MEDICAL TOXICOLOGY OF DRUG ABUSE
To my wife, Kimberly; my son, Colin; my daughter, Shannon; and my son-in-law, Michael, whose love and support sustains me through this continuing project.
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It is a great pleasure for me to write this Foreword, as I have known Don Barceloux professionally for many years and we have collaborated on various projects particularly for the American Academy of Clinical Toxicology. Dr. Barceloux first established himself as a distinguished and successful author with the publication in 1988 of the first edition of Medical Toxicology: Diagnosis and Treatment of Human Poisoning, which he co-authored with the late Matthew Ellenhorn. Dr. Barceloux’s reputation for producing systematic books of great quality was further enhanced in 2008 by the publication of the first volume (of four) of Medical Toxicology, which was entitled the Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants and Venomous Animals; he wrote 171 of the 185 chapters. At the time of publication, this book had no rival, and that continues to be the case. I use it on a daily basis in my clinical practice.

While a substantial number of textbooks on clinical toxicology have been published in the last two decades, none has focused primarily on drug abuse. Equally, many books on drug abuse have been published over the same period, but none has been written from the perspective of the clinical/medical toxicologist.

For this reason I welcome, and indeed have been waiting eagerly for, the publication of the second volume in the Medical Toxicology series, which uses the same helpful format as volume 1. Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants provides in-depth up-to-date coverage of psychoactive agents that are abused, including newer designer drugs and psychoactive plants. Detailed information is provided on the pathophysiology, toxicokinetics, clinical effects (including the features associated with abstinence syndromes and reproductive abnormalities), treatment, and prevention of drug abuse. In addition, there are sections on epidemiology, on the chemical structure and physiochemical properties of the abused substances, on impurities introduced during synthesis, on the interpretation of the results of laboratory testing, and on the characteristics and geographical distribution of psychoactive plants. All but six of the 66 chapters in the present volume were authored by Dr. Barceloux himself; the remainder have been written by other acknowledged experts. After reading the book in proof I am confident its impact and usefulness will be similar to volume 1.

I commend this excellent book to the reader.

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Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants is the second book in the Medical Toxicology Series that divides Medical Toxicology into the four following areas: Natural Substances, Drugs of Abuse, Occupational and Environmental Exposures, and Pharmaceutical Overdose. The book series is designed to provide in-depth, evidence-based coverage of the most important toxins affecting humans. This book covers a variety of older psychoactive drugs and newer designer drugs of abuse including recently popularized drug (e.g., methcathinone, mephedrone, Salvia divinorum, kratom). Information on a particular substance is discussed in the book commonly associated with the subject. Consequently, the most important psychoactive plants are discussed in the Drug Abuse book rather than the Natural Substances book, so the reader interested in information on drug abuse will not have to search two books. Pharmaceutical drugs (e.g., hydrocodone, morphine, oxycodone) used primarily for therapeutic purposes will be covered in the book on Pharmaceutical Overdose. Conversions for length and temperature in metric and imperial systems are provided to ease the use of this book by an international readership, whereas the metric system for mass and concentrations are retained to limit any confusion about doses in the United States. This book is designed as a convenient reference for answers to questions regarding exposure, pathophysiology, clinical effect, detection, and treatment of toxicity associated with drugs of abuse.

The format of this book follows the first book in the Medical Toxicology Series, Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals. When the reader is familiar with the templates used in the book series, the consistency of the organization allows the reader to easily locate the appropriate information necessary for decisions regarding the sources, effect, regulation, and management of toxic exposures. The following list provides organizational details on the material under the headings for each drug:

History includes facts about the discovery, past abuse, and earlier complications of drug abuse.

Botanical Description helps the reader identify the characteristics and geographic distribution of psychoactive plants.

Identifying Characteristics includes the chemical structure, physiochemical properties, and the terminology associated with the specific drug of abuse.

Exposure discusses the epidemiology, trends, sources, production processes, impurities added during synthesis of the drug, profiling of confiscated drugs, and common methods of misuse.

Dose Effect covers clinical data on the drug doses associated with overdose and fatalities in humans. The book emphasizes dose-related effects rather than adverse or idiosyncratic reactions.

Toxicokinetics discusses the disposition of the drug in the body including the absorption, distribution, biotransformation, and elimination along with maternal and fetal kinetics, tolerance, and drug interactions.

Histopathology and Pathophysiology presents information on the mechanisms of action and toxicity, autopsies, and postmortem changes associated with drug abuse.

Clinical Response provides data on the clinical features of toxicity following the illicit use of the drug including the onset, duration, and type of clinical effects (behavioral abnormalities, mental disorders, medical complications). Additionally, this section discusses reproductive abnormalities, fatalities, and any
symptoms associated with an abstinence syndrome following cessation of use.

**Diagnostic Testing** presents information important to the interpretation of the clinical significance of laboratory testing. This section includes current analytic methods to identify and quantitate the drug in biologic and confiscated material, effects of storage on analytic results, biomarkers of exposure in blood, urine, and postmortem material, abnormalities detected by imaging studies and ancillary tests, and driving impairment associated with use of the drug.

**Treatment** includes current information on the management of toxic effects associated with drug misuse and abuse including recommendations for first responders, life-threatening problems associated with overdose, the use of antidotes, and supportive care.

*Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants* focuses on scientifically confirmed facts about specific drugs of abuse based on the medical literature and clinical experience. References are documented to validate the information and to provide sources for further inquiry. My hope is that this interdisciplinary, evidence-based approach will increase communication between traditional clinical settings and fields aligned with Medical Toxicology including those in analytic laboratories, universities, regulatory agencies, and coroner’s offices . . . and thus, encourage more inquiry into the pathophysiology, clinical effects, biomarkers, treatment, and prevention of drug abuse.

**Donald G. Barceloux, MD**

*November 28, 2011*
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The writing of this book required the review of thousands of references and the technical assistance of Joseph Babi and Alice Amador from the UCLA Biomedical Library.

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Her comprehensive index is a valuable guide to the reader.
PART 1

SYNTHETIC and SEMISYNTHETIC CHEMICALS
Chapter 1

AMPHETAMINE and METHAMPHETAMINE

AMPHETAMINE

HISTORY

Amphetamine is a prototypical, noncatecholamine, sympathomimetic drug; the chemical structures of amphetamine, catecholamine-type neurohumoral transmitters (i.e., epinephrine, norepinephrine, dopamine), and the naturally occurring ephedrine are similar. Although some Chinese herbal folk remedies contained sympathomimetic drugs 5,000 years ago, Nagai did not isolate ephedrine from ma huang (Ephedra vulgaris) until 1887. Lazar Edeleano synthesized amphetamine in the same year. Chen and Schmidt introduced ephedrine into Western medicine in the 1920s following their experience with the traditional Chinese herb, ma huang.

Early US medical research on the pharmacologic effects of amphetamine began in the late 1920s during attempts to find a synthetic alternative for the use of ephedrine to treat asthma. In the late 1920s, Alles and Prinzmetal introduced the use of racemic β-phenylisopropylamine (d, l-amphetamine sulfate) as a decongestant and bronchodilator. Beginning in 1932, the Smith Kline & French Company marketed Benzedrine® (racemic β-phenylisopropylamine) as an inhaler for the treatment of nasal congestion and as an analeptic for the treatment of fatigue. Over the next decade, the medical applications for amphetamine were extended beyond its use as a decongestant and general stimulant to include appetite suppression, and as a treatment for narcolepsy and hyperactivity syndrome in children. However, in 1937, recognition of the abuse potential of amphetamine and its related compounds resulted in the restriction of the sale of amphetamine as a prescription drug in the United States. Nevertheless, both the Axis and the Allies extensively used amphetamines to counter battle fatigue and to maintain alertness in their troops during World War II; amphetamines were issued in survival kits. After the war, widespread parenteral abuse of amphetamines occurred in Japan. Similar problems with amphetamine abuse occurred in Sweden during the 1950s and early 1960s.

The first major epidemic of amphetamine abuse in the United States occurred from the 1940s to the 1960s. Case reports and articles from the American lay press documented the intravenous (IV) and oral abuse of amphetamine extracts from Benzedrine inhalers during the 1940s and 1950s. Methods of abuse included the ingestion of folded paper strips containing amphetamine from the inhalers and the ingestion of amphetamine-moistened strips that were wrapped in cigarette paper and then dipped in coffee. Abuse of amphetamine from these papers occurred despite the addition of emetine and picric acid by the manufacturers. As a method to reduce the abuse Benzedrine® inhalers, manufacturers replaced the synthetic racemic amphetamine base (β-phenylisopropylamine) with the congener propylhexedrine. Marketing of this new product (Benzedrex®, B.F. Ascher & Co., Lenexa, KS) began in 1949. In 1959, the US Food and Drug Administration (FDA) restricted the use of these inhalers as a prescription drug because of the IV and oral abuse.

In the United States, IV amphetamine use with inhalant extracts was widespread during the 1950s and 1970s.
Rampant IV drug use with methylphenidate and illicit amphetamines also occurred in the San Francisco drug culture during the 1960s. Possibly promoted by the use of amphetamine compounds commonly prescribed for the treatment of obesity and depression, the illicit use of amphetamine during this time primarily involved the diversion of drugs from pharmaceutical stocks. Initially, amphetamine and the d-isomer of amphetamine (dextroamphetamine) were listed as schedule III drugs; however, in 1971, these compounds were added to the list of schedule II drugs (i.e., drugs that have medical use, but significant abuse potential) in an attempt to limit the diversion of these drugs to illicit markets. Widespread IV amphetamine abuse among heroin addicts occurred in Washington, DC, as a result of the disruption of heroin supplies in the early 1970s; amphetamine control measures abruptly ended the substitution of amphetamine for heroin.11 Until the mid-1970s, medical indications for amphetamine compounds included several common conditions (depression, fatigue, weight reduction). Subsequently, the FDA restricted the legal use of amphetamines to narcolepsy, hyperkinetic behavior in children, and short-term weight reduction. The use of amphetamine compounds for weight reduction is highly controversial; the Canadian government banned the use of amphetamine compounds for weight reduction in 1971. Case reports of amphetamine toxicity were relatively uncommon during the 1980s with use occurring primarily in deserts in the Southwestern United States.12

IDENTIFYING CHARACTERISTICS

Structure

Amphetamine (CAS No.300-62-9) is racemic β-phenylisopropylamine consisting of a phenyl ring substituted with an isopropylamino side chain. Amphetamine and the parent compound of sympathomimetic amines (β-phenethylamine) are structurally similar. Addition of hydroxyl substitutions on 3′-(meta-) and 4′-(para-) positions of the phenyl ring of phenethylamine produces the basic building block of the catecholamine neurotransmitters (epinephrine, norepinephrine, dopamine). Amphetamine compounds are not catecholamines because of the absence of aromatic hydroxyl moieties. Figure 1.1 compares the chemical structure of amphetamine, methamphetamine, and catecholamine neurotransmitters.

The phenylisopropylamines have a chiral center at the α-carbon, which allows enantiomers of differing biological potencies. The dextrorotatory (d-) isomer of amphetamine is commercially available as dextroamphetamine (CAS:51-64-9, Dexedrine®). Alteration of the phenyl ring (e.g., chlorphentermine, fenfluramine) and the ethylamine side chain (e.g., propylhexedrine, diethylpropion, phenmetrazine, phenmetrazine) produces amphetamine derivatives with fewer side effects compared with amphetamine and methamphetamine as demonstrated in Figure 1.2.

Detailed pharmacologic investigations of phenethylamine derivatives demonstrate some basic rules for the structure–activity relationships in this class of compounds. The following 4-position on the phenethylamine nucleus can be substituted resulting in alterations of pharmacologic effect: 1) the amine nitrogen; 2) the carbon atom on the ethyl bridge, which is α to the nitrogen; 3) the carbon atom on the ethyl bridge, which is β to the nitrogen; and 4) the phenyl ring. Addition of a single aliphatic substituent to the nitrogen results in a somewhat prolonged duration of action and increased penetration of the central nervous system (CNS) relative to the nonsubstituted analogue, whereas dissubstitution of the nitrogen abolishes nearly all stimulant

![Figure 1.1](image-url)
AMPHET AMINE and METHAMPHETAMINE

Physiochemical Properties

Amphetamine compounds are lipophilic, weak bases with pKₐ values ranging from 8.8–10.4. The pKₐ of amphetamine is 10.13. The drug base often is combined with HCl to form the hydrochloride salt, which has a melting point of 170–175°C.

FIGURE 1.2. Amphetamine and related amphetamine structures.®

activity. Increasing anorectic effects result from the addition of a small aliphatic group to the α-carbon. Substitution of the β-carbon with a hydrogen bonding entity (e.g., hydroxyl moiety as in ephedrine or pseudoephedrine) produces strong stereochemical preferences with the (R) absolute configuration at this stereo-center having substantially greater adrenergic activity than the (S) configuration. Addition of alkoxy substituents to the phenyl ring (e.g., methylenedioxymethamphetamine [MDMA], mescaline) increases serotonergic activity and imparts hallucinogenic properties to the compound.


**Terminology**

Although amphetamine refers specifically to racemic β-phenylisopropylamine, the term *amphetamine* frequently refers to several structurally related compounds (e.g., methamphetamine, fenfluramine, phentermine, synthetic amphetamine analogues) that share similar pharmacologic and toxicologic properties with amphetamine. Amphetamine is a contraction of the older description of the prototypical compound, α-methylphenethylamine. Old trade names for amphetamine compounds include the following: Benzedrine (d,l-amphetamine), Biphetamine (d,l-amphetamine), Dexedrine (d-amphetamine), and Dexampex (d-amphetamine). Street names for amphetamine include Amp, Bennies, Black Beauties, Browns, Cranks, Fives, Goey, Hearts, Louee, Speed, Uppers, and Whiz.

**EXPOSURE**

**Epidemiology**

The frequent inclusion of methamphetamine and other structurally similar amphetamine compounds (phenmetrazine, methylphenidate, diethylpropion, propylhexedrine) with racemic and d-amphetamine complicates the interpretation of epidemiologic data on the latter. Most studies on the misuse of prescription stimulants do not separate amphetamine from methylphenidate. Smaller studies with face-to-face interviews reported higher misuse rates, whereas larger, multisite studies reported lower rates. In a study of a convenience sample of 1,811 undergraduates at a large-public US research university, the reported lifetime rate of the illegal use of prescription stimulants (d-amphetamine, methylphenidate) was 34%. A multisite study of 10,904 US college students reported a lifetime misuse and past year misuse of prescription stimulants (d-amphetamine, methylphenidate) of 6.9% and 4.1%, respectively.

**Sources**

Approved indications for d-amphetamine in the United States are narcolepsy and attention deficient hyperactivity disorder (ADHD); off-label uses include the treatment of fatigue in cancer patients and the treatment of dysphoria/depression in combination with antidepressants. Indications for this drug do not include the treatment of obesity, drug dependence, anxiety, or malaise.

Illicit manufacture of amphetamine remains uncommon, partly because the illicit synthesis of amphetamine is more complicated than the illicit synthesis of methamphetamine. Synthesis of amphetamine from benzylmethylketone (phenylacetone, CAS RN: 103-79-7) is a reported method of illicit amphetamine production as displayed in Figure 1.3. The addition of formamide or ammonium formate to benzylmethylketone produces the intermediate, N-formyl amphetamine. Refluxing N-formyl amphetamine with hydrochloric acid produces crude amphetamine that can be refined by extraction, steam distillation, or vacuum distillation. An alternate method for the clandestine synthesis of amphetamine is a 1-step reduction of phenylpropanolamine that directly yields amphetamine base. The production of amphetamine in clandestine laboratories increases the Leuckart-specific impurities (N-formyl amphetamine, 4-methyl-5-phenyl-pyrimidine) and yield of amphetamine compared with legally manufactured amphetamine.

The source of some illicit racemic or d-amphetamine is the diversion of this drug from persons with legitimate prescriptions. Most studies on the use and misuse of prescription stimulants do not separate amphetamine from methylphenidate. In a retrospective review of published studies, the misuse and diversion of prescription stimulants for ADHD ranged from 5–35% among older adolescents and college-age populations. Lifetime diversion rates of stimulant prescriptions from students with legitimate prescriptions ranged from 16–29%, when they were asked to trade, sell, or give the medication to another person.

**Methods of Abuse**

The effects of amphetamine appeal to individuals who interact poorly in social settings and have difficulty internalizing new experiences. Amphetamine use reduces the need for external stimuli by increasing internal arousal mechanisms. In contrast to antisocial,

![FIGURE 1.3. Synthetic preparation of amphetamine from benzylmethylketone.](image)

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schizoid personalities who tend to abuse amphetamines (i.e., the drug interferes with their social, economic, or medical welfare), misuse of amphetamines (i.e., using these drugs for illicit purposes) occurs frequently in individuals trying to enhance performance or endurance. Long-term amphetamine use causes psychologic dependence and tolerance, although physical withdrawal symptoms are typically milder following chronic amphetamine use than chronic opiate or barbiturate use.

**Intermittent Use**

The strong CNS effects of amphetamine persist longer than most other stimulants (e.g., cocaine). Because the use of amphetamine increases physical and mental alertness, these compounds are popular among college students studying for exams, athletes, and truck drivers who require prolonged vigilance or short periods of high energy. Some individuals occasionally ingest 5–20 mg of amphetamine compounds to allay fatigue, elevate mood, or prolong wakefulness. Some professional football players consume amphetamine or other stimulants to induce rage, increase endurance, improve speed, and reduce weight. Amphetamine may improve the performance of tired individuals on repetitive tasks, unless jitteriness or impaired judgment adversely affects performance. The degree of improved athletic performance is relatively small, but this effect may be significant in elite sports. Most sporadic users do not develop a habitual craving for amphetamine. In addition, amphetamine may increase energy expenditures, resulting in excessive fatigue. Drug-induced impairment of judgment may reduce the recognition of the hazardous consequences of fatigue and the subsequent reduction in physical performance. Amphetamine is listed as a prohibited substance by the World Anti-Doping Agency (WADA).

**Chronic Oral Abuse**

Following the chronic daily consumption of 20–40 mg amphetamine, a reduction in amphetamine dose may cause lethargy and depression. Although some initial improvement in alertness may occur, chronic amphetamine use eventually reduces mental and physical performance without awareness by the user. Daily amphetamine doses may increase to 50–150 mg as tolerance reduces the euphoric effects of amphetamine. Polydrug abuse is a common comorbidity in amphetamine abusers, in part, because of the adverse effects of chronic amphetamine abuse including insomnia and agitation.

**Intravenous Abuse**

Intravenous amphetamine users usually begin with abuse of oral amphetamines; then, they progress to IV injections to experience a more intense feeling of pleasure. Other pleasurable feelings that follow the IV administration of amphetamine include a sense of extreme mental and physical power, hyperactivity, hyperexcitability, euphoria, and heightened sexual awareness. As tolerance develops, the dose and frequency of the injections increase substantially. During “runs,” injection of amphetamine occurs every 2 hours throughout the day for 3–6 days until exhaustion causes the user to fall asleep (i.e., “fall out”). Sleep lasts 12–18 hours or longer with more prolonged runs. With the escalation of the amphetamine dose, frightening perceptive experiences occur including hyperacusia, hallucination, illusions, and paranoia. Complications of this form of abuse include violent and bizarre behavior, slovenly dress, emaciated appearance, and major medical complications.

**Dose Effect**

Oral doses in habitual amphetamine users often range from 50–150 mg daily. Anecdotal reports suggest that the IV use of amphetamine begins with the injection of 20- to 40-mg doses, but the dose increases substantially as tolerance develops. Experienced IV amphetamine abusers typically inject from 100–300 mg amphetamine per use; however, as tolerance increases the maximum dose during binges may exceed 1 g without the development of severe complications. The presence of multiple confounding factors complicates the determination of dose-effect relationships following the use of amphetamine including underlying cardiovascular disease (e.g., coronary artery disease, angitis), vascular abnormalities (berry aneurysms), use of other illicit drugs, smoking, reporting bias, duration of abuse, and tolerance. In a case series of 11 patients with neurologic abnormalities associated with amphetamine use, the amphetamine dose ranged from 20–200 mg. However, the chronicity of amphetamine use was not well documented in this case series. In a summary of 9 case reports of myocardial infarction associated with amphetamine use, the route of abuse included chronic oral and nasal amphetamine abuse as well as IV drug use. The limited data and the presence of multiple confounding factors listed above prevented the determination of dose-response relationships. The ingestion of 250 mg amphetamine following by strenuous exercise (i.e., running 1.5 miles) was associated with the development of myoglobinuria and acute renal failure.
TOXICOKINETICS

Absorption

Volunteer studies indicate that peak plasma amphetamine concentrations occur within 1–2 hours following the ingestion of a pharmacologic dose of amphetamine (i.e., 10–25 mg). Complete gastrointestinal (GI) absorption of therapeutic doses of standard-release amphetamine usually occurs by 4–6 hours. Absorption of amphetamine through mucosal surfaces is pH dependent. The illicit use of amphetamines before intercourse as an aphrodisiac by insertion into the vagina (i.e., "balling") suggests that absorption of amphetamine across mucosal membranes also occurs. In a volunteer study, absorption of about 50% and 80% of an amphetamine dose applied to the buccal mucosa occurred within 5 minutes at pH of 8.16 and 9.18, respectively.

Sustained-release preparations are available as resin-bound rather than soluble salts. These compounds produce reduced peak blood concentrations compared with standard amphetamine preparations, but total bioavailability and time to peak concentrations are similar to standard-release preparations. Although experimental studies indicate that amphetamine delays gastric emptying and decreases intestinal motility, there are inadequate data to determine whether this property is clinically significant during amphetamine intoxication.

Distribution

Amphetamine distributes primarily into the kidney, lungs, and brain. The extent of plasma protein binding to amphetamine is relatively low (i.e., about 16–20%) in humans as measured by in vitro equilibrium dialysis. Animal studies indicate that there is substantial interspecies variation in the binding of amphetamine. The protein binding of amphetamine in the plasma of mice is about 17% compared with approximately 40% in the rat. The volume of distribution of amphetamine in therapeutic doses administered to humans ranges from about 3–5 L/kg. Following chronic amphetamine abuse, the volume of distribution increases slightly (up to 6 L/kg). Plasma protein binding, rate of absorption, and volumes of distribution of amphetamine enantiomers are similar.

Biotransformation

The biotransformation of amphetamine and methamphetamine is analogous. Figure 1.4 demonstrates the biotransformation pathways of amphetamine and methamphetamine. Metabolites of amphetamine include active compounds (e.g., p-hydroxyamphetamine, o-hydroxynorephedrine, norephedrine). The major metabolic pathway for amphetamine involves deamination (i.e., hydroxylation at the α-carbon) to phenylacetone; then, oxidation of phenylacetone to benzoic acid followed by the conjugation of benzoic acid with glucuronic acid or glycine. The deamination of amphetamine to phenylacetone probably involves the CYP2C subfamily of cytochrome P450 isoenzymes. Smaller amounts of amphetamine are converted to norephedrine by oxidation. β-Hydroxylation produces the active metabolite o-hydroxynorephedrine, which acts as a false neurotransmitter and may account for some drug effect in chronic users. The metabolism of amphetamine varies substantially between various animal species.

Elimination

Normally, the kidneys excrete about 30% of a therapeutic dose of amphetamine over 24 hours, but the actual amount of urinary excretion is highly pH dependent. In an experimental study involving 4 participants, the urinary excretion of unchanged amphetamine was about four times greater than the excretion of deaminated metabolites (hippuric and benzoic acids), when the urinary pH was acidic (pH 5.5–6.0). However, the urinary excretion of deaminated metabolites and unchanged amphetamine was similar during alkaline conditions (urinary pH 7.5–8.0). In a study of 7 volunteers ingesting 10–15 mg amphetamine sulfate, unchanged amphetamine in the urine during the first 16 hours after ingestion accounted for 2.2–4.2% of the administered dose when the urine pH ranged from 7.8–8.1. However, reducing the urine pH to 4.8–5.1 resulted in urinary excretion of 48–73% of the administered amphetamine dose as unchanged amphetamine during the first 16 hours after ingestion.

Consequently, the plasma elimination half-life of amphetamine is also urine pH dependent. The plasma half-life of amphetamine following a therapeutic dose is approximately 12 hours under normal urinary pH; however, experimental studies demonstrate that the plasma-elimination half-life ranges from 8–10.5 hours following urinary acidification compared with 16–31 hours following urinary alkalization. Furthermore, the d(+)-amphetamine enantiomer is more rapidly metabolized than the l(−)-enantiomer; under alkaline conditions, the mean plasma elimination half-life of the d(+)-amphetamine enantiomer was 12.7 hours compared with 17.0 for the l(−)-enantiomer. Under acidic urine conditions, renal excretion of unchanged amphetamine is the major route of elimination, and