly variations in steroid hormone levels, multiple samples should be collected (morning and evening) to give meaningful results. In these situations, the collection of saliva is considerably more convenient than with plasma.

Saliva can be collected by having the individual spit into a tube or absorption onto a cotton ball. It should be noted, however, that the collection of saliva on cotton balls has been shown to cause significant increases in the levels of DHEA, testosterone, and progesterone. In addition, since most of the analytes are stable at ambient temperatures, samples can be shipped without refrigeration. However, since these specimens are not sterile and are subject to degradation over time by bacteria, samples can be sterile filtered to exclude most of the bacterial contamination.

It has been shown that salivary levels of steroid hormones and other compounds that are protein bound in the serum reflect the unbound and active concentration of those hormones/drugs. Furthermore, Hofman concluded that the use of saliva is an excellent source for the detection and monitoring of hormone and drug levels that offers several advantages (e.g., less expensive and noninvasive) over that of serum testing.

Hair

As of yet, hair analysis is not fully recognized by international sporting committees as an acceptable means to confirm doping abuse. However, analysis of human or

animal hair has been shown by several investigators as being a readily available sample source that complement the analysis of more traditional sample types (e.g., urine, serum). The testing of hair samples for the presence of anabolic substances was shown to be comparable to results from urine samples. Additionally, hair analysis might be useful for retesting samples for verification abuse or to distinguish between exogenous abuses from other forms of unintentional exposure to banned substances. Unintentional exposure to banned substances, as a result of taking legal food supplements (contain banned substances not stated on the label), would be suspected when urine samples were positive and hair samples were negative. In contrast, chronic abuse would be suspected when both urine and hair samples are positive.

Urine drug testing has been used to monitor compliance with the banned substance rules introduced in the mid-1970s by sports authorities. Urine is tested prior to competition, but prolonged periods (latency period) before analysis can defeat these tests. Hair analysis, on the other hand, provides a less time-sensitive complement to the more traditional urine analysis. In studies conducted by Gaillard et al. [137], they developed methods for analyzing hair samples for amphetamines, anabolic steroids and their esters, and corticosteroids.

Hair samples of 50 and 100 mg, respectively, were used to analyze for amphetamines and anabolic steroids (as well as anabolic steroid esters). The procedure for analysis of amphetamines involved an initial digestion with 1 N NaOH, extracted by ethyl acetate, derivatized by TFA, and subsequently analyzed by GC equipped with positive chemical-ionization mass spectrometry. Analysis of anabolic steroids and their esters was somewhat similar to that of the amphetamines. A modification of the amphetamine procedure was used to analyze for anabolic steroids and their esters.

For the analysis of anabolic steroids and their esters, samples were digested in 1N NaOH and highly purified using solid phase extraction on aminopropyl and silica cartridges. Prior to injection, samples were derivatized with MSTFA. Analysis was performed on a GC coupled to a triple quadrupole mass spectrometer.

Results from these tests showed that amphetamines were detected more frequently in the hair (10 out of 19 analyses) than in the urine (6 out of 30 analyses). Furthermore, the anabolic steroids nandrolone and testosterone undecanoate were each found once in hair (2 out of 25 analyses) while none were found in urine (0 out of 30 analyses).

In studies conducted by Dumestre-Toulet et al. [138], they obtained urine and hair samples from several internationally renowned bodybuilders (who were allegedly trafficking doping agents in France). Samples were analyzed by GC/MS for anabolic compounds that included steroids and metabolites, β_2-adenergic agonists *(salbutamol [albuterol], clenbuterol),* ephedrine, and other doping agents. They detected various doping agents in the urine that included several androgens and sympathomimetics. The androgens found were norandrosterone (seven subjects, 4.7–100.7 ng/mL), norethiocholanolone (six subjects, 0.9–161.8 ng/mL), stanozolol (four subjects, 1–25.8 ng/mL), methenolone (four subjects, 2.5–29.7 ng/mL), testosterone (seven subjects, 3–59.6 ng/mL), epitestosterone (seven subjects, 1–20.4 ng/mL). The testosterone/epitestosterone ratio was found to be greater than six (four subjects, 18.5–59.6). The sympathomimetics found were ephedrine (two subjects, 29 and 36 ng/mL) and clenbuterol (three subjects, 0.2–0.3 ng/mL).

Table 15.11 Period of detection for selected doping agents

Agent	Sample type	Routine testing period of detection	Zero-tolerance detection period
Amphetamines	Urine	~3 days	~5 days
	Hair	N/A	~90 days[a]
Androgens-Oral	Urine	N/A	~21 days[a]
Androgens-Injection	Urine	N/A	~9 months
Cocaine/Crack	Urine	~3 days	~5 days
	Hair	Up to days post use	~90 days[a]

[a]Time factor depending on hair length
Aegis Sciences Corporation; http://a1.solidweb.com/ps/AegisLab…e/frm±About_Site_Page

However, analysis of hair samples showed a similar but somewhat different pattern of doping agents that included the androgens nandrolone (three subjects, 1–7.5 pg/mg), stanozolol (four subjects, 2–84 pg/mg), methenolone (two subjects, 17 and 34 ng/ml), testosterone enanthate (five subjects, 0.6–18.8 ng/mg), and testosterone cypionate (teo subjects, 3.3–4.8 ng/mg). In addition to the androgens, they also found ephedrine (two subjects, 0.67 and 10.70 ng/mg), salbutamol (three subjects, 15–31 pg/mg), and clenbuterol (six subjects, 15–122 pg/mg) in the hair samples. Thus, from these results, the investigators concluded that by analyzing both urine and hair samples, they were able to confirm the usage and repetitive exposure to doping substances. Furthermore, by analyzing hair samples concomitant with urinalysis, they were able to reveal substances that were not detected by urine screens alone. The period of detection for different doping agents varies depending on the sample used and drug being analyzed (Table 15.11).

Analytical Approaches

In a study conducted by Kintz et al. [139], they analyzed urine and hair from two male bodybuilders by GC/MS (electron impact) for steroids abuse. The samples were positive for nandrolone, stanozolol, and testosterone, and their respective metabolites, thereby suggesting that hair analysis was a useful supplementary test for urine drug testing in athletes by the International Olympic Committee. Steroid concentrations in the hair were: nandrolone (196 and 260 pg/mg hair), stanozolol (135 and 156 pg/mg hair), and testosterone (46 and 71 pg/mg hair). For purposes of analysis, the hair samples were decontaminated using methylene chloride and approximately 100 mg was hydrolyzed by 1 N sodium hydroxide (15 min @ 95°C) in the presence of deuterated internal standards. The drugs were extracted by ethyl acetate and subsequently silylinated. In another study conducted by Kintz (Kintz et al., 2002) using gas chromatography-tandem mass spectrometry, they showed that methenolone could be detected in hair samples (100 mg each) at concentrations of 7.3 and 8.8 pg/mg following a decontamination step using methylene chloride [149].

Clenbuterol Analyses

Analysis of tissue and mean 24-h plasma concentrations of clenbuterol were determined by Enzyme Immunoassay (EIA) and confirmed by GC/MS. Comparative analytical studies of both methods were conducted previously and the limits of detection (LOD), limits of quantitation (LOQ), and other parameters for both methods have been published. Both quantitation methods were equivalent, and the standard deviations of clenbuterol concentrations for standards and samples were less than 5%. Accordingly, *rac*-clenbuterol concentrations were determined by EIA [140].

Enzyme Immunoassay (EIA)

Analysis by EIA requires only 20 μL of plasma or tissue homogenate volume and has sensitivity to 10 pg/mL clenbuterol. Briefly, wells of a 96-well microtiter tray are incubated with the antibody provided with the kit (1:11 dilution) for 30 min and washed thrice with distilled water. The wells are subsequently dried and either 20 μL of standards (0, 10, 25, 50, 100, 300, 900, 2,700, and 8,100 pg/mL clenbuterol) or samples are added in triplicate. To the samples and standards, 100 μL of conjugate (1:11 dilution) is added and then incubated for 15 min at room temperature. The contents are subsequently discarded, and wells are washed thrice with distilled water (250 μL), followed by the addition of 100 μL substrate/chromogen mix. Trays are incubated at room temperature in the dark for another 15 min, and the reactions terminated by the addition of 100 μL stopping reagent (sulfuric acid solution provided with the kit). Absorbances are read within 1 h at 450 nm on a microtiter plate reader.

Extraction and Derivatization of Clenbuterol for Gas Chromatographic-Mass Spectrometric (GC/MS) Assay

The extraction of clenbuterol from tissue homogenates or plasma is described previously by Abukhalaf et al. [140]. Briefly, 1.0 mL of clenbuterol standards (5, 50, 100 and 200 ng/mL) or samples were loaded into tubes and 25 μL of 2 μg/mL brombuterol (internal standard) was added to a final concentration of 50 ng/mL. Subsequently, 4 mL of 100 mM potassium phosphate buffer (pH 6.0) was added and the buffered extracts were loaded onto pre-equilibrated solid phase silica extraction columns. The columns were then sequentially rinsed with potassium phosphate buffer (pH 6.0), 0.1 N glacial acetic acid, and methanol, respectively. Columns were aspirated for at least 5 min to ensure that the column bed was completely dry and all column washes were discarded. Clenbuterol and brombuterol were eluted from the column with methylene chloride-isopropyl alcohol-ammonium hydroxide (78:20:2 v/v/v). The addition of fresh elution solvent (methylene chloride) to the residue ensured complete removal of water when evaporated to dryness. To the dried clenbuterol samples and standards, 50 μL of freshly prepared trimethylboroxine derivatizing

Table 15.12 Blood steroid levels in male subjects

	Peripheral venous levels		Spermatic venous levels	
Steroid	Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)
Testosterone	3.84	0.63–10.64	255.10	2.85–619.10
Dihydrotestosterone	0.19	0.07–0.28	3.74	0.04–9.71
Androsterone	0.27	0.12–0.47	0.97	0.20–2.15
Androstenedione	1.01	0.26–2.65	11.87	0.97–30.18
17α-Hydroxyprogesterone	1.04	0.48–2.20	37.33	1.68–141.00
Progesterone	0.31	0.02–0.57	10.17	1.51–33.24
Pregnenolone	1.34	0.29–2.39	10.97	0.83–30.10

Source: Hammond et al. [141]

solution (8 μmol trimethylboroxine/mL in dry ethyl acetate) was added, and then incubated for 20 min at 60°C [140].

Tubes containing derivatized clenbuterol and brombuterol were allowed to cool to room temperature, and transferred to auto-sample vials (2 μL injection volume). Analysis was performed on an Agilent 5,890 gas chromatograph equipped with a 5,972 mass selective detector (MSD). The analytes were resolved with an HP 1 MS capillary column cross-linked with 1% phenylmethylsilicone (15 m × 0.25 mm with 0.25 μm film thickness). Inlet pressure programming mode was used to enhance sensitivity. The electron multiplier was operated at 200 V above the tune value. The carrier gas used was ultrahigh purity helium (99.99%) and splitless injection was used. The splitless valve remained closed for 1 min and the initial inlet pressure was 25 psi. The column head pressure was held for 0.5 min, then decreased to 16 psi at a rate of 25 psi/min, and finally maintained at this pressure for the duration of the analysis. This resulted in a flow rate of 1.1 mL/min during the run. The injector temperature was 280°C. The initial oven temperature was 150°C and was held for 1 min; the temperature was programmed to increase at 15°C/min to 215°C, and then increased to 300°C at 35°C/min, and held there for 2 min. The total run time was 9.76 min. The transfer line temperature was held at 280°C. Selected ion monitoring was used to enhance the assay sensitivity. Under these conditions, brombuterol and clenbuterol yielded abundant diagnostic ions with high m/z values.

Hammond et al. [141] determined normal circulating levels of several endogenous steroids in venous blood from human male subjects. Hormone levels were determined by employing specific radioimmunoassays following fractionation of the steroids on microcolumns (hydroxyalkoxypropyl Sephadex) (Table 15.12).

Involuntary Doping and False-Positives

Currently, the International Olympic Committee (IOC) does not support the use of hair analysis in screening doping cases in athletes. The use of such a technique to augment urine analysis could prove to be important especially in discriminating

cases of involuntary doping from those of chronic usage. For example, cases where hair results are negative for doping agents while urine tests are positive suggest acute exposure (substance introduced involuntarily through food or beverage) rather than chronic. Additionally, in cases where urine samples are positive for doping agents, analysis of plasma/saliva and hair samples could be used to confirm the presence of doping agents, thereby helping to avoid reporting false-positives.

Many athletes use legal, nonprescription nutritional supplements in order to help them in their training programs. However, in the studies conducted by Geyer et al. [51], they showed that some dietary supplements containing Chrysin, *Tribulus terrestris*, and Guarana contained several banned substances not stated on the product label. The Chrysin-containing product contained the androgens norandrostenedione and norandrostenediol, while a *Tribulus terrestris* contained the androgens androstenedione, androstenediol, androstenediol, norandrostenedione and norandrostenediol. Further investigation showed that some Guarana-containing products contained the androgens androstenedione, androstenediol, testosterone, and norandrostenedione. Furthermore, the total amount of androgens varied significantly from capsule to capsule, with concentrations ranging from 0.3 to 5,000 g per capsule. Subsequently, when these dietary supplements were administered to healthy volunteers, all urine samples were found to be positive for norandrosterone, a metabolite of the androgen nandrolone. Geyer et al. [51] further reported that 3–4 h post-dose norandrosterone levels ranged between 4 and 623 ng/mL. Additionally, they reported that a female volunteer increased her testosterone/epitestosterone ratio from 0.6 to 4.2.

Green et al. [52] showed that 11 of 12 over-the-counter (OTC) dietary supplements did not conform to labeling requirements established in 1994 by the Dietary Supplement Health and Education Act. The supplements tested were androstenedione, androstenediol, and 19nor-cogeners (nor4 and 5androstene3,17dione and 19nor4 and 5androstene-3β,17-β-diol). One of the brands tested contained 10 mg of the controlled androgen testosterone, while another brand was 77% higher than the amount stated on the label. Furthermore, of 12 brands tested, 11 contained amounts less than the stated amounts. Thus, results from these two tests showed that the labeling on dietary supplements could not be trusted with respect to the content and/or purity. Furthermore, athletes, sports governing bodies, and the medical community need to know this information because of the potential consequences (health risks, positive urine tests, etc.) that may be encountered. Lists of banned substances can be found on the World Anti-Doping Agency Web site (www.wada-ama.org).

Functional Testing

In addition, functional testing of androgenic or anabolic properties, as well as antiandrogenic activity, can be studied in target tissues (e.g., skeletal muscle, gonadal tissue, tumors, etc.) through whole animal models [13]. Some examples of suitable animal models for studying anabolic and/or androgenic effects are the capon-comb

and castrated rats. Additionally, organ cultures and cell culture systems have been employed in numerous experiments and tests as an aid in characterizing the effects of anabolic/androgenic agents. These approaches are especially helpful when trying to establish or confirm anabolic/androgenic activity to an unknown substance that has been characterized by GC/MS and subsequently isolated and purified by HPLC [140].

An example of an organ culture system is with the fine structure of the rabbit epididymidis. In the absence of androgenic/anabolic steroid hormones, the cells show signs of cellular regression (e.g., cell shrinkage, increased number of autophagic vacuoles, loss of smooth endoplasmic reticulum, and loss stereocilia border), whereas in the presence of the appropriate hormones, the cells retain a more normal appearance. The quality (i.e., potency) of the individual androgens can be determined in this type of culture system by the degree of protection given against cellular regression. For example, the potency of support in maintaining the cells in the epididymidis was: *5α-dihydrotestosterone (DHT) ≥ 3α-androstanediol ≥ testosterone > 3β-androstanediol.*

Cell culture models for establishing androgenic or anabolic effects can include cultured skeletal muscle cells. Changes in cellular proteins such as the creatine kinase mm isozyme (CK_{mm}) and structural proteins (myosin heavy chain Types I and II) reflect the degree of anabolism or catabolism occurring. With the use of imaging systems in conjunction with inverted phase contrast microscopy and powerful imaging software, changes in cell size (e.g., hypertrophy or atrophy) can be determined. Systems such as this can also prove useful in toxicology testing where cell vitality can be addressed with such techniques as analysis for apoptosis, trypan blue dye exclusion, changes in the rate of cell proliferation, as well as changes in total cellular protein content. Another advantage of in vitro testing (organ or cell culture) could be in determining the effects of direct drug interactions on target tissues. However, when doing these kinds of tests, it is extremely important to employ proper positive and negative controls. The negative control is that which contains just the bare minimum to just keep the cells alive (e.g., defined, serum-free medium). On the other hand, positive controls are a modification of the negative controls that contain growth supplements such as hormones, growth factors, etc., necessary to support proper growth. Fetal bovine serum can also be added to support growth, but this may mask the true nature of the substances that are being studied since the serum may contain anabolic hormones that support growth. However, the serum may be used as long as a modified negative control also contains serum. An example of dissection medium used for the isolation of follicular cells from ovaries would be Dulbecco's minimal essential medium (DMEM) supplemented with 25 mmol HEPES/L, 100 IU penicillin/mL, 0.1 ng streptomycin/mL, 50 mg gentamicin/mL, and 10 mg amphoteric in B/mL medium. An example of a medium for supporting growth would be DMEM/Ham's F12 medium buffered with 15 mmol HEPES/L and $NaHCO_3$. The medium is further supplemented with 3 mmol (l)-glutamine/L, 100 IU penicillin/mL, 0.1 ng streptomycin/mL, 2.5 mg transferrin/mL, 4 ng sodium selenite/mL, and 0.1% (w/v) bovine serum albumin (BSA fraction V). Cell viability can be established by using trypan blue exclusion [142].

Laboratory Test Interferences

Anabolic/Androgenic Steroids

Treatment with anabolic/androgenic steroids may alter clinical laboratory test results.

Thyroid Function Tests

Androgens have been found to interfere with thyroid function tests by causing decreases in thyroxine-binding globulin. This interaction results in decreases in serum T-4 levels and increases in resin uptake of T-3 and T-4. When measuring free thyroid hormone levels, no changes were observed and no clinical evidence of thyroid dysfunction was observed.

Lysophosphatidylcholine Interference in Hormone Immunoassays

Lysophosphatidylcholine (LPC) has been shown by Lepage et al. [143] to interfere with the formation of antigen–antibody complex in steroid hormone (aldosterone, cortisol, and progesterone) immunoassays, causing plasma levels to be approximately 30% higher than what is actually present. Potentially, this could be true for the androgens as well. It was also shown that the addition of albumin to the samples reduced LPC interference to 7%, while the addition of cholesterol reduced it by 50%. Conclusions from these tests suggested that the ratio existing between serum albumin and LPC should be taken into account.

Hydroxycorticosteroids

Danazol has been reported by Konishi et al. [144] to interfere with the Porter-Silber method for determining total urinary 17-hydroxycorticosteroids.

β-Adrenoceptor Agonists and Antagonists

Treatment with sympathomimetic agents (β-adrenoceptor agonists or antagonists, amphetamines, cocaine) may alter clinical laboratory test results.

Amphetamines

In general, amphetamines can cause a circadian-like increase in plasma levels of corticosteroids, with levels being highest in the evenings. Additionally, amphetamines can potentially interfere with the analysis of steroids in the urine.

Propranolol

Propranolol can cause elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

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References

1. Lippi G, Franchini M, Guidi GC (2008) Doping in competition or doping in sport? *Br Med Bull*. **86**:95–107.
2. Hallakarva Gunnora "Berserkergang" (1996). Stefan's Florilegium Berserkergang-art. http://www.florilegium.org. Accessed 12 June 2010.
3. Lombardo JA (1990) Anabolic-Androgenic Steroids. In: Anabolic Steroid Abuse, Lin GC and Erinoff L. Eds. *NIDA Research Monograph* **102**:60–73.
4. Times Record News; Wichita Falls, Texas; Mon, June 18, 2001. Speed's long history Amphetamine drugs have caused trouble for decades. Jeff Hall, Times Record News www.trnonline.com/archives/2001archives/06182001/local_news/25530.shtml. Jeff Hall may be contacted at (940)-763-7596 or by e-mail at hallj@wtr.com. Accessed 12 June 2010.
5. Goodman LS and Gilman A (1941) Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 1st ed. McGraw-Hill, New York, 1207–1226.
6. Snyder LL (2005) Hitler's henchmen: The Nazis who shaped the Third Reich. Newton Abbot: David & Charles. 2nd Edition. ISBN: 0715320335 9780715320334.
7. Gibbels E (1989) [Hitler's neurologic disease--differential diagnosis of Parkinson syndrome]. *Fortschr Neurol Psychiatr*. **57**:505–517. [German].
8. http://amphetamines.com/amphetam.html (2010) Amphetamine usage and World War II; Adolf Hitler and amphetamines http://amphetamines.com/adolf-hitler.html. Accessed 10 June 2010.
9. Wanjek B, Rosendahl J, Strauss B, Gabriel HH (2007) Doping, drugs and drug abuse among adolescents in the State of Thuringia (Germany): prevalence, knowledge and attitudes. *Int J Sports Med*. **28**:346–353.
10. IOC (2004): http://multimedia.olympic.org/pdf/en_report_817.pdf; http://multimedia.olympic.org/pdf/en_report_1316.pdf and World Anti-Doping Agency (WADA) http://www.wada-ama.org/en/prohibitedlist.ch2. Accessed 10 June 2010.
11. World Anti-Doping Agency (2009). The World Anti-Doping Code. The 2009 Prohibited List. http://www.wada-ama.org/rtecontent/document/2009_Prohibited_List_ENG_Final_20_Sept_08.pdf. Accessed 10 June 2010.
12. Kochakian CD (1990) History of Anabolic-Androgenic Steroids. In: Anabolic Steroid Abuse, Lin GC and Erinoff L. Eds. *NIDA Research Monograph* **102**:29–59.
13. Burtis CA and Ashwood ER (1994) In: Tietz's Textbook of Clinical Chemistry, 2nd ed. W.B. Saunders Company, Philadelphia, PA.
14. Morrison RT and Boyd RN (1974) Organic Chemistry. Morrison and Boyd 3rd ed. Allyn and Bacon, Inc., Boston.
15. Budavari S, O'Neil MJ, Smith A, Heckelman PE and Kinneary JF (1996) The Merck Index, An encyclopedia of chemicals, drugs, and biologicals. 12th ed. Merck Research Laboratories Division of Merck & CO., Inc, Whitehouse Station, NY.
16. von Deutsch DA, Abukhalaf IK, Aboul-Enein HY, Wineski LE, Oster RA, Paulsen DF, and Potter DE (2000) β-agonist-induced alterations in organ weights and protein content: comparison of racemic clenbuterol and its enantiomers. *Chirality*. **12**:137–148.

17. Mukherjee A, Kirkovsky L, Yao XT, Yates RC, Miller DD, Dalton JT (1996) Enantioselective binding of Casodex to the androgen receptor. *Xenobiotica*. **26**:117–122.
18. Hardman JG and Limbird LE (2001) Goodman and Gilman's: The Pharmacological Basis of Therapeuics, 10th ed. McGraw-Hill, New.
19. King DS, Sharp RL, Vukovich MD, Brown GA, Reifenrath TA, Uhl NL, Parsons KA (1999) Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men. *JAMA*. **281**:2020–2028.
20. Meikle AW, Arver S, Dobs AS, Sanders SW, Rajaram L, Mazer NA (1996) Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site- a clinical research center study. *J. Clin. Endocrinol Metab.* **81**:1832–1840.
21. Wang C, Berman N, Longstreth JA, Chuapoco B, Hull L, Steiner B, Faulkner S, Dudley RE, Swerdloff RS (2000) Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study. *J. Clin. Endocrinol. Metab*. **85**:964–969.
22. Zhang GY, Gu YQ, Wang XH, Cui YG, Bremner WJ (1998) A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. *J. Androl.* **19**:761–768.
23. Segura J, Ventura R, Jurado C (1998) Derivatization procedures for gas chromatographic-mass spectrometric determination of xenobiotics in biological samples, with special attention to drugs of abuse and doping agents. matogr. *B. Biomed. Sci. Appl*. **713**:61–90.
24. Simionescu L, Neacsu E, Zimel A, Caragheorgheopol A (1990) The development of a radio-immunoassay system for testosterone (T) and dihydrotestosterone (DHT). Part 2. The preparation of antisera to T. *Endocrinologie*. **28**:107–125.
25. Peng SH, Segura J, Farre M, Gonzalez JC, de la Torre X (2000) Plasma and urinary markers of oral testosterone undecanoate misuse. *Steroids*. **67**:39–50.
26. SmartBodyz Nutrition; http://www.smartbodyz.com; Fort Worth, Texas 76102; Toll Free: 187; SmartBodyz (1-877-627-8263); Telephone: 817-335-1982; Email: webmaster@smartbodyz.com. Accessed 10 June 2010.
27. Broeder CE, Quindry J, Brittingham K, Panton L, Thomson J, Appakondu S, Breuel K, Byrd R, Douglas J, Earnest C, Mitchell C, Olson M, Roy T, Yarlagadda C (2000) Physiological and hormonal influences of androstenedione supplementation in men 35 to 65years old participating in a high-intensity resistance training program. *Arch. Intern. Med*. **160**:3093–3104.
28. Gold Standard Clinical Pharmacology http://www.goldstandard.com/index.html. 2000–2010. Accessed 10 June 2010.
29. Wang C, Swerdloff RS (2002) Should the nonaromatizable androgen dihydrotestosterone be considered as an alternative to testosterone in the treatment of the andropause? *J. Clin. Endocrinol. Metab*. **87**:1462–1466. Review
30. Rittmaster RS, Thompson DL, Listwak S, Loriaux DL (1988) Androstanediol glucuronide isomers in normal men and women and in men infused with labeled dihydrotestosterone. *J. Clin. Endocrinol. Metab*. **66**:212–216.
31. Wang C, Iranmanesh A, Berman N, McDonald V, Steiner B, Ziel F, Faulkner SM, Dudley RE, Veldhuis JD, Swerdloff RS (1998) Comparative pharmacokinetics of three doses of percutaneous dihydrotestosterone gel in healthy elderly men - a clinical research center study. *J. Clin. Endocrinol. Metab.* **83**:2749–2757.
32. Kammerer RC, Merdink JL, Jagels M, Catlin DH, Hui KK (1990) Testing for fluoxymesterone (Halotestin) administration to man: identification of urinary metabolites by gas chromatography-mass spectrometry. *J. Steroid Biochem*. **36**:659–666.
33. Capponi VJ, Cox SR, Harrington EL, Wright CE, Antal EJ, Albert KS (1985) Liquid chromatographic assay for fluoxymesterone in human serum with application to a preliminary bioavailability study. *J. Pharm. Sci*. **74**:308–311.
34. Fenichel G, Pestronk A, Florence J, Robison V, Hemelt V (1997) A beneficial effect of oxandrolone in the treatment of Duchenne muscular dystrophy: a pilot study. *Neurology*. **48**:1225–1226.
35. Fenichel GM, Griggs RC, Kissel J, Kramer TI, Mendell JR, Moxley RT, Pestronk A, Sheng K, Florence J, King WM, Pandya S, Robison VD, Wang H (2001) A randomized efficacy and

safety trial of oxandrolone in the treatment of Duchenne dystrophy. *Neurology*. **56**:1075–1107.
36. Fox-Wheeler S, Heller L, Salata CM, Kaufman F, Loro ML, Gilsanz V, Haight M, Umman GC, Barton N, Church JA (1999) Evaluation of the effects of oxandrolone on malnourished HIV-positive pediatric patients. *Pediatrics*. **104**:e73.
37. Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenas L, Hager A, Ivarsson SA, Karlberg J, Kristrom B, Marcus C, Moell C, Ritzen M, Tuvemo T, Wattsgard C, Westgren U, Westphal O, Aman J (1996) Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J. Clin. Endocrinol Metab*. **81**:635–640 (1996).
38. Berger JR, Pall L, Hall CD, Simpson DM, Berry PS, Dudley R (1996) Oxandrolone in AIDS-wasting myopathy. *AIDS*. **10**:657–662.
39. Guarneri MP, Abusrewil SA, Bernasconi S, Bona G, Cavallo L, Cicognani A, DiBattista E, Salvatoni A (2001) Turner's syndrome. *J. Pediatr. Endocrinol. Metab*. **14**:959–965.
40. Partsch CJ, Weinbauer GF, Fang R, Nieschlag E (1995) Injectable testosterone undecanoate has more favourable pharmacokinetics and pharmacodynamics than testosterone enanthate. *Eur J Endocrinol*. **132**:514–519.
41. Malan PG and Gould RP (1982) Essentials of Endocrinology. Blackwell Scientific Publications, O'Riordan JLH. Ed.
42. Winters SJ (1990). Androgens: Endocrine physiology and pharmacology. In Anabolic Steroid Abuse, Lin GC and Erinoff L. Eds. *NIDA Research Monograph* **102**:113–130.
43. Time Report, Dope into Gold, Jan 19,1998, vol 151, No. 3.
44. East Germany Doping Scandal: Wonder Girls and Steroids by Sarah Naimzadeh. http://serendip.brynmawr.edu/biology/b103/f00/web2/naimzadeh2.html. Accessed 10 June 2010.
45. Dunn JF, Nisula BC, Rodbard D (1981) Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *J. Clin. Endocrinol. Metab*. **53**:58–68.
46. NIDA research reports Anabolic steroids (2010) Director's reports 1995 to 2005. http://search2.google.cit.nih.gov/search?q=research+Reports+%2BSteroids+%2Banabolic+steroids&btnG.x=19&btnG.y=11&btnG=Google+Search&spell=1&client=NIDA_ARCHIVE_frontend&proxystylesheet=NIDA_ARCHIVE_frontend&output=xml_no_dtd&sort=date%3AD%3AL%3Ad1&entqr=3&oe=UTF-8&ie=UTF-8&ud=1&site=NIDA_ARCHIVE. Accessed 10 June 2010.
47. Berendonk B (1991) Doping Dokumente: Von der Forschung zum Betrug [Doping documents: From research to fraud]. Springer-Verlag. Berlin Heidelberg.
48. East Germany Doping Scandal: Forgotten victims of East German doping take their battle to court. Athletes who were given drugs to compete in the name of communism seek £8m compensation. Luke Harding in Berlin; The Guardian, 11/1/2005. http://www.guardian.co.uk/sport/2005/nov/01/athletics.gdnsport3. Accessed 10 June 2010.
49. Palusinski R, Barud W (2000) Effects of androstenedione in young men (Letter to the Editor). *JAMA*. **283**:741.
50. Leder BZ, Longcope C, Catlin DH, Ahrens B, Schoenfeld DA, Finkelstein JS (2000) Oral androstenedione administration and serum testosterone concentrations in young men. *JAMA*. **283**:779–782.
51. Geyer H, Mareck-Engelke U, Reinhart U, Thevis M, Schänzer W (2000) Positive doping cases with norandrosterone after application of contaminated nutritional supplements [Positive Dopingfälle mit Norandrosteron durch verunreinigte Nahrungsergänzungsmittel]. *Deutsche zeitschrift für sportmedizin*. **51**:378–382.
52. Green GA, Catlin DH, Starcevic B (2001) Analysis of over-the-counter dietary supplements. *Clin. J. Sport Med.* **11**:254–259.
53. Tarter RE, Ammerman RT, Ott Peggy J (1998) Handbook of Substance Abuse: Neurobehavioral Pharmacology. Plenum Press, New York and London.
54. Preedy VR, Patel VB, Reilly ME, Richardson PJ, Falkous G, Mantle D (1999) Oxidants, antioxidants and alcohol: implications for skeletal and cardiac muscle. *Front. Biosci*. **4**:e58–66.

55. DeRamundo BM, Volpe A (1990) Effect of steroid hormones and antihormones on hypothalamic beta-endorphin concentrations in intact and castrated female rats. *J. Endocrinol. Invest.* **13**:91–96.
56. Cepero M, Cubria JC, Reguera R, Balana-Fouce R, Ordonez C, Ordonez D (1998) Plasma and muscle polyamine levels in aerobically exercised rats treated with salbutamol. *Pharm. Pharmacol.* **50**:1059–1064.
57. Long SF, Wilson MC, Sufka KJ, Davis WM (1996) The effects of cocaine and nandrolone co-administration on aggression in male rats. *Prog Neuropsychopharmacol Biol Psychiatry*. **20**:839–856.
58. Le Grevès P, Zhou Q, Huang W, Nyberg F (2002) Effect of combined treatment with nandrolone and cocaine on the NMDA receptor gene expression in the rat nucleus accumbens and periaqueductal gray. *Acta Psychiatr Scand Suppl*. **412**:129–132.
59. Murray RL, Chermack ST, Walton MA, Winters J, Booth BM, Blow FC (2008) Psychological aggression, physical aggression, and injury in non-partner relationships among men and women in treatment for substance-use disorders. *J Stud Alcohol Drugs*. **69**:896–905.
60. Wines JD Jr, Gruber AJ, Pope HG Jr, Lukas SE (1999) Nalbuphine hydrochloride dependence in anabolic steroid users. *Am. J. Addict.* **8**:161–164.
61. Stenman UH, Hotakainen K, Alfthan H (2008) Gonadotropins in doping: pharmacological basis and detection of illicit use. *Br J Pharmacol*. **154**:569–583.
62. von Deutsch DA, Abukhalaf IK, Wineski LE, Aboul-Enein HY, Potter DE, and Paulsen DF (2002) Distribution and muscle-sparing effects of clenbuterol in hindlimb suspended rats. *Pharmacol.* **65**:38–48.
63. von Deutsch DA, Abukhalaf IK, Wineski LE, Silvestrov NA, and Potter DE (2003) Changes in muscle proteins and spermidine content in response to unloading and clenbuterol treatment. *Can. J. Physio. Pharm*. **81**:28–39.
64. Wineski LE, von Deutsch DA, Abukhalaf IK, Pitts SA, Potter DE, and Paulsen DF (2002) Muscle-Specific Effects of Hindlimb Suspension and Clenbuterol in Mature, Male Rats. *Cells Tissues Organs*. **171**:188–198.
65. Katzung BG (2007) Basic & Clinical Pharmacology, 10th ed. McGraw-Hill, New York.
66. Schmekel B, Rydberg I, Norlander B, Sjosward KN, Ahlner J, Andersson RG (1999). Stereoselective pharmacokinetics of S-salbutamol after administration of the racemate in healthy volunteers. *Eur. Respir. J*. **13**:1230–1235.
67. von Berg A, Berdel D (1993) [A new beta-2 sympathomimetic drug with longer effectiveness. Comparison with current beta-2 sympathomimetic drugs in therapy of bronchial asthma in childhood]. *Monatsschr. Kinderheilkd*. **141**:53–58.
68. Eudra, (European Agency for the Evaluation of Medical Products: Veterinary Medicines and Information Technology Unit); Clenbuterol. EMEA/MRL/723/99-FINAL Feb 2000. www.ema.europa.eu/pdfs/vet/mrls/072399en.pdf. Westferry Circus, 7 Canary Wharf, E14 4HB LONDON, (Tel: +44 207 418–8569 Fax: +44 207 418–8416)/E-mail: mail@emea.eudra.org. Accessed 10 June 2010.
69. Morales-Olivas FJ, Brugger AJ, Bedate H, Garcia-Diez JM, Morcillo E, Esplugues J (1980) [Clenbuterol: a new partial antagonist of the beta adrenergic receptors (author's transl)]. *Arch. Farmacol. Toxicol*. **6**:131–138.
70. Perez R, Garcia M, Arias P, Gallardo M, Valenzuela S, Rudolph MI (1997) Inhibition of xylazine induced uterine contractility by clenbuterol and nifedipine. *Res. Vet. Sci*. **63**:73–76.
71. Stegmann GF, Bester L (2001) Some cardiopulmonary effects of midazolam premedication in clenbuterol-treated bitches during surgical endoscopic examination of the uterus and ovariohysterectomy. *J. S. Afr. Vet. Assoc*. **72**:33–76.
72. Maltin CA, Delday MI, Hay SM, Innes GM, Williams PE (1990) Effects of bovine pituitary growth hormone alone or in combination with the beta-agonist clenbuterol on muscle growth and composition in veal calves. *Br. J. Nutr*. **63**:535–545.
73. Smith DJ (1998) The pharmacokinetics, metabolism, and tissue residues of beta-adrenergic agonists in livestock. *J. Anim. Sci.* **76**:173–194.

74. Maltin CA, Delday MI, Watson JS, Heys SD, Nevison IM, Ritchie IK, and Gibson PH (1993) Clenbuterol, a β-adrenoreceptor agonist, increases relative muscle strength in orthopedic patients. *Clin. Sci*. **84**:651–654.
75. Bates PC, Pell JM (1991) Action and interaction of growth hormone and the beta-agonist, clenbuterol, on growth, body composition and protein turnover in dwarf mice. *Br. J. Nutr.* **65**:115–129.
76. Reeds PJ, Hay SM, Dorwood PM, and Palmer RM (1986) Stimulation of muscle growth by clenbuterol: lack of effect on muscle protein biosynthesis. *Br. J. Nutr.* **56**:249–258.
77. Reichel K, Rehfeldt C, Weikard R, Schadereit R, Krawielitzki K (1993) [Effect of a beta-agonist and a beta-agonist/beta-antagonist combination on muscle growth, body composition and protein metabolism in rats]. *Arch. Tierernahr*. **45**:211–225.
78. Abukhalaf IK, von Deutsch DA, Wineski LE, Silvestrov NA, Abera SA, Sahlu SW, and Potter DE (2002) Effect of hindlimb suspension and clenbuterol treatment on polyamine levels in skeletal muscle. *Pharmacol*. **65**:145–154.
79. Apseloff G, Girten B, Walker M, Shepard DR, Krecic ME, Stern LS, and Gerber N (1993) Aminohydroxybutane bisphosphonate and clenbuterol prevent bone changes and retard muscle atrophy respectively in tail-suspended rats. *J. Pharmacol. Exp. Therap.* **264**:1071–1078.
80. Girten B, Oloff C, Plato P, Eveland E, Merola AJ, Kazarian L (1989) Skeletal muscle antioxidant enzyme levels in rats after simulated weightlessness, exercise and dobutamine. *Physiologist*. **32** (1 Suppl): S59–S60.
81. Bloomfield SA, Girten BE, Weisbrode SE (1997) Effects of vigorous exercise training and beta-agonist administration on bone response to hindlimb suspension. *J. Appl. Physiol*. **83**:172–178.
82. Desplanches D, Favier R, Sempore B, Hoppeler H (1991) Whole body and muscle respiratory capacity with dobutamine and hindlimb suspension. *J. Appl. Physiol*. **71**:2419–2424.
83. Tryniszewski C (2001) Nurse's Drug Looseleaf. Blanchard & Loeb Publishers, LLC. Blue Bell, PA.
84. Takeo S, Elmoselhi AB, Goel R, Sentex E, Wang J, Dhalla NS (2000) Attenuation of changes in sarcoplasmic reticular gene expression in cardiac hypertrophy by propranolol and verapamil. *Mol. Cell Biochem*. **213**:111–118.
85. Katz I, Lloyd T, Kaufman S (1976) Studies on phenylalanine and tyrosine hydroxylation by rat brain tyrosine hydroxylase. *Biochim Biophys Acta* **445**:567–578.
86. Fitzpatrick PF (2000) The aromatic amino acid hydroxylases. *Adv Enzymol Relat Areas Mol Biol.* **74**:235–294.
87. Siegel GJ, Albers RW, Alganoff BW, Katzman R (1981) Basic Neurochemistry, 3rd Ed. Little, Brown and Company Boston.
88. Hardin AO and Lima JJ (1999) Beta 2-Adrenoceptor agonist-induced down-regulation after short-term exposure. *J. Recept. Signal Transduct. Res.* **19**:835–852.
89. Genazzani AR, Petraglia F, Mercuri N, Brilli G, Genazzani AD, Bergamaschi M, DeRamundo BM, Volpe A (1990) Effect of steroid hormones and antihormones on hypothalamic beta-endorphin concentrations in intact and castrated female rats. *J. Endocrinol. Invest*. **13**:91–96.
90. Cepero M, Perez-Pertejo Y, Cubria JC, Reguera R, Balana-Fouce R, Ordonez C, Ordonez D, and Escudero D (2000) Muscle and serum changes with salbutamol administration in aerobically exercised rats. *Comp. Biochem.. Physiol. C. Toxicol. Pharmacol*. **126**:45–51.
91. Cubria JC, Ordonez C, Reguera RM, Tekwani BL, Balana-Fouce R, and Ordonez D (1999) Early alterations of polyamine metabolism induced after acute administration of clenbuterol in mouse heart. *Life. Sci*. **64**:1739–1752.
92. Turchanowa L, Rogozkin VA, Milovic V, Feldkoren BI, Caspary WF, and Stein J (2000) Influence of physical exercise on polyamine synthesis in the rat skeletal muscle. *Eur. J. Clin. Invest.* **30**:72–78.
93. Westerhof FJ, Zuidhof AB, Kok L, Meurs H, Zaagsma J (2005) Effects of salbutamol and enantiomers on allergen-induced asthmatic reactions and airway hyperreactivity. *Eur Respir J*. **25**:864–872.
94. O'Riordan TG, Mao W, Palmer LB, Chen JJ (2006) Assessing the effects of racemic and single-enantiomer albuterol on airway secretions in long-term intubated patients. *Chest*. **129**:124–132.

95. Hoffman RJ, Hoffman RS, Freyberg CL, Poppenga RH, Nelson LS (2001). Clenbuterol ingestion causing prolonged tachycardia, hypokalemia, and hypophosphatemia with confirmation by quantitative levels. *J. Toxicol. Clin. Toxicol*. **39**:339–344.
96. Avila AH, Morgan CA, Bayer BM (2003) Stress-induced suppression of the immune system after withdrawal from chronic cocaine. *J. Pharmacol. Exp. Ther.* **305**:290–297.
97. www.cyberflex.co.uk/steroidcyclofenil.htm. Accessed 10 June 2010.
98. Lewis MI, LoRusso TJ, and Fournier M (1997) Anabolic influences of insulin-like growth factor I and/or growth hormone on the diaphragm of young rats. *J. Appl. Physiol.* **82**:1972–1978.
99. Wong JM, Forrest KA, Snabes SZ, Zhao SZ, Gersh GE, Kennedy SH (2001) Efficacy of nafarelin in assisted reproductive technology: a meta-analysis. *Hum Reprod Update*, **7**:92–101.
100. www.achilleshealthmart.com. Accessed 10 June 2010.
101. Ishii I, Kitada M (1997) [Multidrug-resistance by induction of inactivation for anti-cancer drugs]. *Nippon Rinsho* **55**:1044–1049.
102. Waddle JR, Fine RL, Case BC, Trogdon ML, Tyczkowska K, Frazier D, Page RL (1999) Phase I and pharmacokinetic analysis of high-dose tamoxifen and chemotherapy in normal and tumor-bearing dogs. *Cancer Chemother. Pharmacol*. **44**:74–80.
103. Lidstrom P, Bonasera TA, Kirilovas D, Lindblom B, Lu L, Bergstrom E, Bergstrom M, Westlin JE, Langstrom B (1998) Synthesis, in vivo rhesus monkey biodistribution and in vitro evaluation of a 11C-labelled potent aromatase inhibitor: [N-methyl-11C] vorozole. *Nucl. Med. Biol*. **25**:497–501.
104. Piotrovsky VK, Huang ML, Van Peer A, Langenaecken C (1998) Effects of demographic variables on vorozole pharmacokinetics in healthy volunteers and in breast cancer patients. *Cancer Chemother. Pharmacol*. **42**:221–228.
105. Alshowaier IA, el-Yazigi A, Ezzat A, Abd el-Warith A, Nicholls PJ (1999). Pharmacokinetics of S- and R-enantiomers of aminoglutethimide following oral administration of racemic drug in breast cancer patients. *J. Clin. Pharmacol*. **39**:1136–1142.
106. Goss PE (1998) Pre-clinical and clinical review of vorozole, a new third generation aromatase inhibitor. *Breast Cancer Res. Treat*. **49** Suppl 1:S59–65; discussion S73–77.
107. Elliott S (2008) Erythropoiesis-stimulating agents and other methods to enhance oxygen transport. *Br J Pharmacol.* **154**:529–541.
108. Zhu Y, D'Andrea AD (1994) The molecular physiology of erythropoietin and the erythropoietin receptor. *Curr Opin Hematol*. **1**:113–118.
109. F.Hoffmann-LaRocheLtd.http://www.roche.com/investors/ir_update/inv-update-2006-04-27.htm. Accessed 10 June 2010.
110. Sirén AL, Fratelli M, Brines M, Goemans C, Casagrande S, Lewczuk P, Keenan S, Gleiter C, Pasquali C, Capobianco A, Mennini T, Heumann R, Cerami A, Ehrenreich H, Ghezzi P (2001) Erythropoietin prevents neuronal apoptosis after cerebral ischemia and metabolic stress. *Proc Natl Acad Sci* USA. **98**:4044–4049.
111. Haroon ZA, Amin K, Jiang X, Arcasoy MO (2003) A novel role for erythropoietin during fibrin-induced wound-healing response. *Am J Pathol*. **163**:993–1000.
112. Sasaki H, Bothner B, Dell A, Fukuda M (1987) Carbohydrate structure of erythropoietin expressed in Chinese hamster ovary cells by human erythropoietin cDNA. *J Biol Chem*. **262**:12059–12076.
113. Skibeli V, Nissen-Lie G, Torjesen P (2001) Sugar profiling proves that human serum erythropoietin differs from recombinant human erythropoietin. *Blood*. **98**:3626–3634.
114. Beullens M, Delanghe JR, Bollen M (2006) False-positive detection of recombinant human erythropoietin in urine following strenuous physical exercise. *Blood*. **107**:4711–4713.
115. Anti-Doping Research. http://www.antidopingresearch.org. "Anti-Doping Research (ADR): One of the world's leading anti-doping research organizations." Accessed on 10-June-2010.
116. Lasne F (2003) Double-blotting: a solution to the problem of non-specific binding of secondary antibodies in immunoblotting procedures. *J Immunol Methods*. **276**:223–226.
117. Koudinov AR (2006) WADA, IOC testing for Erythropoietin is faked. *The Doping Journal*. **3**: 1-5. Available at: http://dopingjournal.org/content/3/1/.

118. Hoffman La Roche – Mircera (C.E.R.A.). http://www.roche.com/med-cor-2006-07-17. Retrieved on 7/11/2009.
119. Canaud B, Mingardi G, Braun J, Aljama P, Kerr PG, Locatelli F, Villa G, Van Vlem B, McMahon AW, Kerloëguen C, Beyer U (2008) STRIATA Study Investigators. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. *Nephrol Dial Transplant*. **23**:3654–3661.
120. Kunishige M, Mitsui T, Akaike M, Kawajiri M, Shono M, Kawai H, Matsumoto T (2003) Overexpressions of myoglobin and antioxidant enzymes in ragged-red fibers of skeletal muscle from patients with mitochondrial encephalomyopathy. *Muscle Nerve*. **28**:484–492.
121. Macdougall IC (2005) CERA (Continuous Erythropoietin Receptor Activator): a new erythropoiesis-stimulating agent for the treatment of anemia. *Curr Hematol Rep*. **4**:436–440.
122. Lundby C, Hellsten Y, Jensen MB, Munch AS, Pilegaard H (2008) Erythropoietin receptor in human skeletal muscle and the effects of acute and long-term injections with recombinant human erythropoietin on the skeletal muscle. *J Appl Physiol*. **104**:1154–1160.
123. Juul SE, Yachnis AT, Christensen RD (1998) Tissue distribution of erythropoietin and erythropoietin receptor in the developing human fetus. *Early Hum Dev*. **52**:235–249.
124. Odell WD, Griffin J (1987) Pulsatile secretion of human chorionic gonadotropin in normal adults. *N Engl J Med*. **317**:1688–1691.
125. Milano M, Collomp R (2005) Erythropoietin and neuroprotection: a therapeutic perspective. *J Oncol Pharm Pract.* **11**:145–149.
126. Abukhalaf IK, Mitchell CD, von Deutsch AW, Wineski LE, Silvestrov NA and von Deutsch DA (2007) Xanthine oxidase and myoglobin release in post-suspended rats. *ASGSB Space Biol. Bull*. **20**:93–94.
127. Henke A, Gromoll J (2008) New insights into the evolution of chorionic gonadotrophin. *Mol Cell Endocrinol*. **291**:11–19.
128. Weber MA, Kinscherf R, Krakowski-Roosen H, Aulmann M, Renk H, Künkele A, Edler L, Kauczor HU, Hildebrandt W (2007) Myoglobin plasma level related to muscle mass and fiber composition: a clinical marker of muscle wasting? *J Mol Med*. **85**:887–896.
129. Takayanagi A, Kobayashi K, Hashimoto K, Kato R, Masumori N, Itoh N, Tsukamoto T (2008) Case of androgenic anabolic steroid abuse caused hypogonadotropic hypogonadism. *Nippon Hinyokika Gakkai Zasshi*. **99**:729–732.
130. Karila T, Hovatta O, Seppälä T (2004) Concomitant abuse of anabolic androgenic steroids and human chorionic gonadotrophin impairs spermatogenesis in power athletes. *Int J Sports Med.* **25**:257–263.
131. van de Kerkhof DH, de Boer D, Thijssen JH, Maes RA (2000) Evaluation of testosterone/epitestosterone ratio influential factors as determined in doping analysis. *J. Anal. Toxicol*. **24**:102–115.
132. Kjeld JM, Puah CM, Joplin GF (1977) Rise of unconjugated sex hormones in human urine on storage. *Clin. Chim. Acta*. **80**:285–291.
133. Kjeld JM, Puah CM, Joplin GF (1979) Labile testosterone conjugate in human urine: further evidence. *Clin. Chim. Acta.* **93**:227–233.
134. Rantonen PJ, Penttilä I, Meurman JH, Savolainen K, Närvänen S, Helenius T (2000) Growth hormone and cortisol in serum and saliva. *Acta Odontol Scand*. **58**:299–303.
135. Vapaatalo H, Karkainen S, Senius KE (1984). Comparison of saliva and urine samples in thin-layer chromatographic detection of central nervous stimulants. *Int. J. Clin. Pharmacol. Res*. **4**:5–8.
136. Hofman LF (2001) Human saliva as a diagnostic specimen. *J. Nutr*. **131**:1621S–1625S.
137. Gaillard Y, Vayssette F, Pepin G (2000). Compared interest between hair analysis and urinalysis in doping controls. Results for amphetamines, corticosteroids and anabolic steroids in racing cyclists. *Forensic Sci. Int*. **107**:361–379.
138. Dumestre-Toulet V, Cirimele V, Ludes B, Gromb S, Kintz P (2002) Hair analysis of seven bodybuilders for anabolic steroids, ephedrine, and clenbuterol. *J. Forensic. Sci*. **47**:211–214.
139. Kintz P, Cirimele V, Sachs H, Jeanneau T, Ludes B (1999) Testing for anabolic steroids in hair from two bodybuilders. *Forensic. Sci. Int*. **101**:209–216.

140. Abukhalaf IK, von Deutsch DA, Parks BA, Wineski LE, Paulsen DF, Abul-Enein HY, and Potter DE (2000) Comparative analytical quantitation of clenbuterol in biological matrices using GC-MS and EIA. *Biomed Chromatogr*. **14**:99–105.
141. Hammond GL, Ruokonen A, Kontturi M, Koskela E, Vihko R (1977) The simultaneous radioimmunoassay of seven steroids in human spermatic and peripheral venous blood. *J. Clin. Endocrinol. Metab*. **45**:16–24.
142. Harper JM, Mackinson I, Buttery PJ (1990) The effects of beta agonists on muscle cells in culture. *Domest. Anim. Endocrinol*. **7**:477–484.
143. Lepage N, Roberts KD, Langlais J (1993) Interference of lysophosphatidylcholine in hormone radioimmunoassays. *Clin Chem*. **39**:865–869.
144. Konishi H, Minouchi T, Yamaji A (2001) Interference by danazol with the Porter–Silber method for determination of urinary 17-hydroxycorticosteroids. *Ann. Clin. Biochem*. **38**:277–279.
145. Ahn YS (2000) Efficacy of danazol in hematologic disorders. Acta Haematol **84**:122–129.
146. Fujisawa K, Tani P, Piro L, McMillan R (1993) The effect of therapy on platelet-associated autoantibody in chronic immune thrombocytopenic purpura. Blood. **81**:2872–2877.
147. Otawa M, Kuriyama Y, Iwase O, Kawanishi Y, Miyazawa K, Aizawa S, Nehashi Y, Nakano M, Toyama K (1997) [Possible role of immunocompetent cells on periodic exacerbation of idiopathic thrombocytopenic purpura]. *Rinsho Ketsueki* **38**:331–335.
148. Convertino VA, Polet JL, Engelke KA, Hoffler GW, Lane LD, Blomqvist CG (1995) Increased beta-adrenergic responsiveness induced by 14 days exposure to simulated microgravity. *J. Gravit. Physiol*. **2**:P66–P67.
149. Kintz P, Cirimele V, Dumestre-Toulet V, Villain M, Ludes B (2002) Doping control for methenolone using hair analysis by gas chromatography-tandem mass spectrometry. *J. Chromatogr. B. Analyt Technol. Biomed. Life Sci*. **766**:161–167.
150. Jarsch M, Brandt M, Lanzendörfer M, Haselbeck A (2008) Comparative erythropoietin receptor binding kinetics of C.E.R.A. and epoetin-beta determined by surface plasmon resonance and competition binding assay. *Pharmacology*. **81**: 63–69.
151. Veng-Pedersen P, Freise KJ, Schmidt RL, Widness JA (2008) Pharmacokinetic differentiation of drug candidates using system analysis and physiological-based modeling. Comparison of C.E.R.A. and erythropoietin. *J Pharm Pharmacol*. **60**:1321–1334.

Additional Reading

Akahane K, Furukawa Y, Ogiwara Y, Haniuda M, Chiba S. Beta-adrenoceptor blocking effects of a selective beta 2-agonist, mabuterol, on the isolated, blood-perfused right atrium of the dog. *Br. J. Pharmacol*. **97**:709–716 (1989).

Amemiya K, Asano T, Arika T, Nakamura M, Kudoh M. Special toxicology-physical dependence potential, antigenicity and mutagenicity of mabuterol. *Arzneimittelforschung*. **34**:1685–1686 (1984).

Amemiya K, Kudoh M, Suzuki H, Saga K, Hosaka K. Toxicology of mabuterol. *Arzneimittelforschung*. **34**:1680–1684 (1984).

Baronti A, Lelli M, Manini G, Verdiani P. Procaterol metered aerosol in patients with chronic obstructive pulmonary disease. *Int. J.Clin. Pharmacol. Res*. **7**:363–368 (1987).

Baselt RC, Cravey RH. Disposition of Toxic Drugs and Chemical in Man, 4th ed. Chemical Toxicology Institute Foster City, CA, (1995).

Beastall GH, Ratcliffe WA, Thomson M, Semple CG. Trilostane interference with steroid assays. *Lancet*. **1**:727–728 (1981).

Bowers LD. Analytical advances in detection of performance-enhancing compounds. *Clin. Chem*. **43**:1299–1304 (1997).

Brambilla G, Cenci T, Franconi F, Galarini R, Macri A, Rondoni F, Strozzi M, Loizzo A. Clinical and pharmacological profile in a clenbuterol epidemic poisoning of contaminated beef meat in Italy. *Toxicol. Lett*. **114**:47–53 (2000).

Brasch J, Flader S. Human androgenic steroids affect growth of dermatophytes in vitro. *Mycoses*. **39**:387–392 (1996).

Brown J, Clasper C, Smith T, Lomax MA. Effects of a beta 2-adrenergic agonist, cimaterol and corticosterone on growth and carcass composition of male rats. *Comp. Biochem. Physiol*. **102**:217–220 (1992).

Byrem TM, Beermann DH, Robinson TF. The beta-agonist cimaterol directly enhances chronic protein accretion in skeletal muscle. *J. Anim. Sci*. **76**:988–998 (1998).

Byrem TM, Robinson TF, Boisclair YR, Bell AW, Schwark WS, Beermann DH. Analysis and pharmacokinetics of cimaterol in growing Holstein steers. *J. Anim. Sci*. **70**:3812–3819 (1992).

Cardoso LA and Stock MJ. Effect of clenbuterol on growth and body composition during food restriction in rats. *J. Anim. Sci*. **74**:2245–2252 (1996).

Chance WT, Zhang X, Zuo L, Balasubramaniam A. Reduction of gut hypoplasia and cachexia in tumor-bearing rats maintained on total parenteral nutrition and treated with peptide YY and clenbuterol. *Nutrition*. **14**:502–507 (1998).

Chikhou F, Moloney AP, Austin FH, Roche JF, Enright WJ. Effects of cimaterol administration on plasma concentrations of various hormones and metabolites in Friesian steers. *Domest. Anim. Endocrinol*. **8**:471–480 (1991).

Doping notes: Kohl positive for CERA; details of Ricco's doping; Asif's doping appeal adjourned; Thomas gets home confinement. New York Times; Published: Monday, October 13, 2008. http://www.nytimes.com/2008/10/13/sports/13iht-doping13.16915406.html. Accessed 10 June 2010.

Eisen EJ, Croom WJ Jr, Helton SW. Differential response to the beta-adrenergic agonist cimaterol in mice selected for rapid gain and unselected controls. *Anim. Sci*. **66**:361–371 (1988)

Fischer W, Lasek R, Muller M. Anticonvulsant effects of propranolol and their pharmacological modulation. *Pol. J. Pharmacol. Pharm*. **37**:883–896 (1985).

Galan Martin AM, Marino JI, Garcia de Tiedra MP, Marabe JJ, Caballero Loscos MJ, Marino MM. Determination of nandrolone and metabolites in urine samples from sedentary persons and sportsmen. *J. Chromatogr. B. Biomed. Sci. Appl*. **761**:229–236 (2001)

Germouty J, Aubert J, Clavier J, Paramelle B, Voisin C. [Long-term tolerability of formoterol in chronic obstructive bronchopathies]. *Allerg. Immunol*. (Paris). **24**:342–347 (1992)

Gleixner A, Sauerwein H, Meyer HH. Probenecid, sulfinpyrazone and pyrazinamide do not inhibit urinary excretion of the beta 2-adrenoceptor agonist clenbuterol in cattle. *Food Addit. Contam*. **13**:603–608 (1996).

Gleixner A. Probenecid markedly reduces urinary excretion of ethinylestradiol and trimethoprim slightly reduces urinary excretion of clenbuterol. *Food Addit. Contam*. **15**:415–420 (1998).

Grassi V, Daniotti S, Schiassi M, Dottorini M, Tantucci C. Oral beta 2-selective adrenergic bronchodilators. *Int. J. Clin. Pharmacol. Res*. **6**:93–103 (1986).

Gregorevic P, Williams DA, Lynch GS. Effects of leukemia inhibitory factor on rat skeletal muscles are modulated by clenbuterol. *Muscle Nerve*. **25**:194–201 (2002).

Groot MJ, Schilt R, Ossenkoppele JS, Berende PL, Haasnoot W. Combinations of growth promoters in veal calves: consequences for screening and confirmation methods. *Zentralbl Veterinarmed. A*. **45**:425–440 (1998).

Guentert TW, Buskin JN, Galeazzi RL. Single dose pharmacokinetics of mabuterol in man. *Arzneimittelforschung*. **34**:1691–1696 (1984).

Gupta MK, Singh M. Evidence based review on levosalbutamol. *Indian J Pediatr*. **74**:161–167 (2007).

Hamada K, Kihana T, Kataoka M, Yoshioka S, Nishio S, Matsuura S, Ito M. Urinary disturbance after therapy for cervical cancer: urodynamic evaluation and beta2-agonist medication. Int. Urogynecol. J. Pelvic Floor Dysfunct. 10:365–370 (1999).

Harri M. Beta blockade and physical training in rats. *Ann. Clin. Res*. 14 Suppl **34**:168–172 (1982).

Hernandez-Carrasquilla M. External contamination of bovine hair with beta2-agonist compounds: evaluation of decontamination strategies. *J. Chromatogr. B. Biomed. Sci. Appl*. **767**:235–243 (2002).

Horiba M, Murai T, Nomura K, Yuge T, Sanai K, Osada E. Pharmacokinetic studies of mabuterol, a new selective beta 2-stimulant. II: Urinary metabolites of mabuterol in rats and their pharmacological effects. *Arzneimittelforschung*. **34**:1668–1679 (1984).

Huang H, Gazzola C, Pegg GG, Sillence MN. Differential effects of dexamethasone and clenbuterol on rat growth and on beta2-adrenoceptors in lung and skeletal muscle. *J. Anim. Sci*. **78**:604–608 (2000).

Hunt DG, Ding Z, Ivy JL. Clenbuterol prevents epinephrine from antagonizing insulin-stimulated muscle glucose uptake. *J. Appl. Physiol*. **92**:1285–1292 (2002).

Ishizaki O, Daidohji S, Kimura K, Shibuya K, Horiguchi T, Sekiwa M. Reproduction studies with mabuterol in rats. *Arzneimittelforschung*. **34**:1687–1690 (1984).

Kawakami Y. First clinical studies on mabuterol. A summarizing report. *Arzneimittelforschung*. **34**:1699–1700 (1984).

Kazlauskas R, Trout G. Drugs in sports: analytical trends. *Ther. Drug Monit*. **22**:103–109 (2000).

Kim J, Shigetomi S, Tanaka K, Yamada ZO, Hashimoto S, Fukuchi S. [The role of beta 2-adrenoceptor on the pathogenesis of insulin resistance in essential hypertension]. *Nippon. Naibunpi. Gakkai. Zasshi*. **70**:521–528 (1994).

Lacey RJ, Cable HC, James RF, London NJ, Scarpello JH, Morgan NG. Concentration-dependent effects of adrenaline on the profile of insulin secretion from isolated human islets of Langerhans. *J. Endocrinol*. **138**:555–563 (1993).

Lavoie JL, Calderone A, Beliveau L. A farnesyltransferase inhibitor attenuated beta-adrenergic receptor down regulation in rat skeletal muscle. *Am J Physiol Regul Integr Comp Physiol* **282**:R317–322 (2002).

Le Bizec B, Bryand F, Gaudin I, Monteau F, Poulain F, Andre F. Endogenous nandrolone metabolites in human urine: preliminary results to discriminate between endogenous and exogenous origin. *Steroids*. **67**:105–110 (2002).

Longcope C. Adrenal and gonadal androgen secretion in normal females. *Clin. Endocrinol Metab*. **15**:213–228 (1986).

Lotharius J, Falsig J, van Beek J, Payne S, Dringen R, Brundin P, Leist M. Progressive degeneration of human mesencephalic neuron-derived cells triggered by dopamine-dependent oxidative stress is dependent on the mixed-lineage kinase pathway. *J Neurosci*. **25**:6329–6342 (2005).

Matsumoto K, Ojima K, Ohta H, Watanabe H. Beta 2- but not beta 1-adrenoceptors are involved in desipramine enhancement of aggressive behavior in long-term isolated mice. *Pharmacol. Biochem. Behav*. **49**:13–18 (1994).

McEvoy JD, McCaughey WJ, Cooper J, Kennedy DG, McCartan BM. Nortestosterone is not a naturally occurring compound in male cattle. *Vet. Q*. **21**:8–15 (1999).

Merck Manual, www.merck.com/pubs/mmanual/section22/chapter305/305a.htm

Miyata T, Kai H, Furusawa K, Nakamura H, Saito M, Okano Y, Takahama K. Secretomotor and mucolytic effects of mabuterol, a novel bronchodilator. *Arch. Int. Pharmacodyn. Ther*. **288**:147–160 (1987).

Mueller RK, Grosse J, Lang R, Thieme D. Chromatographic techniques--the basis of doping control. *J. Chromatogr. B. Biomed. Appl*. **674**:1–11 (1995).

Murakami K, Nakagawa T, Yamashiro G, Araki K, Akasofu K. Adrenal steroids in serum during danazol therapy, taking into account cross-reactions between danazol metabolites and serum androgens. *Endocr. J*. **40**:659–664 (1993).

Murtha PE, Zhu W, Zhang J, Zhang S, Young CY. Effects of Ca++ mobilization on expression of androgen-regulated genes: interference with androgen receptor-mediated transactivation by AP-I proteins. *Prostate*. **33**:264–270 (1997).

Nakamura M, Yamaya M, Fukushima T, Sekizawa K, Sasaki H, Takishima T. Effect of mabuterol on tracheal mucociliary clearance of magnetized iron particles in anesthetized dogs. *Respiration*. **58**:33–36 (1991).

Nielen MW, Vissers JP, Fuchs RE, van Velde JW, Lommen A. Screening for anabolic steroids and related compounds in illegal cocktails by liquid chromatography/time-of-flight mass spectrometry and liquid chromatography/quadrupole time-of-flight tandem mass spectrometry with accurate mass measurement. *Rapid Commun. Mass Spectrom*.**15**:1577–1585 (2001).

O'Connor RM, Butler WR, Finnerty KD, Hogue DE, Beermann DH. Acute and chronic hormone and metabolite changes in lambs fed the beta-agonist, cimaterol. *Domest. Anim. Endocrinol*. **8**:537–548 (1991).

Puls I, Beck M, Giess R, Magnus T, Ochs G, Toyka KV. [Clenbuterol in amyotrophic lateral sclerosis. No indication for a positive effect]. *Nervenarzt*. **70**:1112–1115 (1999)
Ramos F, Castilho MC, Silveira MI. Occurrence of beta 2-adrenergic agonist residues in urine of animal meat producers in Portugal. J. AOAC Int. **81**:544–548 (1998).
Robert Dawson, Editorial, BMC News, 2000
Sainz RD, Wolff JE. Effects of the beta-agonist, cimaterol, on growth, body composition and energy expenditure in rats. *Br. J. Nutr*. **60**:85–90 (1988).
Saugy M, Cardis C, Robinson N, Schweizer C. Test methods: anabolics. *Baillieres Best Pract Res. Clin. Endocrinol. Metab*. **14**:111–133 (2000).
Schmidt EW, Ulmer WT, Rominger KL. Pharmacokinetics and pharmacodynamics of beta 2-agonists (in the light of fenoterol). *Respiration*. **62**:190–200 (1995).
Shinohara Y, Baba S. Stable isotope methodology in the pharmacokinetic studies of androgenic steroids in humans. *Steroids*. **55**:170–176 (1990).
Simon M, Babich-Armstrong M. 17-Hydroxycorticosteroids in urine. *Clin. Chim. Acta*.**103**:101–108 (1980).
Stallion A, Zhang FS, Chance WT, Foley-Nelson T, Fischer JE. Reversal of cancer cachexia in rats by cimaterol and supplemental nutrition. *Surgery*. **110**:678–684 (1991).
Taguchi S, Yoshida S, Tanaka Y, Hori S. [Simple and rapid analysis of trenbolone and zeranol residues in cattle muscle and liver by stack-cartridge solid-phase extraction and HPLC using on-line clean-up with EC and UV detection]. *Shokuhin. Eiseigaku. Zasshi*. **42**:226–230 (2001).
Thomas DP, McCormick KM, Jenkins RR. Effects of beta-adrenergic blockade on training-induced structural adaptations in rat left ventricle. *Eur. J. Appl. Physiol. Occup. Physiol*. **57**:671–676 (1988).
Touchstone JC., Steroids. In Handbook of Chromatography, G. Zweig and J. Sherma, Eds. CRC Press, Boca Raton, FL, (1986).
Walker HC, Romsos DR. Effects of cimaterol, a beta-adrenergic agonist, on energy metabolism in ob/ob mice. *Am. J. Physiol*. **255**:R952–960 (1988).
Wiseman LR, Spencer CM. Vorozole. *Drugs Aging* **11**:245–250; Discussion 251–252 (1997)
Wu AH. Mechanism of interferences for gas chromatography/mass spectrometry analysis of urine for drugs of abuse. *Ann. Clin. Lab. Sci*. **25**:319–329 (1995).
Yen JT, Mersmann HJ, Nienaber JA, Hill DA, Pond WG. Responses to cimaterol in genetically obese and lean pigs. *J. Anim. Sci*. **68**:2698–2706 (1990).
Yoon JM, Lee KH. Gas chromatographic and mass spectrometric analysis of conjugated steroids in urine. *J. Biosci*. **26**:627–634 (2001).
Yoshimura T, Kurita C, Nagao T, Usami E, Nakao T, Watanabe S, Kobayashi J, Yamazaki F, Tanaka H, Inagaki N, Nagai H. Inhibition of tumor necrosis factor-alpha and interleukin-1-beta production by beta-adrenoceptor agonists from lipopolysaccharide-stimulated human peripheral blood mononuclear cells. *Pharmacol*. **54**:144–152 (1997).

Websites

www.musclesurf.com Accessed 10 June 2010.
www.teenbodybuilding.com Accessed 10 June 2010.
www.vermontnutrition.com Accessed 10 June 2010.
http://amphetamines.com/adolf-hitler.html Accessed 10 June 2010.
http://teens.drugabuse.gov/mom/tg_meth2.php Accessed 10 June 2010.

Part VII
Legal Aspects

Chapter 16
Drug Interaction Litigation

Stephen A. Brunette

Abstract This chapter provides an overview of the theories of liability and defenses that have emerged in drug interaction litigation in recent years, in a "case study" format. It includes exemplary civil cases filed by individuals against physicians (Sect. 1), pharmacists (Sect. 2), and drug manufacturers (Sect. 3), and by a physician against a drug manufacturer (Sect. 4). Exemplary cases of judicial scrutiny of forensic evidence of causation in drug interaction litigation are also reviewed (Sect. 5). Cases that do not involve drug interactions are not within the scope of this chapter.

Drug interaction law varies among jurisdictions and within jurisdictions over time. Accordingly, the reader is advised to consult local counsel to ascertain the law applicable to a particular case in which the reader may be involved.

Keywords Litigation • Liability • Defenses • Cases

Actions Against Physicians

A civil action against a physician based on an injury allegedly caused by an adverse drug interaction must establish that the physician owed a particular duty to the plaintiff, the standard of care that governed fulfillment of that duty, that the physician breached that duty, and that the breach of duty was the cause in fact and proximate cause of the plaintiff's injury.

A physician may be found negligent for prescribing drugs which he knows to have potentially adverse interaction effects, failing to monitor a patient after prescribing

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such drugs, and failing to warn the patient of the potential adverse interaction effects. In *Whittle v. United States,* 669 F. Supp. 501 (D DC 1987), for example, a patient went to an Army medical center for treatment of headaches and depression. She was seen by a psychiatric resident who diagnosed various psychological disorders and possible migraine headaches. He prescribed Nardil, an anti-depressant monoamine oxidase inhibitor (MAOI), and Fiorinal, a barbiturate consisting of butalbital, caffeine, and aspirin. She died of butalbital poisoning after a few months on these prescriptions.

The decedent's husband filed a medical malpractice action. The undisputed evidence established that MAOIs interfere with the ability of the liver to metabolize barbituates, allowing the barbituates to remain in the blood stream at high levels for a longer period of time; that as a result of this "prolongation" effect, taking Nardil in combination with a barbituate such as Fiorinal increases the possibility that a second, supplemental ingestion of Fiorinal will push the barbituate level in the blood to toxic levels; and that the MAOI can convert the non-toxic Fiorinal regimen into a potentially toxic one. The evidence also showed that because of the "prolongation" or "potentiation" effect, the pharmacological literature recommends that barbituates should be administered at a reduced dose when taken concurrently with Nardil.

The defendant physician's records showed that he was aware of the potential adverse interaction effects of Nardil and Fiorinal, but he testified that his intention was to discontinue the Fiorinal when the Nardil reached therapeutic levels. The evidence established that the physician had not informed the patient of potential adverse interaction effects of these drugs, and was negligent in continuing to prescribe large volumes of Fiorinal to the decedent at a time when she was also taking Nardil, and in failing to take any steps to reduce or to monitor the decedent's usage of Fiorinal at a time when she was taking a maximum or near maximum daily dose of Nardil.

A physician may not have a duty to warn of the risks of possible drug interactions that are unproven, or where the likelihood of the risk occurring is extremely remote. In *Jones v. United States,* 933 F. Supp. 894 (N.D. Cal. 1996), for example, a husband and wife filed a wrongful birth action against the United States under the Federal Tort Claims Act, seeking costs and damages associated with raising their daughter, alleging that the child was born because US Army doctors negligently failed to warn the mother that Penicillin-VK, prescribed prophylactically prior to oral surgery, could interfere with the effectiveness of her Triphasil-28 birth control pills.

The plaintiffs offered expert testimony of two expert witnesses – a board-certified obstetrician-gynecologist and a pharmacist – to show that penicillin interferes with the effectiveness of the birth control pills. Following a *Daubert* hearing, the court ruled their testimony inadmissible. (See Sect. 5, below, for a detailed discussion of this court's *Daubert* analysis.)

Concerning the defendant physicians' duty, the court reasoned that, under California law, a physician has a duty of reasonable disclosure of the available choices with respect to a proposed therapy and of the dangers inherently and potentially involved, but this duty does not require the physician to conduct a "mini course in medical science" or to discuss "the relatively minor risks inherent in common procedures, when it is common knowledge that such risks inherent in the procedure are of very low incidence." The physician must disclose any known risks of death or

serious bodily injury, must explain in lay terms the complications that might possibly occur, and must disclose "such additional information as a skilled practitioner of good standing would provide under similar circumstances." Expert testimony as to the standard of care in this case led the court to conclude that, because the existence of the alleged drug interaction is unproven and its likelihood extremely remote, the standard of care in Monterey County in 1992 did not require a warning in the extremely common practice of prescribing antibiotics.

See also Crisostomo v. Stanley, 857 F.2d 1146 (7th Cir. 1988) [action allowed to proceed against a physician who prescribed Zyloprim where physician failed to advise patient to discontinue use if adverse reaction occurred; action against manufacturer dismissed where plaintiff failed to establish that manufacturer knew of drug's danger; evidence suggested that Zyloprim may cause skin rash independently or in interaction with ampicillin].

Where there is no specific contraindication for a possible adverse drug interaction on the manufacturer's label, the physician may have a viable defense to an action based on an alleged failure to warn. In *Silves v. King,* 970 P.2d 790 (Wash. App. 1999), an emergency room physician prescribed indomethacin, a non-steroidal anti-inflammatory drug, to a patient for treatment of gouty arthritis in his toe. The physician knew the patient was also taking heparin, an anti-coagulant, for blood clotting problems, and that the Physician's Desk Reference (PDR) advises caution when prescribing indomethacin to patients with coagulation defects. The PDR contained no specific contradindication for prescribing both indomethacin and heparin. Approximately 2 weeks after taking both the drugs, the patient suffered pulmonary hemorrhage and was thereafter unable to return to work. A jury found the physician had not violated the standard of care in prescribing both the drugs. The jury did find, however, that the physician had failed to obtain the patient's informed consent, but that her failure to obtain informed consent was not the proximate cause of the patient's injury. The verdict in favor of the physician was affirmed on appeal.

In addition to possible civil litigation for negligence in prescribing drugs with potential adverse interaction effects, a physician's license to practice medicine may be revoked under appropriate circumstances. In *Johnson v. State Medical Board of Ohio,* 1999 Ohio App LEXIS 4487 (Ohio App 1999), a physician admitted that he had, over the years, developed a style of practice which incorporated a "poly-pharmacy" approach to the prescription of medication, in which he would prescribe two narcotic analgesics, generally from different schedules, for patients with complaints of pain who he "was sure" were not drug abusers. He testified that he instructed the patients to use the medications only as needed for comfort and to use the lower scheduled drug when possible. He believed that his patients abided by his instructions, took the medications only as needed and did not abuse the medications.

The medical board's expert testified that the practice of "poly-pharmacy" is not appropriate; that there is no justification for prescribing narcotic analgesics and benzodiazepines concurrently due to the risk of additive central nervous system depressant effects; that when prescribing two narcotics with the intention that the drugs be used alternatively, a physician should not prescribe a complete renewal of

both prescriptions; that there is little therapeutic benefit in prescribing two narcotics over a long period of years; that a physician should prescribe narcotic medications for a diagnosis of chronic pain only after the physician has done everything that can be done in a diagnostic, therapeutic, and curative sense and has documented the results; and that abrupt termination of narcotic and benzodiazepine medications, after having been maintained on those medications for years, is dangerous because the patient may have become either physically and/or psychologically addicted to the medications.

The hearing examiner issued a report containing a detailed patient-by-patient summary of the facts concerning the medical care provided by the physician, and a patient-by-patient summary of the testimony of the physician and the board's expert. The examiner concluded that the physician had demonstrated a "reckless and unjustifiable disregard" of his patients' obvious drug-seeking behavior, alcohol abuse, depression and suicidal tendencies, and had disregarded the advice and concerns of consultants, specialists, psychiatrists, psychologists and family members. The examiner also concluded that the physician had prescribed medications which may have caused or exacerbated the symptoms he was treating, and failed to perform diagnostic workups to determine the cause of his patients' problems and/or to seek a cure for them. The examiner rejected the physician's testimony that he had prescribed multiple controlled substances based on his deep concern with his patients' well-being, noting that despite the fact that he had maintained the patients on multiple narcotic analgesics and multiple benzodiazepines for many years, he abruptly discontinued those medications without explanation and without considering that the patients may have become either physically and/or psychologically addicted to the medications. The examiner also noted that when patients complained of symptoms which may have been indicative of serious withdrawal, the physician neither evaluated the patients nor attempted to minimize the effects of withdrawal. The examiner recommended revocation of the physician's license to practice medicine; the board accepted this recommendation and revoked his license; the court of appeals affirmed the revocation. *See also Clausing v. State,* 955 P.2d 394 (Wash. App. 1998) [license revocation affirmed; physician negligently prescribed legend drugs for other than legitimate or therapeutic purposes].

Actions Against Pharmacists

There are three basic views that govern civil litigation against pharmacists in jurisdictions in the United States. One view is that pharmacists have no duty to warn their customers of potential adverse drug interactions, and are shielded from liability under the "learned intermediary" doctrine (Sect. 2.1). Another view is that pharmacists have duties to their customers to the extent that they voluntarily undertake such duties (Sect. 2.2). The third view is that pharmacists, like physicians, have a duty to exercise ordinary care in accordance with the standard of care for their profession, and are subject to civil liability for breaching that duty (Sect. 2.3).

No Duty to Warn: Learned Intermediary Doctrine

Several jurisdictions hold that a retail pharmacy has no general duty to warn a customer or the customer's physicians of potential adverse prescription drug interactions. The case frequently cited as the leading authority for this view – though not a drug interaction case – is *McKee v. American Home Products Corp.,* 782 P.2d 1045 (Wash. 1989). The court affirmed a summary judgment in favor of a pharmacist, where the plaintiff had not filed an affidavit by a pharmacist who knew the standards of practice and care applicable to pharmacists in the State of Washington, to support his claim that a pharmacist had a duty to warn a customer of adverse side effects of long-term administration of Plegine, an appetite suppressant. The court held that because the requisite affidavit had not been filed, there were no issues of material fact concerning the pharmacist's duty to warn, and the summary judgment was therefore appropriate.

The court went beyond its narrow holding, discussed the law of several jurisdictions concerning the duty of a pharmacist to warn of adverse effects of drugs dispensed by the pharmacist, adopted the learned intermediary doctrine for application to pharmacists, and issued an advisory ruling that a pharmacist has a duty to accurately fill a prescription and to be alert for clear errors or mistakes in a prescription, but has no duty to question the judgment of a physician or to warn customers of hazardous side effects of prescription drugs, either orally or by providing the manufacturer's package insert. The dissent would have remanded for trial, and for jury determination of whether the pharmacist's conduct violated the standard of care for pharmacists, as specified in state statutes, regulations and an affidavit filed by the plaintiff's non-pharmacist medical expert.

Various jurisprudential rationales for applying the learned intermediary doctrine to pharmacists were summarized recently by the Massachusetts Supreme Court in *Cottam v. CVS Pharmacy,* 764 N.E.2d 814 (Mass. 2002). The court reasoned that the physician has superior knowledge of the patient's medical history and unique condition, and is therefore in a better position than a pharmacist to decide which information is most pertinent to a particular patient; that imposing a duty to warn on pharmacists would place too heavy a burden on them by requiring that they retain and catalogue every document received concerning a drug, and assure that each document is distributed with the drug; that requiring the pharmacist to provide warnings may cause "risk-averse" pharmacists to institute a policy of warning a customer of all known risks, even minute or unproven risks, which might overwhelm a patient into deciding not to take a medication prescribed by a physician; that pharmacists do not choose which products to make available to consumers, and patients do not choose which products to buy; and that a pharmacist does not have the discretion to alter or refuse to fill a prescription because the risks and benefits of that prescription for that particular patient have already been weighed by the physician.

The doctrine was applied in *Silves v. King,* 970 P.2d 790 (Wash. App. 1999), in which an emergency room physician prescribed indomethacin, a non-steroidal anti-inflammatory drug, to a patient for treatment of gouty arthritis in his toe.

The physician knew the patient was also taking heparin, an anti-coagulant, for blood clotting problems, and that the Physician's Desk Reference (PDR) advises caution when prescribing indomethacin to patients with coagulation defects. A pharmacist employed by the hospital dispensed the prescription, and testified that if she had known the patient was also taking heparin she would have called the physician, but would have dispensed the prescription if the physician advised her to do so, because there were no specific contraindications for taking indomethacin with heparin. Approximately 2 weeks after taking both the drugs, the patient suffered pulmonary hemorrhage and was thereafter unable to return to work. Citing *McKee v. American Home Products Corp.,* 782 P.2d 1045 (Wash. 1989), the court of appeals in *Silves* ruled that the pharmacist had no duty to warn the patient of possible adverse interaction effects of indomethacin and heparin, or to consult with the physician, because there were no specific contraindications for taking both the drugs.

In *Johnson v. Walgreen Co.,* 675 So.2d 1036 (Fla. 1st D.C.A. 1996), the decedent suffered from several health problems, had several physicians who prescribed various medications to him and died of multiple drug toxicity. His widow sued the pharmacy that filled the prescriptions, alleging negligence in failing to warn of adverse drug interactions. The court dismissed the complaint on grounds that the pharmacy's sole duty was to accurately and properly fill all lawful prescriptions, and that it had no duty to warn of potential adverse drug interactions.

The plaintiff in *Johnson* also argued that there was a private right of action against the pharmacist under a state licensing statute that requires pharmacists, in dispensing a prescription, to assess the prescription for potential adverse reactions and interactions with other drugs, and to provide counseling to persons receiving prescriptions if, in the exercise of professional judgment, such counseling is necessary. The court declined to find a private right of action under the statute, but observed that a pharmacist is in a unique position to maintain a comprehensive record of all the medications prescribed to a patient, regardless of the number of physicians who may be prescribing medications for the patient, and that recent trends in federal and state regulatory law do require pharmacists to screen for possible drug interactions. The court concluded that it is for legislatures, not courts, to create a private right of action against a pharmacist for negligence in failing to warn of potential adverse drug interactions of which the pharmacist has knowledge. *Johnson, supra.*

See also Morgan v. WalMart Stores, Inc., 30 S.W.2d 455 (Tex. App. 2000) [acknowledging that pharmacist's role has changed from mere dispenser of medications to professional with vital role in patient treatment, that modern pharmacies use computer systems that can analyze drug interactions and contraindications in seconds, and that pharmacists may undertake to warn customers of same, but holding that under the learned intermediary doctrine, pharmacists have no legal duty to warn of potential adverse effects of prescription medications, absent special circumstances not present in case].

If a pharmacy has actual knowledge of a customer's allergies, and that the prescription in question is likely to have adverse effects on the customer, the learned intermediary doctrine may be inapplicable, and the pharmacy may have a duty to warn a customer and his physician of possible adverse effects of the prescription. *See Happel v. Wal-Mart Stores, Inc.,* 766 N.E.2d 1118 (Ill. 2002).

Voluntary Undertaking

The general rule that a pharmacist owes no duty to warn of possible adverse drug interactions may not apply if the pharmacy voluntarily undertakes to monitor possible drug interactions in filling prescriptions.

The "voluntary undertaking" theory of liability may, for example, impose a duty on the pharmacy to exercise reasonable care in the implementation of a system adopted to monitor drug interactions, and subject the pharmacy to liability for negligence, fraud and violation of a State Consumer Protection statute. *See, generally,* RESTATEMENT (SECOND) OF TORTS, §§323, 324A (1965). In *Baker v. Arbor Drugs, Inc.,* 544 N.W.2d 727 (Mich. App. 1996), the Michigan Court of Appeals reversed a summary judgment entered in favor of a pharmacy, and remanded for trial of the plaintiff's claims that the pharmacy and one of its pharmacists were negligent in the use of a prescription computer system that the pharmacy advertised would detect drug interactions. The patient had been taking Parnate (a monoamine oxidase inhibitor), and was prescribed Ceftin (an antibiotic) and Tavist-D (a decongestant) for treatment of a cold. The pharmacist who filled the prescription testified that the computer system had detected a possible drug interaction, as indicated by the appearance of the letter "I" next to the price on the prescription label for the Tavist-D, but that she had not personally seen the report of the drug interaction because a pharmacy technician overrode the computer system. The pharmacist testified further that she knew that Parnate and Tavist-D should not be taken together, and had she known that the patient was taking Parnate, she would not have filled the prescription for the Tavist-D. The court reasoned that the pharmacy had voluntarily assumed a duty to monitor drug interactions in the prescriptions it filled by implementing the computer system, and advertising to the general public that its computer system would detect harmful drug interactions for its customers. In assuming this duty, the pharmacy is held to a standard of due care in the implementation of the system, and it was for a jury to determine whether the pharmacy breached this duty and was, therefore, negligent under the circumstances. The court also ruled that the case could go to trial on the claims under the MICHIGAN CONSUMER PROTECTION ACT, and for fraud.

See also *Sanderson v. Eckerd Corporation,* 780 So.2d 930 (Fla. App. 2001) [adopted "voluntary undertaking" theory in action against pharmacy alleging negligent use of advertised drug interaction system].

Even under the "voluntary undertaking" theory, however, the extent of the pharmacist's duty will be limited to the extent of the undertaking. In *Frye v. Medicare-Glaser Corporation,* 605 N.E. 2d 557 (Ill. 1992), a decedent's estate alleged that a pharmacy and pharmacist negligently undertook to warn the decedent of the dangers of combining his prescription for Fiorinal with alcohol. The pharmacy's computer system generated suggestions for discretionary warnings that a pharmacist may place on the prescription container, and here suggested three warning labels – one to warn about drowsiness, another to warn about the use of alcohol with the drug, and a third to warn about impairment of the ability to drive. The pharmacist who filled the prescription testified that she knew of possible adverse

effects of the interaction of alcohol and Fiorinal, but she did not include a warning about these effects because she thought the label would offend people and cause them to drink, and she had been "chewed out" in the past for placing this label on prescription containers.

The Illinois Pharmacists Association and the National Association of Boards of Pharmacy filed *Amicus Curiae* briefs in the case, urging the Illinois Supreme Court to impose an affirmative duty on pharmacists to counsel consumers on the dangerous effects of prescription drugs, and arguing that the "learned intermediary" doctrine, which generally imposes the duty to warn on physicians, should not prevent the Court from also imposing a duty to warn on pharmacists. The Court declined to address this issue in its ruling, because neither party had argued for the imposition of such a duty. The Court ruled that the pharmacists' duty was limited to the extent of their undertaking, which in this case consisted only of placing a warning that the prescription may cause drowsiness. The Court declined to rule that the pharmacy had undertaken a duty to warn of all possible interaction effects using a computer system that warned of only some possible interaction effects, but did not warn of other possible interaction effects with, e.g., aspirin, caffeine or barbiturates, and other central nervous system depressants. The Court reasoned that if it imposed a broad duty to warn under the "voluntary undertaking" theory, pharmacies might choose to provide no warnings rather than risk being found negligent in providing incomplete warnings, and this would not support a public policy of encouraging pharmacies to undertake to provide warnings. The court reasoned further that consumers should rely principally on the prescribing physician to warn of all possible drug interaction effects, not on their pharmacies. A dissenting opinion in the case would not have restricted the "voluntary undertaking" theory in this manner, and would have allowed the case to go to trial on the issue of negligence.

Defining the scope of the duty assumed by a pharmacy under the "voluntary undertaking" theory is a fact-specific inquiry, based on the totality of the pharmacy's communications with the patient, and the patient's reasonable understanding, based on those communications, of what the pharmacy has undertaken to provide. Providing a label containing a single warning of a single risk may not be reasonably construed as an undertaking to warn of all adverse effects, but where a pharmacy provides a detailed list of warnings, contraindications or possible adverse interactions – or by way of advertising promises a consumer that it will provide such information – the pharmacy may be found to have a duty to provide a comprehensive list of possible adverse drug interactions. See *Cottam v. CVS Pharmacy,* 764 N.E.2d 814 (Mass. 2002).

Expert testimony may not be necessary to establish the extent of a pharmacy's undertaking, or negligence in failing to warn of possible adverse drug interactions, where the pharmacist's specialized or technical knowledge or performance are not an issue. Where the issues involve only whether a pharmacy made representations that would be deemed an undertaking of a duty to warn, or whether the warning was understandable by a reasonable person, a jury may be allowed to determine these issues without the assistance of expert testimony. *Cottam v. CVS Pharmacy,* 764 N.E.2d 814 (Mass. 2002).

Reasonable Care Required

An increasing number of jurisdictions are holding pharmacists to the professional standard of care that applies to any profession. In *Lasley v. Shrake's Country Club Pharmacy, Inc.,* 880 P.2d 1129 (Ariz. 1994), the Arizona Supreme Court reversed a trial court's ruling that a pharmacy has no duty to warn as a matter of law, and ruled that a pharmacy owes its customers a duty of reasonable care to warn of potential adverse drug interactions. The patient had been prescribed Doriden and codeine for approximately 30 years, received his prescriptions from the defendant pharmacy for approximately 10 years and eventually required in-patient hospitalization for Doriden detoxification, and psychiatric treatment for addiction, major clinical depression and related disorders. He and his family complained that the pharmacy owed a duty of reasonable care in, *inter alia,* advising customers and physicians of potential adverse drug interactions, and relied on an affidavit of an expert and standards of the American Pharmaceutical Association Standards of Practice for the Profession of Pharmacy, to show that the standard of care for pharmacists includes a duty to advise customers of the highly addictive nature of prescribed drugs, and of the hazards of ingesting two or more drugs that adversely interact with one another. The trial court dismissed the complaint, on grounds that a pharmacy has no such duty.

The Arizona Supreme Court reviewed authority from the majority of jurisdictions which hold that a pharmacy has no duty to warn, under various factual circumstances. The Court rejected this majority view, reasoning that it misconstrues the relationship between "standard of care" and "duty" in tort law, in that it first determines details of the standard of conduct for pharmacies, and then concludes that a duty to warn does not exist. The Court reasoned that the threshold question is, instead, whether a duty exists as a matter of law. If the court finds that a duty exists, the second inquiry is whether a defendant who owed a duty to a plaintiff violated the standard of conduct applicable to the field.

Applied to the facts in the case, the court ruled as a matter of law that a pharmacy owes a duty of reasonable care to its customers, and found that the evidence presented to the trial court – consisting of the affidavit and standards described above – was sufficient to raise a question of fact as to whether the pharmacy violated the standard of care in failing to warn its customer of potential adverse interactions and addiction.

Similarly, in *Dooley v. Revco Discount Drug Centers, Inc.,* 805 S.W.2d 380 (Tenn. App. 1990), a 5-year-old, who had been taking Theophylline for 2 years for treatment of asthma, was prescribed Erythromycin by the same physician, and the prescription was filled by the same pharmacy. The Erythromycin package insert warned of possible Theophylline toxicity in patients prescribed Erythromycin, and advised that Theophylline dosages be reduced if Erythromycin is prescribed. The pharmacy did not warn the plaintiffs of this possible interaction, and the pharmacist who filled the prescription testified that he was not aware of it. The patient suffered cerebral seizures as a result of toxic levels of Theophylline after the Erythromycin was introduced.

The plaintiff introduced an affidavit and testimony of an expert pharmacist, who stated that the standard of care for pharmacists in the locale required them to maintain a patient profile and alert a patient and his physician when a prescription is ordered for a drug that may adversely interact with another prescription of the patient, and that there exists computer technology that allows pharmacists to identify potential adverse drug interactions, and specifically the adverse interaction between Theophylline and Erythromycin. The court ruled that this evidence raised a question of fact as to whether the pharmacy owed a duty to its customers, including the plaintiff, to discover and warn of potential adverse drug interactions, and ordered the case to go to trial.

In *Horner v. Spolito,* 1 S.W.3rd 519 (Mo. App. 1999), a pharmacist filled two prescriptions for a customer – one for 50, 750 mg. doses of Placidyl, a strong hypnotic drug, which the prescribing physician instructed to be taken once every 8 h; the other for 50, 10 mg. doses of Diazepam, a central nervous system depressant, which the prescribing physician instructed to be taken once every 8 h. Before filling the prescriptions, the pharmacist consulted FACTS AND COMPARISONS, an authoritative pharmacy manual, which indicated that the normal dose for Placidyl was one 500 mg. dose or one 750 mg. dose before bedtime. The manual also warned that the drug's effects were enhanced when combined with other central nervous system drugs, such as Diazepam.

Concerned about the prescribing physician's instructions, the pharmacist called his office and was told the prescription was "okay" because the patient "needed to be sedated throughout the day." The pharmacist filled the prescriptions; the patient was found dead 6 days later; the autopsy revealed that death was caused by multiple medications, especially Placidyl (ethchlorvynol), which was "near the toxic range."

The trial court granted summary judgment in favor of the pharmacist, ruling that he owed no duty to the patient other than to properly fill a legal prescription that had no discrepancies on its face. The Missouri Court of Appeals reversed and remanded for trial, ruling that a pharmacist – like any other professional – has a duty to exercise the care and prudence that a reasonably careful and prudent pharmacist would exercise under the circumstances, and it is up to the jury to determine whether a pharmacist breached that duty in a particular case. That duty may require only that the pharmacist properly fill a legal prescription in some cases, but in others it may require the pharmacist to do more to protect customers from risk that the pharmacist can reasonably foresee. The court relied on state law governing the practice of pharmacy (Mo. Rev. Stat. §338.010.1), and state and federal law and regulations that require a pharmacist to offer to discuss with each customer or his physician the safe and effective use of a prescription drug, based on the pharmacist's education, experience and review of available information about the drug and the patient. The court noted that the federal Omnibus Budget Reconciliation Act of 1990 required states to establish standards for pharmacists to provide such counseling to customers and prescribing physicians. *See* Kenneth R. Baker, *The OBRA 90 Mandate and Its Developing Impact on the Pharmacist's Standard of Care*, 44 DRAKE L. REV. 503 (1996).

See also Happel v. Wal-Mart Stores, Inc., 766 N.E.2d 1118 (Ill. 2002) [pharmacy may have duty to warn of possible adverse reactions where pharmacy has actual knowledge of customer's condition and that prescription is contraindicated].

Compare, Morgan v. WalMart Stores, Inc., 30 S.W.2d 455 (Tex. App. 2000) [acknowledging that pharmacist's role has changed from mere dispenser of medications to professional with vital role in patient treatment, that modern pharmacies use computer systems that can analyze drug interactions and contraindications in seconds, and that pharmacists may undertake to warn customers of same, but holding that under learned intermediary doctrine, pharmacists have no legal duty to warn of potential adverse effects of prescription medications, absent special circumstances not present in case].

A pharmacist may, of course, have a duty to warn of interaction effects if the pharmacist prescribes the remedy. In a case from the archives, *Fuhs v. Barber,* 36 P.2d 962 (Kan. 1934), a physician had prescribed a lead-based ointment for treatment of a skin irritation. When the patient returned to the pharmacist for a refill, the pharmacist recommended a sulphur-based ointment he had invented. The plaintiff's skin turned black from the reaction of the lead and sulphur. The Kansas Supreme Court held the pharmacist had a duty to warn of the possible drug interaction.

Actions Against Pharmaceutical Manufacturers

If a pharmaceutical manufacturer has complied with federal legislative and regulatory requirements for testing and labeling a drug, and if the label provides adequate warnings of all known potential adverse interaction effects, the manufacturer may be shielded from liability under the learned intermediary doctrine (Sect. 3.1). If the manufacturer has been negligent in the testing, manufacturing or marketing of the drug, the manufacturer may be liable to a consumer for this negligence or strict liability (Sect. 3.2). Where circumstances warrant, a manufacturer may face challenges under various other theories of liability, such as breach of implied warranty, breach of express warranty, fraud, negligent misrepresentation, fraud by concealment, civil conspiracy, concert in action (Sect. 3.3). Theories of liability are typically incorporated in a single action, and variations in state law may produce different legal tests, and different outcomes under similar circumstances. The following discussion is not intended to explain peculiarities of state law in these areas. Rather, it reports the law as stated in the drug interaction cases within the scope of this chapter. The reader is advised to seek local counsel in the jurisdiction in which an action is filed for a review of the law applicable to the action.

Learned Intermediary

In *Eck v. Parke, Davis & Co.*, 256 F.3d 1013 (10th Cir. 2001), a patient and his family filed a product liability action against the manufacturers of two prescription drugs – Isocet and Dilantin. The plaintiff's physician had prescribed Isocet to the patient to treat his complaints of tension headaches in 1994 and 1995. In 1997, the patient was referred to an epilepsy specialist who prescribed Dilantin to control the patient's

seizures. The first physician was involved in administering and monitoring the levels of Dilantin. While taking the Dilantin, the patient experienced a tension headache and took two Isocet tablets from his earlier prescription, and shortly thereafter was diagnosed with acute liver failure. The epilepsy specialist testified that she was aware of the medical risk of the interaction of Isocet and Dilantin, but still would have prescribed Dilantin because of the greater risk posed by the patient's seizures. The court held that the plaintiffs failed to controvert this testimony, that the defendant manufacturers were shielded from liability under the "learned intermediary doctrine," and any failure to warn on the part of the defendants was therefore not the proximate cause of Mr. Eck's liver failure.

The plaintiffs had alleged that the defendant manufacturers had failed to label their products with adequate warnings of Dilantin's propensity to interact with acetaminophen, placed defective and unreasonably dangerous products in the market place that caused Mr. Eck's liver failure and were negligent in designing, testing, warning and marketing of their products through their failure to provide adequate instructions or warnings, and by misrepresenting the safety of their products when used in conjunction with one another.

Applying Oklahoma law, the court reasoned that, in order to recover in a failure to warn case against a drug manufacturer, a plaintiff must establish both cause-in-fact (that the product in question caused the injury) and proximate cause (that the manufacturer of the product breached a duty to warn of possible detrimental reactions, and this breach was a substantial contributing factor in causing the harm). Under Restatement (Second) Torts § 402A comment K, certain products, including prescription drugs, are "unavoidably unsafe products" that cannot be made completely safe, but serve a public benefit, so drug manufacturers cannot be held strictly liable merely because of the dangerous propensities of their products. Although the manufacturer has a duty to warn the ultimate consumers of known dangers of prescription drugs and their interactions, there is an exception to this duty – the "learned intermediary doctrine" – under which the manufacturer is shielded from liability where the product is properly prepared and marketed and proper warning is given to prescribing physicians. The prescribing physician acts as a learned intermediary between the patient and the prescription drug manufacturer by assessing the medical risks in light of the patient's needs.

See also Ashman v. SK&F Lab Co., 72 F. Supp. 1401 (N.D. Ill. 1988) [learned intermediary doctrine shielded manufacturer from liability for injury resulting from physician's failure to warn of possible adverse interaction of Tagamet and Halcion; manufacturer's label included warning of possible adverse interaction]; *Cottam v. CVS Pharmacy,* 764 N.E.2d 814 (Mass. 2002) [learned intermediary doctrine is exception to general rule that manufacturer or retailer of unavoidably dangerous product must directly warn all foreseeable consumers of dangers of its product; rationale for doctrine is that physicians have duty to inform themselves about drug and warn patients of dangers they deem necessary and relevant for patients to make informed decision; requiring manufacturer to provide warnings directly to consumer would interfere with doctor-patient relationship]; *Singleton v. Airco, Inc.,* 314 S.E. 2d 680 (Ga. App. 1984) [though not invoking learned intermediary doctrine,

court ruled that manufacturer has duty to warn only physician, and that warnings of risks of interaction of Anectine (succinylcholine chloride) and Ethrane (enflurane) were adequate; summary judgment in favor of manufacturers affirmed].

The learned intermediary doctrine may not shield a manufacturer from liability where the warning to the medical community was not timely, or was delayed for an unreasonable time after the manufacturer learned of the product defects. In *Linnen v. A. H. Robbins Company, Inc.,* 1999 Mass. Super LEXIS 552 (1999), the court declined to enter summary judgment in favor of the manufacturer of fen-phen (fenfluramine and phentermine) under the learned intermediary doctrine, where the evidence suggested that the manufacturer had actual knowledge of the risk of pulmonary hypertension associated with the drugs for more than 1 year before it changed its package insert to advise physicians of this risk, and there was, accordingly, a question of fact as to whether the physician would have warned her patient of this risk before prescribing the drug. The patient died of pulmonary hypertension, allegedly as a result of using the drugs.

Negligence and Strict Liability

In *Bocci v. Key Pharmaceuticals, Inc.,* 974 P.2d 758 (Or. App. 1999), a patient who suffered permanent brain damage due to theophylline toxicity caused by interaction of theophylline (an asthma medication) and ciprofloxican (an antibiotic frequently prescribed to asthmatics for respiratory infections), filed an action against the physician who prescribed theophylline for negligence and failure to diagnose, and against the pharmaceutical company for negligence and strict products liability. The claim against the physician was dismissed; the claim against the pharmaceutical company was resolved at jury trial in favor of the patient. The facts of the case are complex, but necessary for review in order to understand the court's disposition of the case.

The court in *Bocci* found that the drug theophylline is a bronchodilator that has been used to treat asthma for many decades. Theophylline has a narrow therapeutic range: in order to prevent asthma symptoms, the serum levels of the drug in the blood generally must be at least 10 micrograms per milliliter (mcg/ml), but serum levels above 20 mcg/ml can be toxic. Saturation kinetics play a part in the way in which this drug may be metabolized; when the level of the drug in the body increases but the liver's ability to metabolize it does not increase or when the amount of the drug entering the body stays the same but the liver's ability to metabolize it decreases for some reason, saturation can occur. This causes the serum levels of theophylline in the blood to increase. The ability of a body to metabolize theophylline may be affected by many things, such as smoking or the presence of a virus. Interactions between theophylline and other drugs may cause a body to metabolize theophylline at a slower rate, thus increasing the serum levels of theophylline in the blood and leading to theophylline toxicity. Theophylline toxicity can cause nausea, vomiting, headaches, diarrhea, tachycardia, seizures and death.

Before the 1970s, theophylline therapy was difficult because a great deal of monitoring and adjustment of dosage was necessary to keep stable the amount of the drug in a patient's blood at any given time. In the 1970s, Key introduced a new theophylline product, Theo-Dur, a timed-release capsule that it claimed had zero-order absorption. Zero-order absorption occurs when a drug is constantly absorbed by the system and eliminated at the same rate, thus keeping the serum levels of the drug in the blood stable. Key promoted Theo-Dur as being safer than other theophylline products; because of its zero-rate absorption, Key claimed, the risk of "toxic peaks" could be avoided. Key aggressively promoted Theo-Dur to physicians through sales representatives, journal advertising and direct-mail campaigns. Promotional materials also urged patients, physicians and pharmacists not to accept generic or brand-name substitute theophylline products, as switching from Theo-Dur could cause "excessive toxicity." In 1987, the Food and Drug Administration (FDA) informed Key that it must cease claiming that Theo-Dur was superior to other theophylline products due to zero-order absorption, because the claim was not sufficiently supported by clinical data. In 1989, the FDA again found that Key was making false and misleading claims that Theo-Dur was superior to other theophylline products.

In October 1987, Key became aware of several medical journal articles reporting a drug interaction causing theophylline toxicity when both theophylline and ciprofloxacin, a newly available antibiotic often used to treat respiratory tract infections common among asthmatics, were administered. A Key internal memorandum dated October 30, 1987, stated: "Ciprofloxacin produces a 30–113% decrease in theophylline clearance. These effects are significant enough to cause a patient that is stabilized on theophylline to potentially become toxic." In March 1988, Key proposed to the FDA that a warning be added to its Theo-Dur package insert concerning the interaction between theophylline and ciprofloxacin. Key's application for the labeling change, however, was not submitted in proper form, and it was not until March 1989 that the labeling change was approved. The labeling change was not reflected in the 1990 volume of the Physician's Desk Reference (PDR), although it was included in a May 1990 PDR supplement.

Information such as a warning about theophylline–ciprofloxacin interaction is generally imparted to the medical community by drug manufacturers through "Dear Doctor" and "Dear Pharmacist" letters or statograms, through promotional materials sent to physicians or through representatives of pharmaceutical companies (detailers) who call on physicians. Federal regulations allow for distribution of such warnings to physicians before revised labeling is approved by the FDA, and also allow a pharmaceutical company to change its labeling without preauthorization from the FDA in order to add warnings, precautions or information concerning adverse reactions.

Between October 1987, when Key became aware of the theophylline–ciprofloxacin interaction, and Bocci's injury in October 1990, Key took no steps to inform physicians or patients of this potential toxicity problem, although it knew of several cases of serious toxicity and one death caused by the interaction of theophylline and ciprofloxacin. During this period, Key continued to promote Theo-Dur as the only theophylline product that "protects against toxicity."

Bocci began taking Theo-Dur when he was 7 years old. On October 21, 1990, when Bocci was 20 years old, he went to a medical clinic for treatment of a skin rash and was treated by Dr. Davis. Bocci indicated to Dr. Davis that he was not taking any medications, although he was taking 900 mg of Theo-Dur a day. Dr. Davis prescribed ciprofloxacin for the skin rash; Bocci took both ciprofloxacin and Theo-Dur from October 21 to October 26, 1990. On October 27, 1990, Bocci went to an urgent care clinic with symptoms including nausea, vomiting and diarrhea, and was seen by Dr. Edwards. Dr. Edwards discovered that Bocci had been on a stable dose of Theo-Dur for a long time, and, although he considered a diagnosis of theophylline toxicity, he did not diagnose that condition, and did not consult the PDR or the PDR supplement. Dr. Edwards did not think that a patient on a stable dose of Theo-Dur could experience severe theophylline toxicity that could lead to brain damage unless the patient had taken an overdose, because Theo-Dur had been marketed and promoted to him as a "safe" drug. The detailer who had promoted the drug to Dr. Edwards and clinic in 1989 and 1990 testified that he would routinely tell physicians that Theo-Dur had zero-order absorption and that it was safe.

Dr. Edwards testified that he did not make a connection between a patient on a stable dose of a safe drug such as Theo-Dur and a serious toxicity problem. He therefore diagnosed gastroenteritis, treated Bocci with antinausea medication and intravenous fluids, and then sent him home. Several hours later, Bocci had violent seizures and was taken to a hospital emergency room. Anticonvulsant medications were administered but failed to control the seizures, and the physicians attending him had difficulty diagnosing the cause of the seizures. Late that evening, after learning that Bocci had been taking asthma medication, they tested for theophylline toxicity and discovered that Bocci's theophylline level was 63 mcg/ml, well into the toxic range. The theophylline was removed from Bocci's blood through dialysis and the seizures ceased, but Bocci suffered permanent brain damage as a result of the seizures.

A number of physicians testified about their knowledge and understanding of Theo-Dur as of October 1990, when Bocci sustained his injury. Those physicians did not know about the theophylline–ciprofloxacin interaction and did not know that patients stabilized on standard doses of Theo-Dur could experience toxicity problems causing severe seizures such as those experienced by Bocci. Those physicians did not know that blood levels of theophylline should be obtained on patients using theophylline products if the patients experienced nausea and vomiting.

On Bocci's claims, the jury returned a verdict finding that Key was 65% at fault and Bocci was 35% at fault. On Dr. Edwards' cross-claims, the jury found that Key was negligent and that Key's negligence caused Edwards' damages and found that Key had made fraudulent misrepresentations to Dr. Edwards that caused him damage. The jury further found that Key caused 100% of Dr. Edwards' damages. The jury also found clear and convincing evidence that Key had acted with wanton disregard for the health and safety of others and had knowingly withheld from or misrepresented to the FDA or prescribing physicians information known to be material and relevant to theophylline toxicity, in violation of applicable FDA regulations. The court entered a judgment in Bocci's favor including compensatory damages of

$5,621,648.20 and punitive damages of $35 million, and in Dr. Edwards' favor for compensatory damages of $500,000 and $22.5 million in punitive damages.

Failure to comply with state or federal regulations governing the testing, manufacturing and marketing of drugs may establish a prima facie case of negligence. *Batteast v. Wyeth Laboratories, Inc.,* 526 N.E.2d 428 (Ill. App. 1988) [the manufacturer was sued for negligence, strict liability, and willful and wanton conduct; physicians were sued for negligence and willful and wanton conduct]. In *Batteast,* the defendant began manufacturing aminophylline suppositories in 1945, at which time correspondence from the FDA indicated that the suppositories would not be considered a new drug. The manufacturer received no written or verbal FDA approval following this correspondence, and introduced no other evidence that the drug was ever approved for safety. Prior to 1975, the defendants conducted two animal studies on the suppositories, and one human study of absorption rates of the suppositories with a cocoa butter base versus a hydrogenated base. The defendant ceased manufacturing the aminophylline suppositories in 1982, without ever having received FDA approval for marketing the drug and without ever having established the safety and efficacy of the drug, but continued to distribute aminophylline suppositories manufactured by another pharmaceutical company.

In 1972 and 1973, the FDA published two notices stating that aminophylline suppositories require an approved New Drug Application (NDA), and that it would be unlawful to ship suppositories that were not subject to an NDA. The defendant did not respond to these two notices. In 1974, the FDA published a third notice concerning the manufacturing and distribution of aminophylline suppositories, requiring submission of either an ADA or an ANDA by drug manufacturers. The defendant filed its first ANDA with the FDA for approval of its drug in response to this notice. The FDA replied to the application with a notice that biologic availability studies were required before the suppositories could be approved for marketing, and a suggestion that a research protocol be submitted prior to initiation of any studies. The defendant did not submit a protocol in response to this request, received a second request 1 year later, became aware that its ANDA for the aminophylline suppositories would be rejected, but continued marketing the drug until its ANDA was officially rejected by the FDA in 1983. The court ruled that evidence of this chronology was admissible as proof of negligence under state law which provided that violation of a statute or ordinance designed to protect human life or property is prima facie evidence of negligence. The court rejected the defendant's argument that the FDA regulations were not intended to protect the infant plaintiff. *Batteast v. Wyeth Laboratories, Inc.,* 526 N.E.2d 428 (Ill. App. 1988).

A drug may be deemed unreasonably dangerous because of the absence of an adequate warning or sufficient information accompanying the product, because the product may be "unavoidably unsafe" without such warning or information. *Batteast v. Wyeth Laboratories, Inc.,* 526 N.E.2d 428 (Ill. App. 1988) [*See* RESTATEMENT (SECOND) OF TORTS § 402A, comment k (1965)]. The determination as to the adequacy of warnings that are included in a package insert of a drug distributed to the medical profession is a question that is within the province of the trier of fact. In *Batteast,* the court found the evidence sufficient to support the plaintiffs' contention that a

manufacturer's aminophylline suppositories were unreasonably dangerous due to the lack of adequate warnings accompanying the product. Numerous communications from the FDA concerning risks of the product and requests that the manufacturer change its package insert to advise physicians of those risks, established that the manufacturer was aware of certain risks involved in administering aminophylline suppositories to children but failed to warn the medical profession of those risks. Specifically, the court found that the package insert failed to warn physicians of the following risks: (1) severe intoxication and death have followed rectal administration because of hypersensitivity or overdosage; (2) adverse reactions include circulatory failure and respiratory arrest; (3) absorption from rectal administration is unreliable and there is great variation from patient to patient in dosage needed in order to achieve a therapeutic blood level; (4) when prolonged or repeated use is planned, blood levels must be monitored to establish and maintain an individualized dosage; (5) toxic synergism may result when aminophylline is combined with other sympathomimetic bronchodilator drugs; (6) tonic and clonic convulsions are an adverse reaction to the use of aminophylline treatment; (7) indications of aminophylline poisoning are often masked by the patient's other symptoms; (8) no formal recommendation had ever been made concerning the advisability of cutting any dosage of an aminophylline suppository in half; and (9) enemas should be utilized for rectally administered overdosage.

The *Batteast* court reasoned further that full and complete disclosure concerning the potential adverse reactions of a drug is necessary to enable a health care provider to render an informed decision regarding utilization of the drug, and that in this case the lack of knowledge of these warnings seriously impaired the treating physician's ability to properly formulate a risk benefit analysis for the drug aminophylline, to determine whether aminophylline should be utilized and to institute appropriate measures to insure that the drug was used effectively and safely. The court concluded that the warnings contained in the package insert distributed with the defendant's aminophylline suppositories were clearly inadequate for the medical profession as a whole, and specifically for the plaintiff's physician.

Even if a drug is found to be unreasonably dangerous, its defective condition must be established to be a proximate cause of the injury before a plaintiff can recover. *Batteast v. Wyeth Laboratories, Inc.,* 526 N.E.2d 428 (Ill. App. 1988). A proximate cause of an injury is any cause which, in natural or probable sequence, produced the injury. It need not be the only cause, nor the last or nearest cause; it is sufficient if it concurs with some other cause acting at the same time, which in combination with it, causes the injury. In *Batteast,* the evidence supported a jury finding that the manufacturer's distribution of an inherently dangerous drug, without obtaining FDA approval and without providing instructions or warnings of possible adverse interaction effects, was the proximate cause of the plaintiff's injury. The treating physician testified that he would not have ordered the defendant's aminophylline suppositories for the infant plaintiff if he had been made aware of the risk of death to children from hypersensitivity to the drug, or if he had known of the potential dangers listed in the "Adverse Reactions" section of FDA guidelines that were not incorporated into the manufacturer's labeling. The physician testified further

that when he was treating the infant, he was not aware of the patient-to-patient variation in absorption of aminophylline, and that if the manufacturer had alerted him to this fact, and of the difference in dosages necessary to achieve the therapeutic range, he would have been able to treat the infant with individual dosages monitored by blood studies. Under these circumstances, and the fact that other causes may have contributed to the infant's injury did not absolve the manufacturer of liability for its failure to market the drug in a safe condition through the utilization of adequate warnings, and a jury finding that the failure to provide such warnings was the proximate cause of the infant's injuries was reasonable. *Batteast v. Wyeth Laboratories, Inc.,* 526 N.E.2d 428 (Ill. App. 1988).

A manufacturer will not be liable if the plaintiff fails to establish that the defendant's drug was the proximate cause of the plaintiff's injury. In *Haggerty v. The Upjohn Company,* 950 F. Supp. 1160 (S.D. Fl. 1996), for example, the plaintiff failed to establish causation where the plaintiff's expert failed to rule out other possible causes of the plaintiff's behavior, including, *inter alia,* that the plaintiffs injuries – incurred when the plaintiff jumped from a balcony – may have been caused by the plaintiff's consumption of alcohol and an unknown number of Valium tablets, along with one tablet of Halcion manufactured by the defendant, before he jumped from the balcony (*see* detailed discussion of the court's *Daubert* analysis in Sect. 5, below).

Causation will not be established of the evidence which shows that the patient knew of the risk of adverse drug interaction, but consented to take the drug after having been informed of the risk. *See Eck v. Parke, Davis & Co.*, 256 F.3d 1013 (10th Cir. 2001) [evidence established that defendant's drugs interacted to cause a patient's liver failure, but the manufacturer was not liable because evidence also established that patient was aware of risk of drug interaction but decided to take drug despite risk].

Where a person's death may have been caused by taking excessive doses of a combination of prescribed pain medications, the fact that the patient took excessive doses may not bar a plaintiff's recovery where the evidence establishes that it is not unusual for a patient in extreme pain to take more than the prescribed dosage, and that a physician may even have verbally advised the patient to take more than the prescribed dosage if necessary to alleviate the pain. In *Dean v. K-Mart Corp.,* 720 So.2d 349 (La. App. 1998), a patient died from respiratory failure due to the combination of prescribed opiates, benzodiaprezines and propoxyphene, which the patient was taking to alleviate the pain from a work-related injury. The court ruled that even if the patient was taking excessive doses, this would not break the causal chain between his work-related injury and his death from the prescribed medications. One caveat: this was a workers' compensation case, in which a claimant must establish causation but need not establish fault on the part of the defendant in order to receive benefits. It may have limited value as precedent in a tort case in which the plaintiff must establish both negligence and causation by a preponderance of the evidence.

Multiple Theories of Liability

A cluster of cases have challenged the manufacturer of Parlodel, a drug used to inhibit postpartum lactation, and Methergine, a drug used to reduce the size of the uterus and postpartum hemorrhage, in actions based, *inter alia,* on strict liability in tort, negligence, breach of implied warranty, breach of express warranty, fraud, negligent misrepresentation, fraud by concealment, civil conspiracy, concert in action, loss of consortium and seek punitive damages based on the defendant's conduct. *See, e.g., Eve v. Sandoz Pharmaceutical Corp.*, 2001 U.S. Dist. LEXIS 4531 (S.D. Ind. 2001); *Globetti v. Sandoz Pharm. Corp.,* 111 F. Supp. 2d 1174, 1176 (N.D. Ala. 2000)]; *Glastetter v. Novartis Pharm*., 107 F. Supp. 2d 1015 (E.D. Mo. 2000); *Brumbaugh v. Sandoz Pharm. Co.,* 77 F. Supp. 2d 1153 (D. Mont. 1999); *Hollander v. Sandoz Pharm. Corp.,* 95 F. Supp. 2d 1230, 1238-39 (W.D. Okla. 2000)].

In each of these cases, the defendant filed pre-trial motions in limine and requested *Daubert* hearings, to challenge the scientific reliability of the plaintiffs' evidence of medical causation. In some of these cases the defendants succeeded in striking the plaintiffs' medical and scientific evidence of causation [e.g., *Glastetter*; *Brumbaugh*; *Hollander*]; in others, the trial court ruled the medical and scientific evidence admissible, and allowed the cases to go forward [e.g., *Eve; Globetti*]. The evidence offered by both the sides was essentially the same in all of the cases, and is summarized in detail in the context of the *Daubert* analyses in Sect. 5, below.

Cross-Claims by Physicians or Pharmacists Against Pharmaceutical Manufacturers

In *Bocci v. Key Pharmaceuticals, Inc.,* 974 P.2d 758 (Or. App. 1999), the defendant physician filed a cross-claim against the defendant pharmaceutical manufacturer for negligence and fraud, where the manufacturer's promotions had endorsed its product, Theo-Dur (theophylline), as a safe drug; the promotions had been the subject of a Food and Drug Administration (FDA) letter of adverse findings that advised the manufacturer to cease promoting the drug as safe, and there was other evidence that the company knew about adverse and fatal interactions between theophylline and ciprofloxacin that were not communicated to the physician. The physician claimed that the manufacturer's promotions were a substantial contributing factor to his failure to diagnose and treat the plaintiff's theophylline toxicity, and were therefore cause in fact and proximate cause of the plaintiff's brain injury that was caused by the misdiagnosis. This cross-claim resulted in a $23 million verdict for compensatory and punitive damages in favor of the physician. The $23 million award to the physician was upheld as not excessive in *Bocci v. Key Pharmaceuticals, Inc.,* 22 P.3d 758 (Or. App. 2001).

Reliability of Forensic Evidence of Causation

The Parlodel/Methergine cases described in Sect. 3, above, provide an excellent example – taken as a whole – of the factors a trial court may consider in ruling on the admissibility of medical and scientific evidence of causation, and of the fact that cases with essentially the same facts may be resolved differently, depending on the manner in which a particular court exercises its discretion in ruling on the admissibility of medical and scientific evidence. The complex undisputed facts, as summarized by the *Eve* court, established as follows.

In the Fall of 1989, the plaintiff – a healthy 29-year-old woman with no obstetrical or other pre-existing health problems – delivered a child by caesarean section, and was given a routine 3-day prescription for Methergine to stop postpartum hemorrhage. She had elected not to breast feed her baby, so was also given a 2-week prescription for Parlodel (an ergot alkaloid) to prevent lactation. She took the prescriptions simultaneously while in the hospital without incident, and was discharged with instructions to take the remaining Parlodel pills until the prescription was gone. She began experiencing severe headaches the day after discharge, took Tylenol (acetaminophen) without success, then tried Sudafed (pseudoephedrine), also without success.

One day later, "the really big pain came in," it "felt like there was some liquid started to run through the back of my head and it felt like somebody had a brick pounding it inside my head." She was admitted to the emergency room for treatment of the headache, presented as dysthartic, slightly confused, aphasic with right hemiparesis, blood pressure of 166/89 and a CT scan revealed that she had suffered an intracerebral hemorrhage ("ICH") or stroke.

A routine drug screen conducted on admission indicated the presence of pseudoephedrine and acetaminophen (which, in limited circumstances, can be vasoconstrictors and can elevate blood pressure) and caffeine. During her hospitalizations for the stroke and subsequent rehabilitation, several cerebral angiograms, MRI and CT scans revealed no evidence of alternative causes of her ICH – such as aneurysm, alteriol venous malformation ("AVM"), microemboli or micotic emboli – so her physicians concluded that the etiology of the stroke was unknown.

The plaintiff's physician testified that both Parlodel and Methergine are considered to be vasoconstrictors, and opined to a reasonable degree of medical probability, based on the vasoconstrictive action of these drugs, that Parlodel and possibly the Methergine were contributing factors to her stroke, and that in a normal delivery, the postpartum period itself would not significantly increase the risk of stroke. Plaintiffs' experts – a physician and a toxicologist – had worked directly with Parlodel safety issues prior to any Parlodel litigation. The physician had served on the FDA when Parlodel was first approved for Parkinson's disease, and the toxicologist had researched the toxicology of Parlodel and published an article on the subject in a peer-reviewed journal. Using differential diagnosis, these experts ruled out, to a reasonable degree of medical certainty, alternative causes of her stroke other than Parlodel.

Concerning the pharmacology and history of Parlodel, it was undisputed that the active ingredient of Parlodel is bromocriptine mesylate ("bromocriptine"), one of several ergot alkaloids; it differs structurally and physically from other ergot alkaloids in that a bromine atom has been added; it prevents lactation from occurring by blocking the secretion of the hormone prolactin, which acts on the breasts to induce the secretion of milk; it is typically prescribed for 14 days for this purpose. It had been sold since 1978; the FDA had approved it in 1980 for use in preventing postpartum lactation in women who could not or elected not to breast-feed; the manufacturer withdrew the Parlodel indication for prevention of physiological lactation in 1994, after receiving notice that the FDA would be filing a notice of opportunity and hearing to withdraw Parlodel for that indication. Parlodel remained FDA-approved at the time of trial for the treatment of Parkinson's Disease, amenorrhea (absence of menses), galactorrhea (abnormal production of breast milk) and acromegaly (chronic hyperpituitarism).

Concerning the pharmacology and history of Methergine, it was undisputed that the active ingredient of Methergine is methylergonovine maleate, also an ergot alkaloid; it is vasoconstrictor that has been reported in some patients to cause immediate and transient elevations in blood pressure. Methergine had been sold by the defendant and used for routine management after delivery of the placenta, postpartum atony, postpartum hemorrhage and postpartum subinvolution, since the late 1940s, and remained FDA approved for these purposes at the time of trial. There were no epidemiologic or controlled scientific studies showing an increased risk of stroke among patients of any type who take Methergine, either in conjunction with Parlodel or otherwise.

Concerning the Plaintiffs' claims alleging fraud, misrepresentation and failures to warn, it was undisputed that the FDA reported problems among women receiving Parlodel in conjunction with other ergot derivatives such as Methergine in 1983, and suggested revisions in both the Adverse Reactions and Warnings sections of the defendant's package insert to include the reports of adverse reactions, as well as a statement regarding use of Parlodel in women who had already received or were receiving other ergot alkaloids. Specifically, an FDA Bulletin on December 1, 1983, discussed the adverse drug reactions ("ADRs") reported to it regarding Parlodel taken with other ergots in a publication entitled "ADR Highlights," noting that "in the present bromocriptine labeling it may be difficult for the physician to identify bromocriptine as another ergot alkaloid," and that use of bromocriptine "with other ergot alkaloids as well as its use with vasoconstrictive drugs may represent a hazard to the postpartum women." It was also undisputed that in October, 1983, the defendant received a doctoral thesis written by a French physician, Dr. Bousbacher, regarding the side effects of Parlodel in postpartum women. In March 1985, the FDA specifically requested that Parlodel should be "contraindicated" for women diagnosed with "toxemia of pregnancy" and for those who had also received other ergot alkaloids after delivery, including specifically, Methergine and Cafergot, and specifically instructed the defendant to make these revisions within 6 months or by the next package insert printing, whichever came first.

The defendant refused to contraindicate Parlodel and other ergots in 1985 and for the entire period Parlodel was marketed for prevention of postpartum lactation. Within 1 week of the FDA request, the defendant's Marketing Department was asked to quantify the use of Methergine or Ergotrate to determine the effect on sales of the FDA-requested contraindication with Parlodel. "The feeling among Marketing Management was that Methergine or Ergotrate was always used in delivery so that a contraindication would virtually wipe out Parlodel's use" in the prevention of postpartum lactation. The defendant expected to generate $35 million in Parlodel sales for this use in 1985, and concluded at an internal meeting in 1985 that the Methergine/Cafergot-Parlodel contraindications request was "prejudicial" to the defendant "by naming two of [defendant's] products." The defendant replied to the FDA with an opposition to any revision of its labeling, but said it was willing to contraindicate the use of Parlodel in women with "toxemia of pregnancy."

The FDA sought additional adverse reaction reports follow-up, reiterated its belief that the defendant was withholding information and substituting its interpretation of diagnoses for the treating physicians' diagnoses, approved a change in the Methergine package insert but requested a new revision to include a Drug Interaction subsection "with information about concurrent administration of other vasoconstrictors," such as Methergine. Some of the defendant's medical personnel urged that the Parlodel/Methergine contraindication be included in the package insert; the defendant's management deemed the labeling changes would be "catastrophic"; the final Methergine package insert never adopted the explicit language warning against the concomitant administration of Parlodel with Methergine.

The plaintiff's physician testified that his understanding regarding the recommendations for the concomitant use of ergot alkaloids was that "for any prolonged period of time, the two used together was not recommended," so he was not aware, in 1989, of any problem in prescribing Methergine for only 2 days along with Parlodel.

In 1987, at the FDA's request, the defendant updated the Parlodel package insert to include a reference to adverse effects such as seizure, stroke and MI, and issued a "Dear Doctor" letter to inform physicians of the labeling changes. The FDA "did not like the appearance of the 'Dear Doctor' letter" and found that it "reflected" a "promotional tone." Further, an FDA physician did not receive a copy of the "Dear Doctor" letter, and "a canvas of ten ACOG [American College of Gynecologist] members attending [an FDA meeting] revealed that only one member recalled receiving the letter." The defendant commissioned a study in 1988 entitled "Physicians Reactions to a New Communication on the Use of Parlodel in Postpartum Lactation," which concluded that "Despite the previous mass mailing of a letter to OB/GYNs that described the remote possibility of serious side effects with patients who take Parlodel for postpartum lactation, this information did not reach a slight majority of the physicians in this study." The plaintiff's treating physician testified that he did not receive one.

The defendant aggressively marketed Parlodel throughout the late 1980s, and in 1987 issued an internal memo to its sales force explaining that while it had "modified the Parlodel package insert," the sales representatives were instructed: "Remember, this issue should not be mentioned unless a discussion is initiated by

the physician." One of the defendant's sales representatives testified that he recalled the memo, and that "by August of 1987 we knew that the medication was hurting a lot of people, and we knew the FDA wanted the company to pull the medication and the more pressure the FDA put on the company to pull the medication, the more ardently the company [was] 'wining and dining the sales reps' to encourage us to promote the drug harder because there was a, I would generalize it as, a general fog over the sales reps because we knew what we were doing was wrong, it's as simple as that." One of the defendant's physician "thought leaders" admitted in his deposition that despite his touting the benefit of Parlodel for lactation suppression to other doctors at hospital meetings, he never prescribed Parlodel or any lactation suppressant to any of his obstetrical patients.

In 1988, the FDA Fertility and Maternal Health Drugs Advisory Committee found that "drugs are not to be used routinely to suppress lactation. . . . Drugs should only be available to women with specific conditions, such as women who deliver stillborns."

The defendant commissioned an epidemiology study to examine the relationship between Parlodel and strokes and seizures in postpartum women, the results of which suggested, in 1988, that women taking Parlodel were at an increased risk of having strokes (relative risk 8.44) and late occurring seizures (finding a "substantial positive association" of 60% increased risk) and that for patients taking Parlodel with ergonovine/Methergine "there is an extremely positive association between bromocriptine and late-occurring seizures among those who received ergonovine," and that these women were at a 49-fold increased risk of having a late occurring seizure. The author of the study agreed under oath that, based on the study data, Parlodel is a risk factor for postpartum women for late occurring seizures, alone and in conjunction with ergonovine/Methergine. The previously mentioned study of physicians' reactions to the "Dear Doctor" letter also found that the results of the epidemiological study would be a deciding factor in influencing physicians' future prescribing practices for Parlodel.

The defendant publicly maintained the position that the epidemiological study "reinforces the safety" of Parlodel. The defendant's "Parlodel Business Plan" for 1989 assured that "a comprehensive defense plan has been established hinging on positive results of the [epidemiological] study. Promotional efforts will increase . . . ." In late 1988, the defendant issued a "Parlodel Update" to the "field force personnel," stating that the epidemiological study "did not find an association between the use of Parlodel and reports of seizures – which can occur spontaneously in women who have recently given birth," and that "In our opinion, the data clearly reinforce the safety of Parlodel in treating postpartum lactation."

A January, 1989 memo from the President of the defendant's research institute noted that the epidemiological study found a "strong positive association between ergonovine use, Parlodel and seizure."

An epidemiologist of the defendant who attended the data presentation meeting opined that the data "is supportive of an interaction between bromocriptine and ergonovine." The defendant's Associate Director of Medical Operations wrote, with respect to the epidemiological study, "There was a subset of the group, however,

with a significantly elevated risk for late-occurring postpartum seizure: this group comprised of those who also received ergonovine had a 49-fold greater risk of seizures. With this in mind, I recommend that we amend our package insert so that Parlodel is contraindicated in women who have also received ergonovine." One day after the data presentation meeting, an officer of the defendant requested that the defendant "recut the data on late-onset seizures using 48 and 96 hours as the cut off. This may change all data on ergonovine combination problems." He also urged "in the final report, the information on the risk of drug interaction should not be the major conclusion."

The defendant never placed a contraindication regarding bromocriptine and ergonovines in its package insert, and did not mention the "extremely strong positive association" for late-occurring seizures in women who had received Methergine/ergonovine after delivery in its sales brochure, "A Comforting Thought." The only information provided to prescribing physicians in the sales brochure was that there was no effect, and even a possible protective effect, for seizures from Parlodel use.

In mid-1989, the 12-member Fertility and Maternal Health Drugs Advisory Committee ("FDA Advisory Committee") unanimously reaffirmed its 1988 recommendations, stated that there is no need for prophylactic treatment other than analgesics and breast support for postpartum breast engorgement, that it had not been provided with evidence that bromocriptine was a safe and effective treatment for symptoms of postpartum breast engorgement, and unanimously recommended that neither hormones nor bromocriptine "should be used for this indication because they have not been shown to be equally or more effective than analgesics and breast support, and because they may induce adverse medical effects."

The defendant reacted to these findings and recommendations with an internal memorandum to its sales force that the FDA Advisory Committee recommendation that drugs no longer be used for postpartum lactation prevention "was based on beliefs of the committee members that there is 'no need' for pharmacologic therapy for lactation suppression," that the recommendations were "advisory only," and that Parlodel "can continue to be prescribed with confidence." The defendant's "selling Strategy" for the third and fourth quarters of 1989 told sales representatives to continue to sell Parlodel aggressively. A sales representative testified that "we were just advised that Parlodel was obviously receiving a lot of heat in the journals and from the FDA and that we needed to bleed every dollar that we could get out of Parlodel before the FDA just put a stop to it." He testified further that sales representatives were "never instructed to stop pushing Parlodel" because the "reality of the situation is that Parlodel represented millions and billions of dollars over time, and it was, in fact, the company's cash cow. . . .".

In late 1989, the FDA again found that no drugs, including Parlodel should be used for prevention of postpartum lactation, "because they have not been shown to be equally effective than [aspirin and breast binding], and they may induce adverse medical effects." In September 1989 – the month before the plaintiff's prescription – the FDA requested that the defendant withdraw Parlodel from the market for this purpose. In October 1989, the defendant refused, and stated that: "Parlodel should

not be used routinely but should remain available for specific circumstances under which the physician and patient decide that the drug is indicated . . . We believe in choice of therapy . . . must be left to an informed decision made jointly by a patient and her physician."

The plaintiff's physician testified he was never informed that in 1989, the FDA requested that the defendant withdraw Parlodel and that the defendant refused. He testified that he would have liked to have known the FDA's concerns, but no drug representative contacted him.

The 1989 package inserts for Parlodel and Methergine contained FDA-required and FDA-approved language. The package insert in effect for Parlodel at the time of the plaintiff's prescription stated, in pertinent part, as follows:

> WARNINGS . . . .
> Fifteen cases of stroke during Parlodel(R) (bromocriptine mesylate) therapy have been reported mostly in postpartum patients whose prenatal and obstetric courses had been uncomplicated. Many of these patients experiencing seizures and/or strokes reported developing a constant and often progressively severe headache hours to days prior to the acute event. Some cases of stroke and seizures during therapy with Parlodel(R) (bromocriptine mesylate) were also preceded by visual disturbances (blurred vision, and transient cortical blindness). Four cases of acute myocardial infarction have been reported, including 3 cases receiving Parlodel(R) (bromocriptine mesylate) for the prevention of physiological lactation. The relationship of these adverse reactions to Parlodel(R) (bromocriptine) mesylate is not certain.
> …
>
> ADVERSE REACTIONS.…
> Physiological Lactation
> Serious adverse reactions include 38 cases of seizures (including 4 cases of status epilepticus), 15 cases of stroke, and 3 cases of myocardial infarction among postpartum patients. Seizure cases were not necessarily accompanied by the development of hypertension. An unremitting and often progressively severe headache, sometimes accompanied by visual disturbance, often preceded by hours to days many cases of seizure and/or stroke. Most patients show no evidence of toxemia during the pregnancy.

The package insert in effect for Parlodel at the time of the plaintiff's prescription included the following language providing a warning regarding the administration of Parlodel with other ergot alkaloids such as Methergine:

> Although there is no conclusive evidence which demonstrates the interaction between Parlodel (bromocriptine mesylate) and other ergot alkaloids, concomitant use of these medications is not recommended. Particular attention should be paid to patients who have recently received other drugs that can alter blood pressure.

The package insert in effect for Methergine at the time of the plaintiff's prescription included the following language:

> Drug Interactions. Caution should be exercised when Methergine (methylergonovine maleate) is used concurrently with other vasoconstrictors or ergot alkaloids.

The 1989 PDR contained the same information about Parlodel as the package insert.

The plaintiff's physician testified that he relied on the PDR or the promotional literature distributed by the drug representative before prescribing a drug, and that

he was aware at the time of the prescription in 1989 that "uncontrolled hypertension, toxemia of pregnancy, [and] sensitivity to any ergot alkaloids" were contraindications for prescribing Parlodel.

When the FDA initially approved the defendant's first application to market the drug Parlodel in 1978, the FDA conditioned its approval on the basis that the defendant would conduct a clinical study of the safety and efficacy of Parlodel in humans. The defendant completed the clinical testing for this study in 1981, but, despite FDA requests, had not submitted the report of this study as of 1994 at which time an internal memorandum stated that the study ". . . is a skeleton in our closet that could cause embarrassment given the current sensitive situation with Parlodel. [The study] is a long term safety and efficacy study run as a condition of approval of the original FDA back in 1978. It still has not been submitted to the FDA." The defendant submitted the data to the FDA in 1996, after the FDA withdrew Parlodel from the market for use in preventing postpartum lactation. The final report of the study did not include the causal assessments based on a number of ADRs, which showed that the defendant had concluded that at least one patient did in fact suffer from Parlodel-related hypertension.

Plaintiffs' expert toxicologist, after reviewing the case reports of the patients in the study, found that: "11/57 [of] patients in the second limb of that study demonstrated increases of their blood pressure . . . one patient was listed in the [defendant's] internal report as having developed hypertension, with Parlodel listed as the cause. This causation assessment, done by [defendant], was not included in their report of the FDA." Other defects identified in the study and the report by the plaintiff's experts included: the defendant dropped hypertensive patients from the studies, buried blood pressure readings in reams of clinical data, without providing corresponding reference in the summary reports provided to the FDA; 28 cases of hypertension were not presented to the FDA in the respective clinical trial summary reports; in one Parlodel clinical trial, a critically important incident of "extreme, uncontrolled hypertension" suffered by a patient after taking Parlodel was neither reported nor presented to the FDA in summary reports for that study; the defendant concealed from the FDA the existence of animal studies, conducted prior to Parlodel's approval for human use, that revealed Parlodel's vasoconstrictive properties; and the author of one of the animal studies testified before FDA subcommittees in 1988 and 1989, and repeatedly told physicians, that the drug is not a vasoconstrictor, and can only cause vasodilation. A scientist of the defendant, charged with collecting Parlodel data for submission to the FDA, admitted that the defendant knew it was required by law to submit all animal studies to the FDA as part of the drug application process.

Concerning the relevance of the foregoing facts to the defendant's motion in limine, the court found that epidemiology is the study of disease patterns and risks in human populations; in a typical epidemiologic study, an epidemiologist compares the health of people exposed to a substance to that of persons not so exposed to determine whether the exposure to the substance is associated with an increased rate of disease; epidemiologic studies typically provide an estimate of "relative risk," which is the ratio of the incidence of a disease in exposed individuals to the

incidence in unexposed individuals; a relative risk of 1.0 means that the incidence in the groups is the same, that is, the exposure has no association with the disease, and if the study is properly performed, a relative risk below 1.0 means that the exposure is associated with the absence of the disease, whereas a relative risk significantly above 1.0 means that exposure is associated with an increased risk of the disease.

The court found that an adverse event report ("ADR") is a report made to a drug company or the FDA that a particular patient who was taking a particular drug experienced a particular medical problem; and these reports can be made by laypersons as well as doctors, but most are submitted by doctors.

The court found that case reports are "reports in medical journals describing clinical events in one or more individuals. They report unusual or new disease presentations, treatments, manifestations, or suspected associations between two diseases, effects of medication, or external causes." [citing Federal Judicial Center, Reference Manual on Scientific Evidence, at 374 (2d ed. 2000)].

The court found that "relative risk" cannot be derived from case reports; that no epidemiologic or controlled scientific studies have been performed showing an increased risk of stroke among patients of any type who take Methergine, either in conjunction with Parlodel or otherwise; and that there are no studies in live, intact animals showing that Methergine causes stroke.

Given this background, the court considered the defendant's motion in limine and request for a *Daubert* hearing on the admissibility of these witnesses' opinions, and exercised its discretion to admit the testimony under the *Daubert* trilogy. *See Daubert v. Merrell Dow Pharm.*, 509 U.S. 579, 125 L. Ed. 2d 469, 113 S. Ct. 2786 (1993); *General Elec. Co. v. Joiner*, 522 U.S. 136, 139 L. Ed. 2d 508, 118 S. Ct. 512 (1997); *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 152, 143 L. Ed. 2d 238, 119 S. Ct. 1167 (1999). The court reviewed other rulings in Parlodel litigation in which the admissibility of the same plaintiffs' experts had been ruled either admissible [*citing*, e.g., *Kittleson v. Sandoz Pharm. Corp.,* No. CIV 98–2277, 2000 WL 562553 (N.D. Minn. Mar. 3, 2000); *Globetti v. Sandoz Pharm. Corp.,* 111 F. Supp. 2d 1174, 1176 (N.D. Ala. 2000)] or inadmissible [*citing*, e.g., *Glastetter v. Novartis Pharm.*, 107 F. Supp. 2d 1015 (E.D. Mo. 2000); *Brumbaugh v. Sandoz Pharm. Co.,* 77 F. Supp. 2d 1153 (D. Mont. 1999); *Hollander v. Sandoz Pharm. Corp.,* 95 F. Supp. 2d 1230, 1238-39 (W.D. Okla. 2000)], and ruled the testimony admissible in this case.

There was no dispute in any of the Parlodel cases that there was no epidemiological evidence to support the witnesses' opinions, that their opinions were based only on case reports, rechallenge reports, animal studies, comparisons of the ergot bromocriptine to other ergots, FDA regulatory actions and internal documents of the defendant. The court in *Eve* reasoned that epidemiological evidence may be the best scientific evidence that can be presented, but noted that *Daubert* simply requires reliable evidence. The court found that the witnesses relied on the methodology of differential diagnosis, a method widely used by medical clinicians to identify medical conditions so they may be treated and that the cumulative evidence upon which the witnesses relied satisfied the *Daubert* requirements of

scientific reliability. The court specifically relied on the reasoning of *Globetti, supra,* in making its ruling, as follows:

> Plaintiffs argue powerfully that an epidemiological study of the association of Parlodel and AMI is not practical because of the relative rarity of AMIs among postpartum women. To gather a population of postpartum women with a sufficient sub-population of those who have suffered an AMI to be statistically significant would require hundreds of thousands, if not millions, of women. The evidence suggests that AMI occurs in postpartum women at the rare rate of 1–1.5 per 100,000 live births. Thus, even in a study of one million women, the sub-populations of those suffering an AMI would be only ten to fifteen women, far from enough to allow drawing any statistically significant conclusions. In short, the best scientific evidence is that presented by plaintiff's experts. *Globetti*, 111 F. Supp. 2d at 1179 (footnote omitted) (emphasis added).
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> In a footnote, the *Globetti* court further noted, "While not suggested by defendant, the court notes that it would be medically and scientifically unethical to attempt a control-group experiment. To do so would require administering Parlodel to women and exposing them to the possibility of life-threatening events like AMI and stroke. Indeed, to prove the association between Parlodel and AMI or stroke, the scientist would have to expect a certain number of deaths among the test subjects." *Globetti*, 111 F. Supp. 2d at 1179 n.5.

Eve, supra. The reader is referred to cases cited above for judicial reasoning that resulted in the exclusion of the evidence that was admitted in the *Eve* case.

Another good example of the application of the *Daubert* trilogy to the medical and scientific evidence in drug interaction litigation is *Jones v. United States,* 933 F. Supp. 894 (N.D. Cal. 1996). Here, a husband and wife filed a wrongful birth action against the United States under the Federal Tort Claims Act, seeking costs and damages associated with raising their daughter, alleging that the child was born because US Army doctors negligently failed to warn the mother that Penicillin-VK, prescribed prophylactically prior to oral surgery, could interfere with the effectiveness of her Triphasil-28 birth control pills. The plaintiffs offered expert testimony of two expert witnesses – a board-certified obstetrician-gynecologist and a pharmacist – to show that penicillin interferes with the effectiveness of the birth control pills.

The court held a *Daubert* hearing to determine whether the expert testimony was sufficiently reliable to be admitted. The court found that neither of the witnesses had conducted independent research in the area of antibiotic/oral contraceptive interaction, that the physician's opinion was based solely on published articles he read during the 7 h in which he did research in preparation for his testimony, and concluded that their opinions were not based on objective, verifiable evidence that was derived from scientifically valid principles. The court found that the evidence showed, at most, that there is anecdotal support for the hypothesis that an unexplained interaction between certain antibiotics and oral contraceptives may reduce the effectiveness of the contraceptives, but did not establish a proven, cause-and-effect relationship that the court considered necessary to satisfy the *Daubert* standard.

Specifically, the court found that although the witnesses' claimed that their opinions were supported by numerous scientific articles, a careful reading of the articles revealed that many of their authors came to conclusions that differed from the conclusions of the plaintiffs' witnesses; that the witnesses extracted data from articles that found no statistically significant correlation between antibiotic use and

increased failure of oral contraceptives, and relied on the data to reach conclusions contrary to conclusions reached by the authors of the articles. The court stated that "This tactic does not qualify as good science." Furthermore, the court found that the only articles that supported the experts' opinions were are not based on controlled, scientific studies, but on anecdotal case reports, reviews of research done by other people, or studies that lacked a control group, and were therefore not based on scientific method.

The plaintiffs also relied on the package labeling of the Triphasil-28 as evidence of causation. The label warned that certain antibiotics may "possibly" have an effect on oral contraceptive effectiveness. The court found this warning to be even less probative of causation than the inconclusive studies upon which plaintiffs' experts relied, and stated that ". . . a boilerplate warning on a drug package insert may reflect no more than an overly cautious response to possible liability, not scientific proof of causation." The court concluded that the plaintiffs' experts ". . . did not rely on a single, controlled study that showed a statistically significant correlation between antibiotic use and decreased effectiveness of oral contraceptives. Consequently, the Court finds that Plaintiffs' evidence does not satisfy the first prong of the *Daubert* standard."

The court reasoned further that under California law, a plaintiff must establish both general causation – "that the Defendant's conduct increased the likelihood of injury," and specific causation – "that the defendant's conduct was the probable, not merely a possible, cause of the injury."

To establish general causation, the court stated that the plaintiffs would have to show that there is a scientifically validated interaction between Penicillin-VK and Triphasil-28 birth control pills that made it more likely that the plaintiff would become pregnant while taking both drugs than if she were taking birth control pills alone, and that the evidence did not meet this requirement. The court found to the contrary, based on the testimony of the plaintiffs' experts. They testified that antibiotics kill bacteria in the digestive system, thereby interfering with the mechanism by which oral contraceptives release estrogen into the woman's body, thereby lowering estrogen levels in a manner that reduces the contraceptive effect of the birth control pills and allows the woman to ovulate and become pregnant. The court observed, however, that Triphasil-28 birth control pills have two components, estrogen and progestin, and that each component has independent contraceptive effect. The progestin component is metabolized differently than the estrogen component, and the plaintiffs' experts presented no scientific evidence to show that antibiotics interfere with metabolization of progestin. Even if scientific evidence showed that antibiotics interfered with the estrogen component, the court inferred that the progestin component would still prevent pregnancy.

To establish specific causation, the court stated that the plaintiffs would have to show that the interaction between Penicillin-VK and Triphasil-28 birth control pills was the probable, not merely a possible, cause of plaintiff's pregnancy, which would require them to show that such an interaction occurs at more than double the rate of the known failure rate for oral contraceptives alone. The court found no competent testimony on this issue, and found that none of the articles relied upon by the plaintiffs'

experts were controlled, broad-based studies of the existence of an interaction between antibiotics and oral contraceptives, let alone the rate at which such an interaction occurs.

The court concluded that the plaintiff failed to prove by a preponderance of the evidence that she became pregnant during the time that she was taking Penicillin-VK. Expert testimony concerning the length of time between conception and the ability of the pregnancy test to detect a pregnancy, and the date of administration of the antibiotic, supported a contrary conclusion that she conceived before she began taking the antibiotics. Proximate cause was, accordingly, not established.

Similar scrutiny was applied by the court in rejecting the plaintiff's causation expert in *Haggerty v. The Upjohn Company*, 950 F. Supp. 1160 (S.D. Fl. 1996). The plaintiff injured his neck while working as a drywall installer, underwent surgery for a herniated disc and was released with a post-surgical prescription for Halcion (triazolam, a benzodiazepine) to help him sleep. He claimed that the warnings that accompanied the Halcion were inadequate and failed to warn him of potential side effects, which allegedly caused him to engage in bizarre behavior, with severe consequences.

Specifically, he claimed that one night, approximately 2 months after his release from the hospital, he took one Halcion tablet, went to bed at approximately 6:30 p.m., and that his next recollection was waking up in a hospital room the following morning with a fractured back. He alleged that ingestion of the Halcion tablet significantly altered his behavior, causing him to become belligerent, aggressive, suffer from hallucinations and conduct himself in a bizarre and agitated fashion, culminating in his leaping from the balcony on the second story of his apartment complex. Additionally, on that same evening, the plaintiff reportedly assaulted and threatened his live-in girlfriend with a knife, assaulted his 8-year old son and a neighbor, and walked around his apartment and building without clothing. He alleged further that as a result of his Halcion-induced conduct on the evening of April 20th, his live-in girlfriend obtained a restraining order to prevent him from returning to his apartment, his two children from a prior marriage who had been residing with him were adjudicated dependent and placed in foster care, and upon his discharge from the hospital he was arrested for aggravated assault, battery, aggravated battery and indecent exposure, for which he was ultimately imprisoned and lost his parental rights over his two children.

The defendant manufacturer contended that the Plaintiff misused Halcion by ingesting numerous tablets of the drug concurrently with large quantities of alcohol and an unknown number of Valium tablets. The defendant also presented evidence of the plaintiff's long history of alcohol and poly-substance abuse, frequent physical attacks on the women with whom he had lived, usually occurring while he was under the influence of alcohol and testimony of several experts that the defendant suffered from various psychiatric personality disorders.

The defendant filed a motion in limine to exclude the testimony of the plaintiff's causation expert, who possessed a Ph.D. in pharmacology, and a motion for summary judgment on grounds that her opinion was inadmissible, and the plaintiff therefore lacked any evidence that the defendant's drug caused his injuries.

The plaintiff's expert testified at the hearing on the motion in limine that, in her opinion, Halcion caused the psychiatric and behavioral effects experienced by the plaintiff in the evening in question. She testified that her opinion was based on a review of spontaneous reports of adverse medical events involving Halcion collected by the Food and Drug Administration in its Spontaneous Reporting System ("SRS"), along with anecdotal case reports appearing in the medical literature, references in textbooks to non-Halcion studies of psychomotor agitation in rats and mice, peer reviewed articles summarizing primary clinical findings which she had not personally reviewed, newspaper articles from the lay press, correspondence to the FDA from a public interest group, a secondary summary prepared by Dr. Anthony Kales which provided a detailed listing of primary citations with abstracts of primary findings, and European post-marketing surveillance reports. She testified further that she had not performed any independent research on the alleged adverse side effects of Halcion.

The plaintiff's expert also testified that she employed an inductive reasoning process to arrive at her conclusions, which she called "differential etiology" or "differential diagnosis," by which she arrived at a conclusion about the cause of the plaintiff's conduct by considering possible causes and attempting to eliminate all other possible causes but the Halcion. The court found it significant, however, that the witness cited no epidemiological studies to support a causal relationship between Halcion and the plaintiff's conduct, that she did not perform a clinical examination of, or even meet, the plaintiff before forming her opinion on causation, that she did not consider any psychiatric or psychological evaluations or diagnoses of the plaintiff before forming her opinion and was unaware of a psychological evaluation that resulted in a diagnosis of borderline personality disorder in the plaintiff, that she had not read two psychological evaluations which indicated that, because of his personality defects, the plaintiff was likely to express his anger in an unpredictable and explosive manner, and was at risk for displaying unprovoked and exaggerated aggressive outbursts. The witness testified further that another possible cause of the plaintiff's conduct, which ought to have been considered in her differential diagnosis, was significant drug interaction or abuse of alcohol, and that all of the plaintiff's behavior on the evening in question could have been the result of alcohol intoxication, which would have worsened any existing psychological or psychiatric disorder he may have. Finally, the witness had not reviewed the rescue report from the evening in question, which indicated the plaintiff drank six or seven beers and had taken an unknown number of Valium tablets on that evening.

Based on the foregoing, the court found that the plaintiff's expert's opinion was not based on scientifically valid principles, was inadmissible, and granted the defendant's motion for summary judgment.

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Globetti v. Sandoz Pharm. Corp., 111 F. Supp. 2d 1174, 1176 (N.D. Ala. 2000)
Haggerty v. The Upjohn Company, 950 F. Supp. 1160 (S.D. Fl. 1996)
District of Columbia Circuit
Whittle v. United States, 669 F. Supp. 501 (D DC 1987)
Arizona
Lasley v. Shrake's Country Club Pharmacy, Inc., 880 P.2d 1129 (Ariz. 1994)
Florida
Johnson v. Walgreen Co., 675 So.2d 1036 (Fla. 1st D.C.A. 1996)
Sanderson v. Eckerd Corporation, 780 So.2d 930 (Fla. App. 2001)
Georgia
Singleton v. Airco, Inc., 314 S.E. 2d 680 (Ga. App. 1984)
Illinois
Batteast v. Wyeth Laboratories, Inc., 526 N.E.2d 428 (Ill. App. 1988)
Frye v. Medicare-Glaser Corporation, 605 N.E. 2d 557 (Ill. 1992)
Happel v. Wal-Mart Stores, Inc., 766 N.E.2d 1118 (Ill. 2002)
Kansas
Fuhs v. Barber, 36 P.2d 962 (Kan. 1934)
Louisiana
Dean v. K-Mart Corp., 720 So.2d 349 (La. App. 1998)
Massachusetts
Cottam v. CVS Pharmacy, 764 N.E.2d 814 (Mass. 2002)
Linnen v. A. H. Robbins Company, Inc., 1999 Mass. Super LEXIS 552 (1999)
Michigan
Baker v. Arbor Drugs, Inc., 544 N.W.2d 727 (Mich. App. 1996)
Missouri
Horner v. Spolito, 1 S.W.3rd 519 (Mo. App. 1999)
Ohio
Johnson v. State Medical Board of Ohio, 1999 Ohio App LEXIS 4487 (Ohio App 1999)
Oregon
Bocci v. Key Pharmaceuticals, Inc., 974 P.2d 758 (Or. App. 1999); *later proceeding*, 22 P.3d 758 (Or. App. 2001)

Table of Cases

Tennessee
Dooley v. Revco Discount Drug Centers, Inc., 805 S.W.2d 380 (Tenn. App. 1990)
Texas
Morgan v. WalMart Stores, Inc., 30 S.W.2d 455 (Tex. App. 2000)
Washington
Clausing v. State, 955 P.2d 394 (Wash. App. 1998)
McKee v. American Home Products Corp., 782 P.2d 1045 (Wash. 1989)
Silves v. King, 970 P.2d 790 (Wash. App. 1999)

References

1. Kenneth R. Baker, *The OBRA 90 Mandate and Its Developing Impact on the Pharmacist's Standard of Care*, 44 Drake L. Rev. 503 (1996).
2. Reference Manual on Scientific Evidence (Federal Judicial Center, 2000)
3. Restatement (Second) of Torts, §§323, 324A
4. Restatement (Second) of Torts § 402A, comment k
5. *Attorneys' Fees in Product Liability Suits,* 53 ALR4th 414
6. *Cause of Action Against Drug Manufacturer for Failure to Warn of Side Effects Associated With Prescription Drug,* 3 COA 815
7. *Duty of Medical Practitioner to Warn Patient of Subsequently Discovered Danger from Treatment Previously Given,* 12 ALR4th 41
8. *Federal Pre-emption of State Common Law Products Liability Claims Pertaining to Drugs, Medical Devices, and Other Health-Related Items,* 98 ALR Fed 124
9. *Liability of Hospital, or Medical Practitioner, Under Doctrine of Strict Liability in Tort, or Breach of Warranty, for Harm Caused by Drug, Medical Instruments, or Similar Device Used in Treating Patient,* 54 ALR3d 258
10. *Liability of Manufacturer or Seller for Injury Caused by Drug or Medicine Sold*, 79 ALR2d 301
11. *Liability of Manufacturer or Seller for Injury or Death Allegedly Caused by Failure to Warn Regarding Danger in Use of Vaccine or Prescription Drug,* 94 ALR3d 748
12. *Liability of United States Under Federal Tort Claims Act for Damages Caused by Ingestion or Administration of Drugs, Vaccines, and the Like, Approved as Safe for Use by Government Agency,* 24 ALR Fed 467
13. *Physician's Liability for Injury or Death Resulting from Side Effects of Drugs Intentionally Administered To or Prescribed For Patient,* 45 ALR3d 928
14. *Products Liability: Admissibility of Expert or Opinion Evidence as to Adequacy of Warning Provided to User of Product,* 26 ALR4th 377
15. *Products Liability: Strict Liability in Tort Where Injury Results from Allergenic (Side-Effect) Reaction to Product,* 53 ALR3d 298
16. *Promotional Efforts Directed Towards Prescribing Physician as Affecting Prescription Drug Manufacturer's Liability for Product-Caused Injury,* 94 ALR3d 1080
17. *Strict Products Liability: Liability for Failure to Warn as Dependent on Defendant's Knowledge of Danger,* 33 ALR4th 368

Chapter 17
Psychotropic Medications and Crime: The Seasoning of the Prozac Defense

Michael Welner, Roy Lubit, and Jada J. Stewart

Abstract This chapter discusses those cases where examinees present a history of having been treated with psychotropic medication during the time of the offense. In such cases, forensic mental health professionals are consulted to address questions related to the mental capacities of a defendant at the time of an alleged crime. Related questions revolve around whether the medication is in part, wholly or not at all responsible for the crime. Attention drawn to the most notable cases has prompted psychiatrists to scrutinize the causal relationship between various medications and violent behaviors. The follow paragraphs explore the issue of psychotropics and crime within the medical community and among lawmakers – concluding that examining behavioral reactions to medications or combinations of medications is among the most complex medico-legal questions facing forensic psychiatrists

Keywords Prozac • Psychotropic medications • Crime • Forensic psychiatrist

Forensic psychiatrists are often asked to explore and assess the mental state of a defendant at the time of an alleged crime in order to opine on both the defendant's criminal responsibility (for prospective insanity and diminished capacity defenses), and as part of pre-sentencing efforts. When an examinee presents a history of having been treated with psychotropic medication at the time of the offense, the possible role of that medication in affecting the defendant's mental state needs to be addressed.

To appraise the possible influence of the psychotropic medication on the defendant's criminal behavior, the psychiatrist needs to address the following issues:

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Was the treatment responsible for the crime?
Was the disease being treated responsible for the crime?
Were both the treatment and disease responsible for the crime?
Were neither responsible for the crime?

Such is the complexity of human choices and criminal behavior, and the influence of neurophysiology interacting with the environment. Untangling the potential confounding factors is a fascinating challenge.

Defense strategies attributing crime to antidepressants, fluoxetine (Prozac) in particular, drew widespread attention in the 1990s [1]. Inspired by 1990 case reports published by a respected Harvard psychiatrist suggesting a strong link between Prozac and suicide, some defense attorneys attempted to attribute homicidal violence to the antidepressant medications that defendants were taking [2]. The controversy over a connection heightened when plaintiffs brought civil damages suits against Eli Lilly, manufacturer of Prozac, following violent events and suicides.

The most celebrated of these Prozac cases involved no criminal defense at all. Joseph Wesbecker, a depressed employee of Standard Gravure Printing Company in Louisville, Kentucky, walked into company offices in September 1989 armed with an AK-47 and four other weapons. He proceeded to shoot and kill eight co-workers and wound 12 others, before killing himself [1].

Mr. Wesbecker had a long and bitter relationship with his employer. He had been speaking of mass homicide as early as 1 year prior to the attack. Several weeks before the rampage, he had started taking Prozac. His medical history took on posthumous relevance when, 5 years later, 28 plaintiffs filed a 50 million-dollar lawsuit against Eli Lilly, manufacturers of Prozac.

Although the case settled – while a jury deliberated to a verdict exonerating Prozac – the controversial backdoor wrangling did little to quell the controversy. Nearly 200 civil suits followed; other medicines were also charged in civil complaints, including SSRI cousins sertraline (Zoloft) and paroxetine (Paxil) [1, 3]. The pharmaceutical companies scored an impressive streak of victories, and civil lawsuits petered out. Still, enough points of debate within the medical community exist to this day, and questions have not been fully relegated to the past.

The attention drawn to these notorious cases prompted psychiatrists to scrutinize the causal relationship between various medications and violent crimes. German reports of five times higher rates of suicides or attempted suicides in patients taking Prozac further promoted a discourse within the medical community and among lawmakers, while Eli Lilly scrambled to protect the reputation of its wildly successful medicine [4].

The subsequent deliberation included research and the convening of a special panel by the Food and Drug Administration. In 1991, that panel concluded that there was no link between Prozac and suicide. The FDA panel added that the bad outcomes were more likely a product of poor monitoring of depression by treating professionals [5]. Nevertheless, skeptics pointed to testimony before the Panel by a respected psychiatrist who was involved in the earlier studies of the drug. He had testified of a cluster of symptoms, “anxiety, panic attacks, poor concentration and insomnia,” that was associated with a higher risk of suicide in patients prescribed Prozac [6].

Whether it was the quality of available research exonerating Prozac and its cousin SSRI medicines from homicidality and suicidality – or the product of tremendous legal resources invested by pharmaceutical companies to confront civil and even criminal cases that blamed their product – criminal court verdicts have overwhelmingly rejected Prozac defenses thus far [7].

There have, however, been exceptions. On September 7, 1999, Douglas D. Lund of Annapolis, Maryland was arrested for attempted murder after an attack on his wife. His case was to become, to this day, the most successful use of a medication defense. Mr. Lund had no previous history of violence. He had been diagnosed in the past with attention-deficit hyperactivity disorder, and had recently received a diagnosis of depression; his treatment included the antidepressant sertraline (Zoloft).

At the time of the crime, Mr. Lund was experiencing sleeplessness, and had asked his wife Jo Ann to go for a drive at 3 AM. While driving, and without a word, Mr. Lund unhooked her seat belt, crashed the car into a steel fencepost, pushed her out of the car and began striking her head into the pavement and choking her. Then, he carried her to the nearby grass, as she pleaded with him to spare her life and to put her down. Without explanation, Lund then flagged down a passing motorist who called 911. Mrs. Lund suffered a broken back, collarbone, and finger. Based on medical testimony that Mr. Lund's diagnosis was bipolar disorder, manic, a judge found Mr. Lund not guilty by reason of insanity. He was released to the community in February 2001. His wife, an assistant state's attorney, supported him through his prosecution. Nevertheless, she filed for divorce.

There are numerous other medications that can have a marked impact on an individual's mental state. Some medicines can precipitate manic episodes and fuel violent behavior. In such settings, legal insanity might be a viable defense. In Mr. Lund's case, a diagnosis of substance-induced mania was plausible, in light of the potential for antidepressant medication to induce a hypomanic or manic episode in an individual with major depressive disorder or bipolar disorder [8–10].

Even for those who do not have so extreme a reaction as mania, or the more muted hypomania, agitation may result from virtually all antidepressants. Such a behavioral change, while not rising to a level of insanity, could sufficiently mitigate criminal responsibility to affect sentencing. Table 17.1 lists serotonergic and other antidepressants with their frequency of causing agitation.

Concerning the newest antidepressant Cymbalta (duloxetine), meta-analysis of 12 placebo-controlled trials ($n = 2{,}996$) found no evidence of an increase in risk of suicidal behaviors or ideation with duloxetine compared with placebo in patients with major depressive disorder. However, aggression and anger have been reported especially early in treatment and after treatment discontinuation [11]. Therefore, circumstances of a given case might reflect what has been identified in controlled research conditions; and thus, might be more viably applied.

Traditionally, psychiatrists have observed that suicidal risk often coincides with clinical *improvement*. This has generally been explained as the result of patients finally having the energy to act upon impulses that had existed all along [12]. Such an explanation should be considered in assessing violent crime, particularly of a suicidal nature, that occurs during a period when clinical records present a patient undergoing treatment, even showing symptomatic improvement.

Table 17.1 A list of serotonergic and other antidepressants causing agitation

Antidepressant	Incidence of agitation (%)
Cymbalta	5
Celexa	3
Paxil	1.1
Prozac	>1[a]
Zoloft	6

For those that do not have so extreme a reaction as mania, or the more muted hypomania, agitation may result from virtually all antidepressants. Such a behavioral change, while not rising to a level of insanity, could sufficiently mitigate criminal responsibility to affect sentencing

[a]PDR notes frequency in text, not table, Physicians Desk Reference © 2008 Medical Economics Montvale, NJ, p. 965

Psychiatric Medications Causing Confusion

Another important mental status effect resulting from psychiatric medications is the serotonin syndrome in which serotonin overload causes frank confusion and disorientation [13]. Each individual experiences sensitivity to serotonin differently, so serotonin syndrome is as much "hypersensitivity" as it is a manifestation of "overload."

The serotonin syndrome may occur even on seemingly low doses of medication, reflecting the metabolic capabilities and relative sensitivities of the individual [14]. It is best considered when a crime reflects very disorganized and disoriented behavior, and the victim is engaged without premeditated plotting. The perpetrator continues to be confused following the crime, but the confusion abates as the serotonergic medication is metabolized out of the system, providing that the offender stops taking it. The following is a hypothetical scenario:

> Sheila M. is living with her boyfriend Mark. Their relationship is warm and supportive. After developing panic attacks, Sheila is placed on an SSRI. One day, Sheila begins to show signs of frank confusion and disorientation. Mark calls Sheila's mother to come over and to stay with them.
>
> As all three are in the kitchen, preparing dinner, Sheila picks up a knife and begins stabbing her mother in the back. Mark restrains her, and yells for help. A neighbor calls police. Taken into custody, Sheila babbles about having to cook dinner tonight, and wanting to go buy tomatoes for the salad. Over the next 48 hours, she becomes completely normal. Doctors interviewing her at the jail learn that she has not been taking her medicine since arrest. She exhibits profound regret over the incident when she realizes that it really happened.

A manic cause would be reflected in less cognitive confusion, and in sustained behavioral and mental disorganization, even after the medicine is used up by her system. The motiveless (rational or irrational) crime carried out with a weapon within her reach and toward a closely located and nonthreatening figure are also key points in the history.

Serotonin syndrome also supports the uncommon claim of legal insanity because the defendant lacked awareness of the "nature and consequences" of his actions.

Most insanity defense arguments focus on the lack of appreciation of wrong. A higher level of disorganization is needed to disable a person from recognizing the very nature and consequences of his actions.

One case from the year 2000 trumpeted as a successful Prozac defense by hungry opponents of psychiatry was not exactly that. Still, the case of Chris DeAngelo bears close consideration for the issues it raises about interactions, illness, and the role of intoxicants.

Mr. DeAngelo, a married insurance salesman from Derby Connecticut, had no criminal history and no known financial trouble. Yet, he was ultimately implicated in several bank robberies, and left himself open to being shot by police officers who responded to the incident that resulted in his finally being caught. Subsequently, it was learned that Mr. DeAngelo had been treated with Prozac and alprazolam (Xanax). He raised an insanity defense, and the prosecutor on the case agreed to the plea [15].

Closer scrutiny of Mr. DeAngelo accompanied his subsequent hospitalization, especially as doctors deliberated whether he should be released to the community. Although Mr. DeAngelo had been diagnosed with having had a manic episode induced by the Prozac he had been prescribed, more details continued to emerge about his problematic drinking. Eventually, his inability to maintain sobriety on passes outside the hospital became a pivotal issue interfering with his release. The history that later became available on Mr. DeAngelo raised serious questions concerning what really led to his crimes. Was it the Prozac? The illness? The booze? Or the alprazolam? Or a combination? [16] What originally appeared to be a successful Prozac defense may have been a fortuitous outcome abetted by prosecutorial naiveté or dishonest forensic investigation, or both. This case reminds us of the need to do a full evaluation of an examinee.

Benzodiazepines

Overshadowed by the SSRIs, benzodiazepines – especially alprazolam – are documented and appreciated within the medical literature as responsible for unusual and sometimes quite dramatic changes in behavior [17]. Given that these medicines are designed to calm, and even to induce sleep, violent behavior is idiosyncratic. Idiosyncratic rage reactions in people taking benzodiazepines are not dose-dependent, but rather reflect a person's peculiar sensitivity.

The first report of such a reaction appeared in 1960, concerning chlordiazepoxide (Librium) taken by a man who went on to assault his wife for the first time in their 20-year marriage [18]. Since then, paradoxical rage has been reported with a variety of benzodiazepines, particularly alprazolam [19]. Paradoxical rage is most likely to occur in individuals with histories of idiosyncratic reactions to alcohol and other medicines, and with borderline personality disorder [20].

Case reports have identified assaults resulting from alprazolam, but not homicides; this may reflect the divide between the populations that inspire clinical research and those examined within the different priorities of the forensic system. The physician who studies or reports his patient who has subsequently killed displays unprecedented humility and intellectual integrity.

Bond demonstrated, in a sample of 23 patients treated with alprazolam for panic disorder, an increased likelihood of aggressive response to provocation [21]. This finding describes disinhibition, a phenomenon also attributed to alcohol. It is the same disinhibition exploited by rapists who secure their prey by slipping benzodiazepines such as flunitrazepam into their victims' drinks [22]. The same drug has been used by gangs to ease their disinhibition to carry out violent crimes [23]. Disinhibited by accident? Disinhibited by design? Was the crime provoked? How provoked? Unprovoked? The complexity of disinhibition mandates caution and scrutiny as to the circumstances preceding the instant crimes.

In addition to disinhibition, benzodiazepines can cause confusion, especially in the elderly and in the brain injured [24, 25]. Confusion from benzodiazepines results from their action as a general central nervous system depressant, affecting GABA nerve cell receptors located all over the brain [26]. This effect is to be contrasted with mania or agitation, but may have a significant impact on violence and crime that occurs in institutional settings, or by geriatric defendants.

The benzodiazepine-derivative, Triazolam (Halcion), which has both a sedating and properties, has had a controversial past. Within the medical literature, Triazolam caused violent reactions, confusion, and anxiety with greater incidence than other benzodiazepines [27]. Such side effects have been linked to the composition and therapeutic properties of triazolam, particularly its short elimination half-life and high potency.

In the current climate of psychopharmacology, benzodiazepines have fallen out of favor despite their tremendous advantages in the treatment of acute anxiety. The quality of relief provided by benzodiazepines is such that many people abuse these medicines [28]. The abuse can, if unchecked, advance to physical dependence [29]. Even those who responsibly take benzodiazepines may become physically dependent upon them risking severe withdrawal reactions if forced to suddenly stop them because of travel, surgery and postoperative hospitalization, or simply running out [30]. Withdrawal from benzodiazepines could be seen as a mitigating factor for violence committed during withdrawal.

Other medicines have been developed, including the SSRIs, which do not lead to physiological dependence. Still, because of the speed with which benzodiazepines produce relief of anxiety and panic, they maintain a secure place in the psychotropic armamentarium. For this reason, their relevance to future questions of medication-induced crime continues, perhaps with the most legitimate defense potential.

Given the unexpectedness of a rage reaction, alprazolam seems ideally suited to the defense of involuntary intoxication. Indeed the precedent setting case of Florida, *State v. Boswell*, involved a defendant who was indicted for first-degree murder of a police officer and convicted by a jury of murder in the second degree. Upon appeal, it was established by Dr. James Poupko, toxicology expert, that at the time of the crime, Boswell was taking Prozac and Xanax, which had reached toxic levels [31]. The original trial decision was reversed and the case remanded for a new trial.

Psychiatric diagnostic classification accounted for alcohol idiosyncratic intoxication until DSM-IV, when the concept was discarded as controversial [8, 32]. Still, there is ample documented understanding that some are exquisitely sensitive to the effects of alcohol, in that they become unexpectedly explosive upon drinking [33].

What Is Involuntary Intoxication (Legally)?

Guided by enduring common law, cases from the nineteenth century invoked the following definition for involuntary intoxication [34]:

> That if a person by the unskilfulness of his physician, or by the contrivance of his enemies, eat or drink such a thing as causeth such a temporary or permanent phrenzy … this puts him into the same condition, in reference to crimes, as any other phrenzy, and equally excuseth him [35]

In practice, defenses of involuntary intoxication have only been supported in American courts when accident, fraud or contrivance, coercion, or mistake led to the intoxication. However, many cases predated sophistication about the effects of medications, and dealt with a pharmacopoeia that included bootlegged moonshine [36]. The very notion of drug interactions was as remote as the computer.

Not surprisingly, most court rulings of note on involuntary intoxication have dealt with cases where the defendant consumed alcohol or illicit drugs. Consistent interpretation of law is found where the defendant willingly consumed the intoxicant, and/or was aware of its possible effects; or had previous experience and familiarity with a combination of medicine and intoxicant. In those instances, courts have ruled the intoxication voluntary [35, 37, 38].

What about intoxication that transpires when someone slips something into a drink, or laces a marijuana cigarette, for example? Is this involuntary or voluntary intoxication? Courts have ruled that spiking a substance that the defendant knew was intoxicating, and ingested nonetheless, does not constitute involuntary intoxication, even when the individual is surprised by the ultimate effects on his behavior or thinking [39]. On the other hand, when a more ordinary item, such as coffee, was laced, courts have upheld involuntary intoxication [40].

When the intoxicant's effects are unexpected, and attributed to the additive effects of debilitating illness, courts have ruled intoxication voluntary when the defendant was aware of his disability, but still chose to take in what he knew was an intoxicant [41].

On the other hand, laws may be more accommodating if a defendant drank alcohol or took an illicit drug to relieve suffering from an illness which was inadequately treated [42].

Courts have also addressed questions of involuntary intoxication where no alcohol or illicit drug was among the agents taken. Depending on the state, rulings have yielded important precedents. Defense claims have been supported when a wrong medicine was administered by an acquaintance [43]; and, when a person compliant with a regular prescription suffered unexpected effects [44]. The latter echoes the aforementioned scenario of idiosyncratic rage fueled by prescribed alprazolam or other benzodiazepines.

Nevertheless, courts in some states have ruled against the defense in cases, in which the defendant knew that the medicine would have problematic effects if taken at higher doses than were prescribed [45]; knew he had a inherited predisposition to a sensitive reaction to a medicine [46]; had been erratically compliant with the prescribed medicine [43]; or, in cases where the defendant had engaged in activities incompatible with the known side effects of the medicine [47].

The latter case is especially important to those charged with driving while intoxicated who invoke medication defenses, given that standard practice of informed consent is for physicians to advise their patients taking psychotropics of the potential effects on their ability to operate a motor vehicle or heavy machinery [48]. In actuality, most psychotropics, properly dosed, should not so interfere. Drug companies emphasize such warnings in their product literature to limit their own prospective liability and to pacify the FDA, which controls access to the American marketplace.

However, many medicines, including SSRIs, may cause alcohol to accumulate in the system [49]. Those who drink even small amounts might later discover – after they are pulled over and given Breathalyzer tests – that their alcohol blood levels were higher than they had anticipated.

Even as we understand more about drug interactions and metabolism, the cases from earlier years underscore what we even see today: the most common legitimate connection between psychotropic drugs and crime arises when the medicines interact with illicit drugs and alcohol to produce unexpected effects [50]. Because this scenario does not necessarily mitigate responsibility, especially if the defendant knowingly consumed a potential intoxicant, a full inventory of the contributing conditions and agents consumed is pivotal.

Other than the distinction between known intoxicants and medicines, the most important aspect of the law in this area concerns what criteria relating to the defendant's thinking are needed to establish involuntary intoxication. In many states that fashion their law after the model penal code, the defendant must prove that the intoxication rendered him unable to appreciate right from wrong, or the criteria for that state's insanity defense [51, 52].

Other classes and types of psychotropic medicines, including antipsychotics and mood stabilizers, are far less likely to lead to disinhibition or paradoxical rage, or to impact criminal and moral responsibility. Irritability may be attributed to antipsychotics if akathisia is present, but the legal significance of such an effect is pertinent only to mitigation – if at all clinically significant [53]. The leap from irritability to impact on choices and appreciation of wrong strains credulity. However, attorneys should note that the atypical antipsychotic risperidone has been reported to cause mania in rare circumstances [54].

Of the mood stabilizers, only carbamazepine has been associated in case reports with paradoxical rage [55]. This may be of greater likelihood in child and adolescent populations. Carbamazepine is also an anti-seizure medicine; it is therefore important to establish the reason the defendant was taking the medicine in the first place. The possibility of an idiosyncratic reaction cannot supersede the more likely scenario of undertreatment for the emotional or behavioral condition prompting the prescription of the drug in the first place.

Antipsychotics are essentially calming medicines that are administered to organize thoughts and to promote an attachment to reality [56]. Mood stabilizing medicines have powerful beneficial effects on impulse control [57]. Some medicines are even likely responsible for preventing violence. Clozapine and lithium, in particular, have anti-aggressive effects as well as anti-suicidal effects [58–61].

Stimulants prescribed for narcolepsy, ADHD or for dieting can cause agitation and hallucinations [62]. In one chart review, 6% of children on stimulants became psychotic, either becoming slowly paranoid, having hallucinations or having a mood congruent psychosis. The authors believe that the rate is actually higher since clinicians may well have missed children who had problems [63].

Nonpsychiatric Medication with Potentially Important Psychiatric Effects

Accutane, an anti-acne medicine, has followed a similar, if less notorious track record than the SSRIs [10]. Case reports in the literature have identified individuals who developed depression while taking this medicine [64]. Changed mental status as a result of taking the drug has been proposed as a criminal defense, with violence attributed to it [65]. Recent research specifically focusing on the question of an accutane–suicide–violence link has failed to establish a connection. Nevertheless, a high-profile civil lawsuit on the Gulf Coast of Florida will revisit this question in the months ahead.

The case concerns a teenager who flew a private plane into a Tampa skyscraper, killing himself. He expressed, in a suicide note found on his person, an identification with Osama bin-Laden and the September 11 attacks on America. However, he was not Arab, not a Moslem, and had no apparent affiliation to politically aligned groups operating in Florida. His family subsequently filed suit against Roche Laboratories Inc., which is the company that manufactures Accutane (isotretinoin), charging that his actions occurred as a result of the effects of the drug [10, 66].

Given the unexpected nature of many adolescent crimes, the prevalence of acne, and teenagers' search for relief, the acutance–crime link attempts to draw attention in future criminal proceedings.

A number of other medications have been found to affect an individual's mental status in ways that may impact on criminal responsibility.

The smoking cessation drugs varenicline and bupropion (also an antidepressant) can cause agitation and suicidal thoughts. Abuse of a number of over-the-counter (OTC) drugs can cause problems in and of themselves, or when they have a problematic interaction with prescription medication.

Analgesics may produce salicylism, with agitation and hallucinations. Sedative-hypnotic abuse may cause toxic psychosis or the confusion anticholinergic syndrome. An anticholinergic reaction arising from mixing anticholinergic (clozapine, tricyclic antidepressants, benadryl, anticholinergic medications given to treat parkinsonism from antipsychotic medications) can cause delirium and hallucinations (the term excited delirium is used to describe states of confusion and associated marked behavioral disinhibition) [67]. Problems are most likely to arise in the elderly, in individuals with personality problems and in chronically ill individuals, and individuals under stress [68].

Even in the young and less physically vulnerable, steroids can cause hostility, paranoia, delirium, and mania. Steroid abuse has been implicated in even homicidal

violence. Mania can be also be caused by steroids, levodopa and other dopaminergic agents, iproniazid, sympathomimetic amines, triazolobenzodiazepines [69, 70]. Coricidin intoxication can cause agitation, disorientation, and hallucinations [71].

The examining forensic psychiatrist must also inventory over-the-counter and nonprescription medicines and their misuse as well. Over-the-counter sleep aids (Sominex, Nytol, and Sleep Eze), if taken in excess, can cause hallucinations, delirium, and confusion [72]. Pseudoephedrine and dextromethorphan can cause hyperirritability and psychosis, if taken in excessive doses [73]. Various herbal medicines can also be harmful. Herbal remedies have been found responsible for delirium, hallucinations, and confusion [74].

The Disease Is Bigger than the Treatment

Far more likely an issue, for an individual prescribed psychotropic medicines, is the influence of the psychiatric condition itself – or an untreated co-occurring condition – on criminal responsibility. Undertreatment has been shown to be a significant problem of clinical populations. That some of those who are undertreated eventually break the law should not be surprising, especially considering how densely populated the corrections system is densely populated with people with significant psychiatric histories [75].

Medicines that accelerate the metabolism of psychiatric medications can lead to inadvertent undertreatment and may therefore be pertinent to a criminal defense, especially if behavioral changes coincide with the person beginning to take a medication which affects metabolism of a psychiatric medication he is taking. If the patient followed a doctor's instructions, then the unexpected ineffectiveness of the medicine may well be helpful to the defense [76].

When patients drink alcohol or take illicit drugs, along with the antipsychotic, the question may be raised whether the criminal behavior originated from the drugs themselves, or the interaction between the drugs and the antipsychotics. The literature supporting a link between alcohol and illicit drugs and crime is so clear as to eclipse the more indirect possibility of a drug's impact on metabolism of a psychotropic [77].

A defendant who has been compliant with medicines and still undertreated warrants greater appreciation for his limited contribution to the deterioration of his condition than someone who chooses noncompliance. Therefore, attorneys should probe the defendant's insight into the implications of his noncompliance and awareness of potential drug interactions.

Notwithstanding the legal mandate of informed consent, psychiatry in practice rarely addresses the potentials for criminality that might arise, hypothetically, should patients abuse drugs while taking medicines, or skip doses of their prescribed regimen. "You have to take this every day," and "you're not supposed to drink when you are on this, it will make you sick," may not be enough of an explanation why.

The recent trial in Houston, Texas of Andrea Yates demonstrated the relationship between undertreatment and crime. Would Mrs. Yates have stopped taking her medicines if she fully appreciated that she might have become homicidal to her five

children? Certainly not. Tragically, such crimes are so unfathomable – especially in foresight – that we need to be cautious of our expectations about the breadth of informed consent one can expect.

Ultimately, issues of responsibility or sentencing are left to the trier of fact, and the point of what a patient should have known about medication compliance and illness relapse is ultimately best resolved by the evidence at hand.

Guidelines for Assessment

Given the many possibilities that must be sorted out in a criminal responsibility evaluation, a few general principles are helpful to guide one in every evaluation.

Past Patterns of Violence Reflect Future Patterns of Violence

Violence and criminality resemble other important positive and negative behaviors in that they are an expression unique to an individual. Those who actually do have a past history of violence became so under circumstances that reflected an interplay of numerous potential factors: their neurochemistry, their interpersonal tendencies, their illness, medicines they took, individual sensitivities, and many other things. While it is certainly possible that these factors may not have been at all a part of the instant offense, ill-advised choices often assume the same dynamics.

This principle is why no history of violence may be a particularly compelling argument in support of a disturbance in brain chemistry, possibly as a result of medication. An unnatural defendant – which has nothing to do with race, socio-economics, or education – is an unnatural defendant for a reason.

Full Medical History

Attention to an examinee's medical history elicits physiological vulnerabilities and allergies, as well as factors which might suggest his vulnerability to a paradoxical or unexpected reaction to a medicine. Imaging studies to consider frontal or amygdala pathology may demonstrate gross structural brain impairment that would make a person more vulnerable to the effects of certain psychotropics, or to environmental provocation.

Other conditions associated with brain damage but which might not show findings on a CT, EEG, MRI, or PET scan are early dementia, AIDS, and neurological diseases. Examining medical problems and a comprehensive review of system helps the examiner to learn of any conditions, which the defendant was self-medicating, and to what degree he has been buffeted by unremitting pain and chronic illness – both associated with a tendency to commit suicide.

A psychiatrist should probe particular patterns of behavior when taking medicines, and which patterns are intended. Determine changes of dose, starting, stopping, and pattern of noncompliance as well. The timing of dose is important. In addition, explore behaviors and patterns of the psychotropics.

History of drug use needs to be gathered in this context, including observations about whether drugs taken had different effects on the defendant than usual, and whether these changes coincided with medication changes or dosing. While it is important to assess intoxication, withdrawal can contribute to criminal choices, irritability, and poor impulse control.

Metabolic potential worsens as a person advances into old age, or in patients with liver disease [78]. These populations may be considered as at risk for drug interactions, or problems arising from accumulated medicines. Even with no previous history of violent behavior, the changes to their physiology may render them vulnerable to untoward effects of medicines dosed at prescriptions that may even be modest. Females show faster metabolic activity of isoenzyme CYP 3A4, particularly in the premenopausal period [79].

Many medications are metabolized by the liver's cytochrome P450 mixed-function oxidase system. One of the most important of these is CYP 3A4, which metabolizes 60% of medications. Many drugs affect the effect of CYP 3A4′s metabolization of medications. Drugs, which induce metabolization, can lead the individual to have subtherapeutic doses of medication and thereby inadvertently lead to undertreatment. Drugs that inhibit metabolization of medications can lead to excessive blood levels and unexpected side effects, including confusion. Forensic evaluators should assess the medications the individual is taking and see if the regimen could be leading to side effects or undertreatment.

The anticholesterol medications known as statins have been reported to cause confusion, agitation, and hallucinations [80]. They are metabolized by CYP 3A4. One hypothesis is that the psychiatric symptoms arise from decreased cholesterol in brain cell membranes [81].

Full Event History

To the extent possible, a moment-by-moment reconstruction of the period leading up to the crime, the period of the crime, and immediately after is essential. The painstaking investigation thus gathers information about what was ingested, why it was ingested, and what emotions were present, and when and how they changed.

The role of the victim in the crime warrants a toxicology profile of the victim as well along with a corresponding history of ingestion history.

Because the significance of so many intoxicants and offending medicines relates to impulsive actions, the examiner should carefully discern the distance in time from triggering events (if there were any) to criminal acts.

Consideration of motive is also a must. The less likely a motive can account for the crime, the more likely the crime was caused by a physiological phenomenon,

including medicines. And, the more likely the involuntariness of an intoxication, if medicines were that physiological pilot light. Level of regret may call attention to a lack of motive. Motiveless crimes are characteristically associated with profound remorse [82].

Collaterals

Of course a defendant will try to present his case in as self-serving a manner as possible. That being the case, the examiner who relies up the defendant as the sole informant does truth a disservice. Identifying and getting access to witnesses, historians, and others with clear and detailed information can confirm the validity of the information. Because so many variables can affect the overall conclusions of the examiner, confirming the truth of the history is essential.

The crime scene can reveal many details about the level of disorganization of the offender. Likewise, an examination of his home, or pictures from where he used drugs, may demonstrate confirmed use where blood levels cannot be determined.

Testing

The case can and should be made for drug and medication tests upon arrest, in the event that a defendant is apprehended shortly after the crime. Of course, civil liberty issues would be confronted, and costs would be problematic. But we can certainly do a better job than at present when only in the fortunate cases of a subpopulation of defendants who are taken to the emergency room are any toxicology tests done. Of that small percentage, the toxicology battery is quite often incomplete.

The mystery of forensic assessments of drug interactions typically deepens because blood analyses are often not done during the period that would yield reliable and useful results. Consequently, toxicologists are often called upon to extrapolate blood levels based on time of ingestion, other medicines and drugs intake, time of eating, and other factors that might accelerate or decelerate breakdown of the medication.

Even when the consulting toxicologist is fortunate enough to gather sufficient information to arrive at a numerical figure for a blood level, that number cannot be considered in a vacuum. Likewise, in a clinical setting, there are those who, at very low levels of a medicine, show pronounced physical and mental effects. Alternatively, there are those for whom levels well above a normal range hardly affect them at all. And postmortem levels of certain drugs frequently differ from expected antemortem levels [82].

Blood levels are therefore to be considered one tool in an overall clinical assessment. Uncommonly, numerical values of the blood levels of a prescribed medicine will yield absolute answers in the investigation of questioned death and criminal and civil responsibility.

Supplementing laboratory study with a complete background investigation about an individual, lethal ideation, possible motives, will attach contextual relevance to the numbers available or arrived at. So too will additional testing, such as hair analysis, which provides a contextual appreciation of the test results of a snapshot in time compared to what he had been taking in recent months.

Testing the defendant's capacity to metabolize drugs through the CYP isoenzyme 2D6 can assist investigations of drug interactions and criminal responsibility [83]. Of course, this is pertinent only if the drugs in question are actually metabolized on the 2D6 isoenzyme. Poor female 2D6 metabolizers may be further hampered by lower activity during the luteal phase of the menstrual cycle [84]. The association of this metabolic change with more dramatic behavioral changes of late-luteal phase dysphoria, or with postpartum events, has yet to be demonstrated.

Psychotropic drugs are metabolized through the isoenzymes CYP 1A2, 2D6, 2C19, and 3A4. Many of these drugs are metabolized through more than one system; therefore, changes in the activation or inhibition of one isoenzyme will not necessarily dramatically alter blood concentrations. Future research will undoubtedly trace more definitive cause–effect relationships between specific isoenzyme activity, specific medicines, interactions, and an influence on a crime. At this stage the presumption of such a link in a given case is just that, without more than the established theoretical pathways. We still likely have not yet identified all of the pathways for all of the drugs.

Further discoveries will also yield important insights on the distinctions within ethnic groups and subpopulations, just as study of the genetic code has yielded unique sequences. Part of the problem is the paucity of available psychotropic and psychopharmacology research data, which includes a large sample of nonwhite, female subjects. We are still some years from the practical application of these ideas to yield conclusions of medical certainty on a given case.

Concluding Thoughts

Assessing the role of medication, or lack of adequate medication, on human behavior and criminal responsibility is one of the most complicated tasks a forensic psychiatrist faces. Various medications, and combinations of medications, can cause agitation, confusion, and even hallucinations and delusions. When assessing criminal responsibility, forensic evaluators need to be familiar with the potential affects of medications and be able to parse out the effects of medication from the impact of the underlying disease and the individual's basic personality and traditional life choices.

References

1. Grinfeld M, Welner M (1998) Pill poisoned? The seasoning of medication defenses. The Forensic Echo, 2(3):4–10
2. Teicher M, Glod C, Cole, J (1990) Emergence of intense suicidal preoccupation during fluoxetine treatment. American J Psychiat 147(2): 207–210

3. Pasternak D, Loci T, Loci T (2000) Can drugs spark acts of violence? U.S. News World Report 128(9): 50
4. Garret, R Prozac revisited: as drug gets remade (2000, May 7) The Boston Globe
5. Walsh MT, Dinan TG (2001) Selective serotonin reuptake inhibitors and violence: a review of the available evidence. Acta Psychiatr Scand, 104:84–91
6. Fawcett J (2001) The Relationship between Depression, Suicidality and Treatment: Hearing before Department of Health and Human Services. Federal Drug Administration Psychopharmacological Drugs Advisory Committee. (testimony)
7. Childs D Cox L (2009, June 4). ABC News Health [Television broadcast]: New York, NY: ABC News
8. American Psychiatric Association. (1987). Alcohol Idiosyncratic Intoxication. Diagnostic and statistical manual of mental disorders (3rd ed. text revision, p. 87). Washington D.C
9. Leverich S, Altshuler LL, Frye MA, et al (2007) Risk of switch in mood polarity to hypomania or mania in patients with Bipolar Depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Focus 5(1):98–106
10. Physicians Desk Reference. (2008). Medical Economics Montvale, NJ
11. Acharya N, Rosen AS, Polzer J P, et al (2006) Duloxetine: meta-analyses of suicidal behaviors and ideation in clinical trials for Major Depressive Disorder. J Clin Psychopharm 26(6):587–594
12. Mittal V, Brown WA, Shorter E (2009) Are patients with depression at heightened risk of suicide as they begin to recover? Psychiatric Serv 60:384–386
13. Brown T M, Skop B P, Mareth T (1996) Pathophysiology and management of the serotonin syndrome. Ann Pharmacother 30(5):527–533
14. Jan-Jhy Pan M D (2003) Serotonin syndrome induced by low-dose venlafaxine. The Annals of Pharmacotherapy 37(2):209–211
15. State of Connecticut v. Christopher DeAngelo, CR 97010866S (Conn. Super., 2000)
16. Bond AJ, Silveira JC (1993) The combination of alprazolam and alcohol on behavioral aggression. J Stud Alcohol 11:30
17. Cole JO, Kando JC (1993) Adverse behavioral events reported in patients taking alprazolam and other benzodiazepines. J Clin Psychiat 54(Suppl):49
18. Ingram IM, Timbury GC (1960) Side effects of librium. Lancet 2: 766
19. Dietch J, Jennings R (1988) Aggressive dyscontrol in patients treated with benzodiazepines. J Clin Psychiat 49(5):184–188
20. Gardner D, Cowdry R (1985) Alprazolam-induced dyscontrol in Borderline Personality Disorder. Am J Psychiat 142(1):98–100
21. Bond AJ, Curran H, Bruce M et al (1995) Behavioural aggression in Panic Disorder after eight weeks' treatment with alprazolam. J Affect Disorders 35(3):117–123
22. Welner M (2001) Drug-facilitated sexual assault. Academic Press, New York
23. Daderman AM, Fredriksson B, Kristiansson M (2002) Violent behavior, impulsive decision-making, and anterograde amnesia while intoxicated with flunitrazepam and alcohol or other drugs: a case study in forensic psychiatric patients. J Am Acad Psychiatry Law 30(2):238–51
24. Bogunovic OJ, Greenfield SF (2004) Practical geriatrics: use of benzodiazepines among elderly patients. Psychiatric Serv 55:233–235
25. Sadock BJ, Sadock AS (2007) Synopsis of psychiatry, 10th edn, Lippincott Williams Wilkins, Philadelphia
26. Roy-Byrne P (2005) The GABA-Benzodiazepine receptor complex: structure, function, and role in anxiety. J Clin Psychiat 66(2):14–20
27. Abrahm J (2002) Transnational industrial power, the medical profession and the regulatory state: adverse drug reactions and the crisis over the safety of halcion in the Netherlands and the UK. Soc Sci Med 55:1671–1690
28. Busto U, Sellers E M, Narango C A, et al (1986) Patterns of benzodiazepine abuse and dependence. Brit J Addict 81:87–94
29. Lader M (1989) Benzodiazepine dependence. Int Rev Psychiatr 1(1–2):149–156
30. Obrien CP (2005) Benzodiazepine use, abuse, and dependence. J Clin Psychiatr 66(2):28–33

31. Boswell v. State, 610 So. 2d 670 (Fla. App. 1992)
32. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th Ed. Text Revision. Washington, D.C
33. Maletzky B (1976) The diagnosis of Pathological Intoxication. J Stud Alcohol 37(9):1215–1228
34. Defense of Drunkenness in English Criminal Law. 49 LQ Rev 528, 533 (1933)
35. Tackett v. Commonwealth. 205 Ky 490, 266 SW 26 (Ky. 1924)
36. Commonwealth v. Walker. 283 Pa 468, 129 A 453 (Pa. 1925)
37. People v. Gerrior. 155 Ill App 3d 949 (Ill. App. 1987)
38. State v. Hall. 214 N.W. 2d 205 (Iowa Sup. 1974)
39. Burchfield v. State. 219 Ga App 40 (Ga. App.1995)
40. Commonwealth v. McAlister, 365 Mass. 454, 313 N.E.2d 113 (Mass. 1974)
41. Jones v. State. 648 P2d 1251 (Okla. Crim. App. 1982)
42. Teeters v. Commonwealth. 310 Ky 546, 221 SW 2d 85 (Ky. 1949)
43. State v. Rippy. 104 NC752, 10 SE 259 (N.C. 1889); State v. McKeon, 201 Ariz. 571, 38 P.3d 1236 (Ariz. App. 2002)
44. Aliff v. State, 955 S.W.2d 891. (Tex. App. 1997)
45. People v. Baker, 42 Cal 2d 550 (Cal. 1954)
46. State v. Gardner, 230 Wis. 2d 32, 601 N.W. 2d 670 (Wisc. App. 1999)
47. Bennett v. State, 161 Ark 496 (Ark. 1923)
48. Simon R, Sadoff R (1992) Psychiatric Malpractice: cases and comments for clinicians. Psychiatric Malpractice: Cases and Comments for Clinicians
49. Kaplan H, Sadock B (1993) Pocket handbook of psychiatric drug treatment. Williams Wilkins, Baltimore
50. Welner M. (2002, May). Medication defenses: myths and realities. Presentation at the American Psychiatric Association Annual Meeting, Philadelphia, PA
51. Miller v. Florida, 805 So. 2d 885, (Fla. App. 2001)
52. Model Penal Code §2.08(4) cmt. (1962)
53. Sachdev P (2005) Neuroleptic-induced movement disorders: an overview. Psychiat Ciln N Am 28(1):255–274
54. Aubry J M, Simon, A E, Bertschy G (2000) Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. J Clin Psychiat 61(9):649–655
55. Pleak R, Birmaher B, Gavrilescu A, et al (1988) Mania and neuropsychiatric excitation following carbamazepine. Journal of American Academy of Child and Adolescent Psychiatry 27(4):500–503
56. Kapur S, Arenovich T, Agid O, et al (2005) Evidence for onset of antipsychotic effects within the first 24 hours of treatment. Am J Psychiat 162(5):939–946
57. Grant J, Odlaug B, Kim S, et al (2007) Impulse Control Disorders: clinical characteristics and pharmacological Management. Psychiatric Times, 24(10), 64–69
58. Kessing L, Sondergard L, Kvist K, et al (2005) Suicide risk in patients treated with lithium. Arch Gen Psychiat 62(8):860–866
59. Meltzer H, Alphs L, Green A, et al (2003) Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). Arch Gen Psychiat 60(1):82–91
60. Naheed M Green B (2001) Focus on clozapine. Curr Med Res Opin 17(3):223–229
61. Sheard M, Marini J, Bridges C et al (1976) The effect of lithium on impulsive aggressive behavior in man. Am J Psychiat 133(12):1409–1413
62. Ling J M, Lopez G P, Cragin LS, et al (2005) Clinical outcome of unintentional amphetamine exposures. Clin Toxicol 43(6):648–649
63. Cherland E, Fitzpatrick R, Fitzpatrick R (1999) Psychotic side effects of psychostimulants: a five year review. Can J Psychiat 44(8):811–813
64. Lamberg L (1998) Acne drug depression warnings highlight need for expert care. Journal of the American Medical Association 279(14):1057
65. Bard M, Welner M (1998) Bad Acne: Guilty Defendant May Bring Med Mal. The Forensic Echo 2(3):23–24

66. Prior T, Baker G (2004) Miscellaneous syndromes: anticholinergic toxicity, clozapine toxicity, and hypertensive crisis with MAOIs. In: Haddad P M, Dusun S, Deakin, B. Adverse syndromes and psychiatric drugs: a clinical guide. Oxford University Press, Oxford
67. Gardner E, Hall R (1982) Psychiatric symptoms produced by over-the-counter drugs. Psychosomatics 23(2):186–190
68. Perry P, Yates W, Andersen K (1990) Psychiatric symptoms associated with anabolic steroids: a controlled, retrospective study. Annals of Clinical Psychiatry 2(1):11–17
69. Morton R, Gleason O, Yates W (2000) Psychiatric effects of anabolic Steroids after burn injuries. Psychosomatics 41(1):66–68
70. Sultzer D L, Cummings J L (1989) Drug-induced mania--causative agents, clinical characteristics and management. A retrospective analysis of the literature. Med Toxicol Adv Drug 4(2):127–143
71. Baker S, Borys D (2002) A possible trend suggesting increased abuse from coricidin exposures reported to the Texas Poison Network: comparing 1998 to 1999. Vet Hum Toxicol 44(3):169–171
72. Griffiths R, Johnson M (2005) Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. J Clin Psychiat 66(9):31–41
73. Roberge R, Hirani K, Rowland P, et al (1999) Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. J Emerg Med 17(2):285–288
74. Ernst E (2003) Serious psychiatric and neurological adverse effects of herbal medicines–a systematic review. Acta Psych Scand 108(2):83–91
75. Fazel, S, Danesh, J, Danesh J (2002) Serious mental disorder in 23,000 prisoners: systematic review of 62 surveys. Lancet 359(9306):545–550
76. Perkins v. United States, 228 F 408 (U.S. App. 1915)
77. Rosenheck R, Chang S, Choe Y, et al (2000) Medication continuation and compliance: a comparison of patients treated with clozapine and haloperidol. J Clin Psychait 61(5):382–386
78. Meyer UA (1996) Overview of enzymes of drug metabolism. J Pharmabio-dynamics 24(5):449–459
79. Thompson D, Pollock B (2001) Psychotropic metabolism: gender-related issues. Psychiatric Times 14(1):47–49
80. Tuccori M F, Testi LA (2008) Statin-associated psychiatric adverse events: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. Drug safety 31(12):1115–1123
81. Tatley M, Savage R (2007) Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. Drug Safety 30(3):195–201
82. Pounder D (1993) The nightmare of postmortem drug changes. Legal Medicine, 163–191
83. Greenblatt D (2001) Symposium at American Association for Geriatric Psychiatry. Annual Meeting, San Francisco, C.A
84. Tamminga W, Wemer J, Oosterhuis B, et al (1999) CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences. Euro J Clin Pharmacol 55(3):177–184

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