# PART 1

# SYNTHETIC and SEMISYNTHETIC CHEMICALS

# I Amphetamines and Phenethylamine Derivatives

# 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.[1] Chen and Schmidt introduced ephedrine into Western medicine in the 1920s following their experience with the traditional Chinese herb, ma huang.[2]

Early US medical research on the pharmacologic effects of amphetamine began in the late 1920s during attempts to find an synthetic alternative for the use of ephedrine to treat asthma.[3,4] In the late 1920s, Alles and Prinzmetal introduced the use of racemic β-phenylisopropylamine (*d*,*l*-amphetamine sulfate) as a decongestant and bronchodilator.[5] 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.[6,7] 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.[8] 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.[9] 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.[10] 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.

*Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants*, First Edition. Donald G. Barceloux.

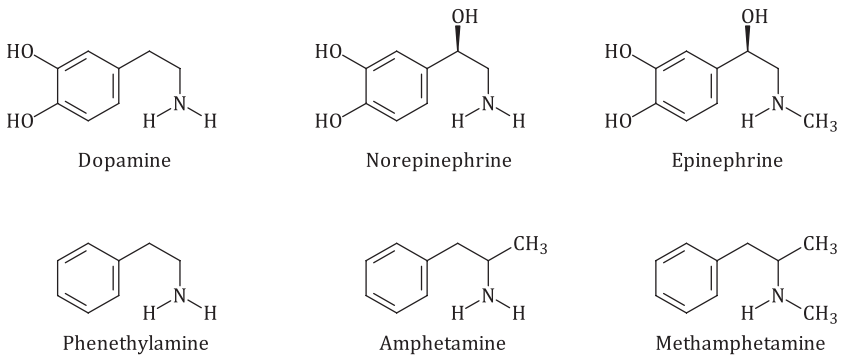



**FIGURE 1.1.** Chemical structures of dopamine, epinephrine, norepinephrine, phenethylamine, amphetamine, and methamphetamine.

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]

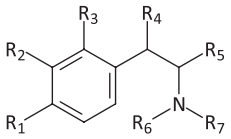
## IDENTIFYING CHARACTERISTICS

### Structure

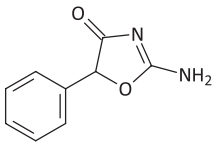
Amphetamine (CAS No.300-62-9) is racemic β-phenylisopropylamine consisting of a phenyl ring substituted with an isopropylamino side chain. Amphetamine and the parent compound of sympathomimetic amines (β-phenethylamine) are structurally similar. Addition of hydroxyl substitutions on 3′-(*meta*-) and 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 biologic 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, phendimetrazine, phenmetrazine) produces amphetamine derivatives with fewer side effects compared with amphetamine and methamphetamine as demonstrated in Figure 1.2.

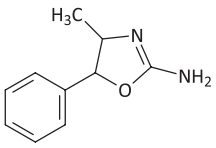
Detailed pharmacologic investigations of phenethylamine derivatives demonstrate some basic rules for the structure–activity relationships in this class of compounds. The following 4-position on the phenethylamine nucleus can be substituted resulting in alterations of pharmacologic effect: 1) the amine 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 disubstitution of the nitrogen abolishes nearly all stimulant



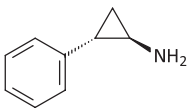

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ |
|---|---|---|---|---|---|---|---|
| **Amphetamine** | H | H | H | H | $CH_3$ | H | H |
| **Benzphetamine** | H | H | H | H | $CH_3$ | $CH_3$ | $CH_2CH_3$ |
| **Cathinone** | H | H | H | =O | $CH_3$ | H | H |
| **Desmethylselegiline** | H | H | H | H | $CH_3$ | H | $CH_2CCH$ |
| **Diethylpropion** | H | H | H | =O | $CH_3$ | $CH_2CH_3$ | $CH_2CH_3$ |
| **Ephedrine** | H | H | H | OH | $CH_3$ | H | $CH_3$ |
| **Fenfluramine** | H | $CF_3$ | H | H | $CH_3$ | H | $CH_2CH_3$ |
| **MDA** | O-$CH_2$-O | | H | H | $CH_3$ | H | H |
| **MDEA (MDE)** | O-$CH_2$-O | | H | H | $CH_3$ | H | $CH_2CH_3$ |
| **MDMA** | O-$CH_2$-O | | H | H | $CH_3$ | H | $CH_3$ |
| **Mescaline** | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | H | H |
| **Methamphetamine** | H | H | H | H | $CH_3$ | H | $CH_3$ |
| **Methcathinone** | H | H | H | =O | $CH_3$ | H | $CH_3$ |
| **Phenelzine** | H | H | H | H | H | H | $NH_2$ |
| **Phentermine** | H | H | H | H | $\{CH_3\}_2$ | H | H |
| **Phenylephrine** | H | OH | H | OH | $CH_3$ | H | H |
| **Phenylpropanolamine** | H | H | H | OH | $CH_3$ | H | H |
| **Pseudoephedrine** | H | H | H | OH | $CH_3$ | H | $CH_3$ |
| **Selegiline** | H | H | H | H | $CH_3$ | $CH_3$ | $CH_2CCH$ |



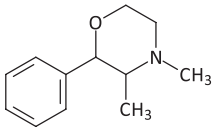
Pemoline



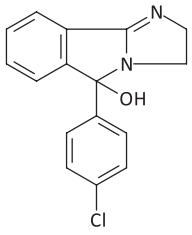
Methylaminorex



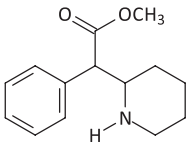
Tranylcypromine



Phendimetrazine



Mazindol



Methylphenidate

**FIGURE 1.2.** Amphetamine and related amphetamine structures.[99]

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 stereocenter 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.

## Physiochemical Properties

Amphetamine compounds are lipophilic, weak bases with $pK_a$ values ranging from 8.8–10.4. The $pK_a$ 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.

## 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.[13] 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.[14]

# 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%.[15] 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.[16]

## 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.[17] 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.[18] 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.[19,20]

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.[21] 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,

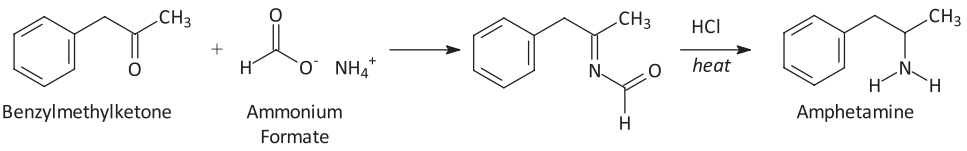



**FIGURE 1.3.** Synthetic preparation of amphetamine from benzylmethylketone.

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.[22] 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.[23] 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.[24] 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).[25]

### *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.[26] 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 hyperacousia, hallucination, illusions, and paranoia.[27] 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.[27] 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, angiitis), 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.[28] 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.[29] 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.[30]

## 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).[31] 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.[32]

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.[33] Although experimental studies indicate that amphetamine delays gastric emptying and decreases intestinal motility,[34] 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.[35] 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.[36] 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).[37] Plasma protein binding, rate of absorption, and volumes of distribution of amphetamine enantiomers are similar.[38]

### 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.[39] The deamination of amphetamine to phenylacetone probably involves the CYP2C subfamily of cytochrome P450 isoenzymes.[40] 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).[41] 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.[42]

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 alkalinization.[41] 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.[38] Under acidic urine conditions, renal excretion of unchanged amphetamine is the major route of elimination, and

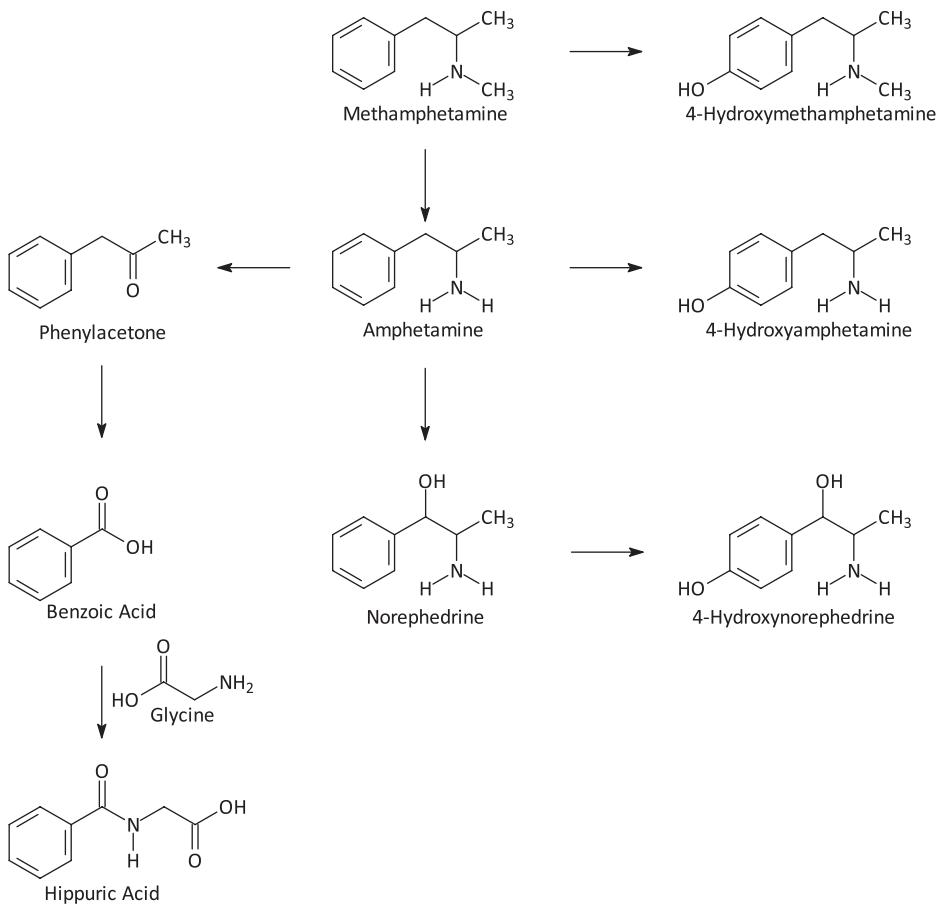



**FIGURE 1.4.** Pathways of amphetamine and methamphetamine biotransformation.

the plasma elimination half-life of the enantiomers is similar.

## Tolerance

Acute tolerance develops to some of the subjective effects of amphetamine. In a study of healthy volunteers receiving a single 20-mg dose of *d*-amphetamine orally, the initial effects of amphetamine on mood dissipate before peak plasma amphetamine concentrations.[43] The maximum subjective ratings of "feel high" occurred between 1.5–2 hours after ingestion, whereas peak plasma amphetamine concentrations occurred about 4 hours after ingestion. In a study of 16 healthy volunteers, the administration of a second 20 mg dose of *d*-amphetamine 48 hours after the first 20 mg dose produced a slight reduction in the ratings for self-reported "feel drug," but all other mood, behavioral, and physiologic effects of *d*-amphetamine were unchanged.[44] Rapid development of tolerance to some of the side effects of amphetamine derivatives occurs during both chronic oral and IV use.

## Maternal and Fetal Kinetics

Amphetamine crosses the placenta.[45] Volunteer studies indicate that *d*-amphetamine readily transfers into breast milk of lactating mothers. In a study of a lactating mother receiving 20 mg racemic amphetamine daily (5 mg every 2 h beginning at 10 AM), the milk/plasma ratio ranged from 2.8–7.5 during the days 10–42 after birth.[46] The corresponding amphetamine concentrations in milk ranged from 55–138 μg/L. In a case series of 4 mothers receiving a median daily *d*-amphetamine dose of 18 mg (range, 15–45 mg), the median milk/plasma ratio was 3.3 (range, 2.2–4.8) with the absolute infant dose of 21 μg/kg daily (range, 11–39 μg/kg/d).[47] Two of the 3 infants tested had detectable concentrations (2 μg/L, 18 μg/L) of *d*-amphetamine in their urine.

## Drug Interactions

In general, the coadministration of amphetamine and monamine oxidase inhibitors is contraindicated because of the potential development of severe hypertension, hyperthermia, and altered consciousness. A case report associated the development of hyperthermia (43°C/109.4°F), agitation, seizures, opisthotonus, and coma in a 41-year-old woman following the administration of *d*-amphetamine, amobarbital, and tranylcypromine.[48] She recovered with intensive supportive measures. *d*-Amphetamine is a substrate for CYP2D6 isoenzymes; therefore, potential drug interactions may occur following the concomitant ingestion of fluoxetine, paroxetine, and, to a lesser extent, sertraline. However, there are inadequate *in vivo* human data to indicate that these potential interactions are clinically significant.

# HISTOPATHOLOGY AND PATHOPHYSIOLOGY

## Mechanism of Action

Amphetamine exhibits a wide range of profound physiologic and behavioral effects in animals as well as humans including alteration of sleep, motor activity, appetite, attention, aggression, sexual behavior, learning, classical conditioning, and operant behavior. At high doses, increased hyperadrenergic effects result from excessive norepinephrine-mediated activity. Amphetamine is structurally similar to the neurotransmitters, dopamine and norepinephrine. The physiologic effects of amphetamine result from the enzymatic inactivation, release, and uptake of catecholamine neurotransmitters (dopamine, norepinephrine), and to a lesser extent, the indoleamine, 5-hydroxytryptamine (serotonin) neurotransmitter.[49] Consequently, amphetamine is a potent indirect agonist at the various monoaminergic receptors.

The mechanism of action of amphetamine is similar to other amphetamine compounds and pharmaceutic derivatives; however, the peripheral and central α- and β-adrenergic effects of these compounds vary. Amphetamine crosses the neuronal membrane predominantly via the neuronal monamine reuptake transporters. Direct drug-monoamine competition for the reuptake transporters by amphetamine inhibits the cellular uptake of catecholamines. By inhibiting intracellular vesicular monamine transporter 2, amphetamine reduces vesicular monoamine storage while increasing extracellular monoamines (dopamine, norepinephrine, serotonin).[50] This inhibition of carrier-mediated active uptake process involving catecholamine uptake transporters mediates the cardiovascular and anorexic effects of amphetamine.

### *Cardiovascular System*

Therapeutic doses of amphetamine raise systolic and diastolic blood pressure and initially slow heart rate. High doses of amphetamine cause tachycardia, palpitations, and dysrhythmias. *l*-Amphetamine is a slightly stronger cardiovascular stimulant than *d*-amphetamine.

### *Central Nervous System*

Behavior. In animal and human studies, low doses of amphetamine are general stimulants that induce alertness, euphoria, increased confidence, gregariousness, enhanced mental and physical activity, and improved self-esteem.[51] Amphetamine increases wakefulness and delays the onset and duration of rapid eye movement (REM) sleep. Withdrawal following chronic use produces the opposite pattern, at least during the first several months after cessation of use. The analgesic effects of amphetamine are minimal with no clinical significance.

Amphetamine increases the concentration of norepinephrine in the periphery and dopamine in the CNS via effects on plasmalemmal and vesicular monoamine transporters (e.g., neuronal dopamine transporter, vesicular monoamine transporter-2).[50] This compound facilitates the release of these neurotransmitters and blocks their reuptake in the presynaptic nerve terminal. The primary site of action in the CNS is the dopamine transporter. The dopamine transporter translocates *d*-amphetamine into the interior of the presynaptic terminal; subsequently, the efflux of dopamine to the synaptic cleft occurs as a result of the release of dopamine from the vesicles in the cytosol. Additionally, *d*-amphetamine inhibits the clearance of dopamine from the synapse by competitively inhibiting the reuptake of dopamine by the dopamine transporter. Cocaine is a much stronger binder of this protein in the synapse than amphetamine.[52]

Amphetamine along with other drugs of abuse (e.g., alcohol, cocaine, heroin, methamphetamine) enhance the release of the neurotransmitter dopamine in the striatum (caudate, putamen, nucleus accumbens) as a result of their effects on the dopamine transporter.[53] Animal studies suggest that brain norepinephrine is responsible for amphetamine-induced locomotor stimulation, whereas dopamine mediates stereotyped behavior similar to amphetamine psychosis in humans as well as craving and addictive behavior.[54]

Children with ADHD (old term: syndrome of minimal brain dysfunction) are characterized by hyperactivity and aggressive behavior. About 75% of these children display improvement in hyperactivity, impulsivity, distractibility, and short-attention span following the administration of amphetamine compounds or analogues. These hyperactive children excrete lower levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of CNS norepinephrine. Studies of children with and without attention deficit hyperactivity disorder (ADHD) suggest subtle differences in psychoeducational test performance in relation to urinary homovanillic acid and MHPG concentrations.[55] The administration of *d*-amphetamine increases the urinary excretion of MHPG in clinical drug responders, but not in nonresponders.[56]

Anorectic Properties. Although amphetamine compounds do not alter metabolic rates at normal therapeutic doses, the use of these drugs ameliorates some of the effects of hunger and fatigue depending on personality type.[57] Weight loss from therapeutic doses of most anorexiant drugs results almost entirely from reduced food consumption, but increased physical activity contributes somewhat to initial weight reduction. At usual doses, tolerance abolishes anorectic properties after several months. Patients often regain lost weight after tolerance develops or drug administration ceases. Racemic amphetamine (*d*-, *l*-amphetamine) was the first drug used for appetite suppression. However, the dextrorotatory stereoisomer (dexamphetamine) is the active anorectic constituent of the racemic mixture of *d*-, *l*-amphetamine. Consequently, the use of dexamphetamine replaced the administration of racemic amphetamine for the treatment of obesity.

## Mechanism of Toxicity

An amphetamine is an indirectly acting sympathomimetic drug that increases the effects of epinephrine in the peripheral sympathetic nervous system and the effects of dopamine, norepinephrine, and serotonin in the CNS. The acute toxicity of amphetamine primarily involves an exacerbation of pharmacologic effects of this drug (i.e., hyperadrenergic state). The psychoactive effects of amphetamine also result from indirect agonist action. Amphetamine displaces catecholamines from binding sites in the storage vesicles after diffusion of these compounds into the cytoplasm. Anxiety, dysphoria, confusion, depression, nausea, vomiting, headache, sweating, apprehension, tremulousness, confusion, and fatigue limit the use of increasing doses of amphetamine despite the development of tolerance.

### *Cardiovascular System*

Excessive sympathetic nervous system activity and vasoconstriction produced by amphetamine causes tachycardia, hypertension, and in susceptible patients, myocardial ischemia and cardiac arrhythmias. Intravenous amphetamine abusers develop the same serious complications (e.g., opportunistic infections) as other IV drug abusers with acquired immunodeficiency syndrome (AIDS).[58]

### *Central Nervous System*

Excessive doses of amphetamine cause stereotyped movements, hyperreactivity, dystonic and dyskinetic postures, and convulsions. The administration of high doses of amphetamine to animals causes long-term depression of both dopamine and serotonin synthesis in various regions of the brain. The long-term functional and pathologic consequences of chronic depletion of dopamine and serotonin for humans are unclear.[59] *d*-Amphetamine is a positive reinforcer under controlled laboratory condition in both animals and humans.[60,61]

The etiology of the intracerebral and subarachnoid hemorrhages associated with amphetamine use is probably multifactorial. Inflammation and necrosis of small cerebral arteries (i.e., vasculitis) secondary to particulate foreign bodies or bacterial endocarditis can develop after IV drug use.[62] Subsequently, the hypertension resulting from amphetamine abuse may cause vessel rupture and hemorrhage in the weakened areas of the vessels. However, vasculitis has occurred during oral acute dextroamphetamine intoxication,[63] amphetamine withdrawal, and therapeutic use of amphetamine as an anorectic drug.[28] The presence of vasculitis after exposure by different routes suggests an immunopathologic mechanism.

## Postmortem Examination

In animal studies, the IV administration of lethal doses of amphetamine produces pathologic changes resembling experimental hyperthermia.[64] Postmortem examination of dogs administered a lethal IV dose of amphetamine sulfate without anesthesia demonstrate nonspecific findings of renal, vascular, pulmonary, and hepatic congestion as well as hemorrhage in the lungs and GI tract.[65] Cardiac changes include subendocardial hemorrhage, necrosis of myocardial fibers, and hemorrhage in the cardiac valve leaflets. There are no specific postmortem findings that separate amphetamine toxicity from other causes of death. Postmortem examination of the hearts from amphetamine abusers may or may not demonstrate structural abnormalities; cerebral

embolism does not usually occur in amphetamine-related fatalities.

## CLINICAL RESPONSE

### Illicit Use

Acute intoxication with amphetamine, methamphetamine, or cocaine produces similar clinical effects, manifesting primarily as an accentuation of pharmacologic effects on the cardiovascular and central nervous systems. A major distinguishing feature is the prolonged effect of amphetamine compared with cocaine; many case series report the clinical effects of methamphetamine and amphetamine without distinguishing the 2 drugs. Altered mental status was the most common complaint of 127 patients presenting to the emergency department following exposure to amphetamine or methamphetamine.[66] Thin-layer chromatography indicated that 37% of these patients used either methamphetamine or amphetamine alone and 26% tested positive for both substances; analysis of urine from the remainder of the patients demonstrated other drugs of abuse. Reported CNS symptoms included agitation, anxiety, confusion, delusions, hallucination, and suicidal ideation. Convulsions occurred in 4 of 127 cases.

Following the ingestion of large doses of amphetamine, CNS symptoms begin within 30–60 minutes and persist for 4–6 hours. Large overdoses, sustained-release preparations, and alkalinization of the urine prolong the clinical features of amphetamine toxicity. Table 1.1 outlines the common clinical features of mild to severe amphetamine (or methamphetamine) intoxication. Case reports associate amphetamine abuse with a variety of organ dysfunction including rhabdomyolysis with myoglobinuria, hyperpyrexia (up to 42.8°C/109°F) with hepatorenal dysfunction and rhabdomyolysis,[67] and disseminated intravascular coagulation (DIC) with end organ failure.[68]

**TABLE 1.1.** Categorization of Symptoms of Amphetamine Toxicity by Severity.

| Severity | Signs and Symptoms |
|---|---|
| Mild | Restlessness, talkativeness, irritability, insomnia, tremor, hyperreflexia, mydriasis, flushing, diaphoresis, combativeness, dry mucous membranes, nausea, vomiting, pallor |
| Moderate | Hyperactivity, confusion, hypertension, tachypnea, tachycardia, premature ventricular contractions, chest discomfort, vomiting, abdominal pain, profuse diaphoresis, mild temperature elevation, impulsivity, repetitive behavior, hallucinations, panic reaction |
| Severe | Delirium, marked hypertension or tachycardia, hyperpyrexia (over 40°C), convulsions, focal neurologic signs, hypotension, coma, ventricular dysrhythmias |

#### *Behavioral Abnormalities*

Small doses of amphetamines produce an elevation of mood and a sense of well-being. Larger doses cause apprehension, volatility, excitement, impulsiveness, aggressiveness, and poor judgment.[26] The effects of amphetamine on aggressive behaviors are complex and the changes in behavior depend on several factors including the drug dosage, the environment, and the individual drug user.[69] Behavior abnormalities during amphetamine intoxication include belligerency, moaning, aggression, hyperactivity, anxiety, frank psychosis, and screaming.[66] Although coma may develop suddenly following IV amphetamine use, the loss of consciousness in a patient with a history of amphetamine exposure should initiate a search for other drugs or complications (cerebral hemorrhage, hyperthermia, end organ failure, DIC).

#### *Mental Disorders*

The development of acute psychosis is a common occurrence after chronic, high-dose amphetamine abuse and rarely after a single large dose of amphetamine.[70] Classically, amphetamine-induced psychoses are paranoid psychoses with delusions of persecution and hallucinations under clear consciousness.[71] In a case series of 146 IV amphetamine abusers attending an outpatient psychiatric clinic, about 35% (50 patients) reported 1 or more psychotic episodes characterized by paranoid delusions, stereotyped behavior, visual and/or auditory hallucinations, and delusions of reference.[72] Psychotic reactions may occur in amphetamine abusers with or without a prior history of a psychiatric disorder, but premorbid schizoid/schizotypal personality and early, heavy amphetamine abuse predispose users to psychosis.[73] Case reports associate hallucinations and stereotyped compulsive behavior with the therapeutic use of amphetamine in patients with compensated schizophrenic personalities.[74]

The typical presentation of amphetamine-induced psychosis involves a patient with appropriate affect, paranoid ideations, delusions of persecution, auditory illusions or hallucinations, labile mood, increased sexual drive, delusions of reference, and a sensation of being watched or followed in the presence of a clear consciousness.[75] Thought disorders are uncommon in patients with amphetamine-induced psychoses. Common behavior changes include volatility, suspi-

ciousness, hyperactivity, aggression, hostility, and anxiety. Tactile hallucinations are distinctive features of amphetamine or cocaine abuse. These alterations of thinking cause formication (delusions of parasitosis) and destructive excoriation of the skin. Feelings of suspiciousness and anxiety may become overwhelming in the psychotic patient. Curiosity and a pleasurable suspiciousness become dysphoria and fixed delusions upon which the chronic user may act violently. Stereotyped, compulsive behavior invariably is associated with amphetamine psychosis. This ritualized conduct involves fixed behavioral sequences such as cleaning, sorting, grooming, counting, pacing, and rearranging. Amphetamine-intoxicated patients usually act appropriately given their intense conviction that their paranoid and delusional state is real. Psychotic symptoms usually disappear within several days, but delusions may remain for days to months, particularly if the psychosis developed following chronic use of high doses of IV amphetamine.

### *Medical Complications*

#### Neurologic

*Acute.* Both ischemic and hemorrhagic strokes are well recognized, but relatively rare complications of all routes of amphetamine abuse. Frequently, patients with these complications have a structural abnormality (aneurysm, arteriovenous malformation).[76,77] In a case-control study of 414 individuals with stroke admitted to an urban hospital, 73 patients (34%) were drug abusers (cocaine, amphetamines, heroin).[78] Almost three-quarters of the strokes in this study were hemorrhagic strokes located primarily in the periphery (e.g., subcortical white matter of cerebral hemispheres). The use of amphetamine is also a strong risk factor for hemorrhagic stroke in more social and economically heterogeneous, urban populations.[79] Most of these patients were chronic drugs users; the typical presentation involved the onset of severe headache with or without nausea within a few hours of amphetamine exposure.[80] Few of these patients lost consciousness, but confusion and disorientation occurred frequently. Depending on the location of the intracranial hemorrhage, other unilateral motor or sensory deficits may develop. The admission blood pressure is usually normal, although some patients present with marked hypertension. Seizures often are not part of the initial presentation, but convulsions may complicate convalescence. Intracerebral hematomas may cause brainstem herniation and death. The average mortality of patents with amphetamine-associated intracranial hemorrhage is approximately 30%, and most survivors have mild residual deficits.

*Chronic.* Habitual use or massive single doses of amphetamine may produce a toxic psychosis characterized by paranoia, delusions, hallucinations, or bizarre violent behavior. The amphetamine user presents as a restless, tremulous individual who is garrulous, suspicious, and anxious. Some individuals become hostile and aggressive. Although memory, orientation, and insight are usually preserved, high or prolonged amphetamine doses may cause the individual to act upon his or her delusions, leading to suicidal or homicidal actions.

#### Cardiopulmonary

Common cardiovascular symptoms and signs during amphetamine intoxication include hypertension, chest pain, palpitations, and dyspnea. Although chest pain frequently occurs following the use of amphetamines, electrocardiographic changes other than sinus tachycardia are uncommon. A few case reports associate the development of an acute myocardial infarction with both recent use of IV amphetamine[81,82] or chronic oral amphetamine abuse.[83] Angiographic studies do not often demonstrate significant coronary artery disease in these relatively young patients. The IV administration of amphetamine has been associated with the development of myocardial injury and pulmonary edema without the presence of significant coronary artery disease. Chest pain occurs in most, but not all, patients presenting to the emergency department with myocardial injury after the use of amphetamine.[29] An acute cardiomyopathy with elevated myocardial band fraction of creatine kinase (CK-MB), mitral valve prolapse, elevated mean capillary wedge pressures, and reduced cardiac output developed 10 hours after IV use of amphetamine.[84] Three hours after the IV administration of 20–60 mg amphetamine, a 24-year-old man presented at an emergency department with pulmonary edema.[85] Coronary angiograms demonstrated patent coronary arteries and a reduced ejection fraction (32%) that normalized after 12 days. The serum creatine kinase concentration peaked at 703 IU on the fourth day.

Case studies of cardiomyopathies following the abuse of amphetamine are rare, and the contribution of drug impurities and predisposing factors to the development of these cardiomyopathies remains unclear. The chronic oral abuse of dextroamphetamine (100 mg/d intermittently for 5 years, continuously for 7 years) was associated with the development of a fatal congestive cardiomyopathy; clinical deterioration occurred during dextroamphetamine withdrawal.[86] The postmortem examination demonstrated normal coronary arteries and a focal myocarditis similar to the myocardial changes associated with pheochromocytomas. Intravenous amphetamine abusers are subject to the same complications (e.g., endocarditis, pulmonary granulomas) as heroin abusers.

## Fatalities

Death from the use of amphetamine is relatively rare except following intentional ingestion of massive amounts of amphetamine or secondary to trauma during amphetamine-induced psychosis; these situations usually involve novice amphetamine users. Nontraumatic deaths related to amphetamine typically involve suicide or the intentional ingestion of amphetamine to avoid criminal prosecution. Mechanisms of nontraumatic deaths associated with the misuse or abuse of amphetamine include the following causes: cardiovascular (acute left ventricular failure, ventricular fibrillation), cerebrovascular (subarachnoid or intraparenchymal hemorrhage, cerebral edema), and hyperthermia (seizures, rhabdomyolysis, DIC, cardiovascular collapse). Predisposing factors for the development of fatal reactions to amphetamine use includes the coadministration of other stimulant or arrhythmogenic drugs, hypokalemia, or preexisting cardiovascular disease.[87] IV drug abusers are subject to the potentially fatal complications of illicit IV drug administration including septicemia, fulminant hepatitis, subacute bacterial endocarditis, cor pulmonale resulting from foreign-body granulomas, necrotizing angiitis, and AIDS.[66]

## Abstinence Syndrome

A withdrawal syndrome may occur in heavy users during the first week following cessation of use. The abstinence syndrome that follows cessation of chronic amphetamine use is relatively mild compared with CNS depressants (e.g., heroin, sedative-hypnotic drugs). Chronic amphetamine and cocaine use produces a similar abstinence syndrome, but there are no common physical symptoms that characterize stimulant withdrawal.[88] Abrupt discontinuance of amphetamine does not produce seizures or life-threatening symptoms, even in those patients who habitually consume large quantities of amphetamine. The symptoms associated with abstinence syndrome following chronic amphetamine use include a dysphoric mood (depression, irritability, anxiety) and psychomotor agitation along with fatigue, insomnia, hypersomnia, poor concentration, paranoia, akathisia, and drug craving.[89] Myalgias, abdominal pain, voracious appetite, and a profound depression with suicidal tendencies may complicate the immediate postwithdrawal period; the intensity of these symptoms usually peaks 2–3 days after cessation of amphetamine use.

## Reproductive Abnormalities

Available evidence suggests that the therapeutic use of *d*-amphetamine during pregnancy does not increase the risk of adverse pregnancy outcomes including teratogenicity.[90,91] The abuse of *d*-amphetamine is associated with prematurity, low birth weight, impaired neurobehavioral development, and increased maternal–fetal morbidity; however, multiple sociologic and economic variables as well as polydrug use complicate the interpretation of the effect of methamphetamine on fetal outcomes.[92]

# DIAGNOSTIC TESTING

## Analytic Techniques

### *Screening*

The most common screening methods for amphetamine in urine involve the detection of the parent compound by immunoassay [Abbott fluorescence polarization immunoassay (FPIA; Abbott Laboratories, Abbott Park, IL); Syva EMIT® (enzyme multiplied immunoassay technique; Siemens Healthcare Diagnostics, Deerfield, IL], radioimmunoassay (RIA; Roche Diagnostic Products Corp., Indianapolis, IN), or thin-layer chromatography (TLC). Colorimetric methods, ultraviolet spectrophotometric procedures, and fluorescence methods are now superseded by immunoassays.[93] The Toxi-Lab TLC® (Varian, Inc., Palo Alto, CA) method can detect amphetamine concentrations ranging from 0.5–3.0 mg/L, but in general the use of TLC methods is less sensitive than the use of immunoassays.[94]

Immunoassays are sensitive methods for screening urine samples for the presence of amphetamine, but these techniques lack specificity. Occasionally, large ingestions of some amphetamine-like compounds may produce false-positive results including over-the-counter inhalers (*l*-isomer of methamphetamine), diet medications (phentermine), or cold preparations (phenylpropanolamine, ephedrine, pseudoephedrine) depending on the urine drug concentration and the type of immunoassay.[95] Relatively high concentrations of illicit amphetamine analogs (methylenedioxyamphetamine [MDA], methylenedioxyethylamphetamine [MDEA], methylenedioxymethamphetamine [MDMA], 3-methoxy-4,5-methylenedioxyamphetamine [MMDA]) also cross-react with some of these screening tests to produce false-positive results, but the cross-reactivity varies between different screening procedures and the concentrations of the substance in the urine sample.[96,97] Metabolism of the antiparkinson drug, selegiline produces *l*- methamphetamine and *l*-amphetamine; however, the ratio of methamphetamine/amphetamine following the biotransformation of selegiline is approximately 2.5 compared with about 10 following the metabolism of methamphetamine.[98]

**TABLE 1.2.** Cross-Reactivity of Amphetamine Immunoassays.[93]

| Drug | RIA | FPIA (TDx®) | EMIT d.a.u.® Polyclonal | EMIT d.a.u.® Monoclonal | EMIT II® |
|---|---|---|---|---|---|
| *d*-Amphetamine | 100 | 90 | 100 | 250 | 100 |
| *d,l*-Amphetamine | 50 | 100 | 100 | 100 | 67 |
| *d*-Methamphetamine | 2.2 | 57 | 30 | 100 | 100 |
| *d,l*-Methamphetamine | — | 57 | — | — | 53 |
| Diethylpropion | 0* | 0 | 0* | — | 0.1 |
| Ephedrine | 0 | 0 | 30 | 2 | 0.7 |
| Fenfluramine | — | 22 | 33 | 10 | — |
| Mephentermine | 0 | 6 | 75 | 10 | 10 |
| Methylenedioxyamphetamine (MDA) | 327 | 465 | 2.6 | 100 | 33 |
| Methylenedioxymethamphetamine (MDMA) | 0.6 | 84 | 2.8 | 33 | 17 |
| Phenylethylamine | 1 | 2 | 32 | 10 | 0.2 |
| Phenmetrazine | 0.1 | 0 | 30 | 1 | 17 |
| Phentermine | 1.7 | 6 | 75 | 333 | 50 |
| Phenylpropanolamine | 2 | 0 | 30 | 1.3 | 0.4 |
| Pseudoephedrine | 0 | 0 | 30 | 1 | 0.3 |

*Abbreviations:* RIA = radioimmunoassay; FPIA = fluorescence polarization immunoassay.
*Significant cross-reactivity with urinary metabolites.

Rapid screening methods with gas chromatography/mass spectrometry separate various sympathomimetic amine compounds, but these confirmation techniques are too technician- and time-intensive for routine use in most hospital laboratories.[99] Phencyclidine, cocaine, caffeine, and barbiturates do not cross-react with reagents in the immunoassays at concentrations up to 1 mg/mL.[100] Table 1.2 lists the cross-reactivity of various immunoassays. The radioimmunoassay (Roche RIA) is relatively specific for *d*-amphetamine. Cross-reactivity occurs primarily with its major metabolite, *p*-hydroxyamphetamine, and the illicit hallucinogenic drug, *p*-methoxyamphetamine. Phenylpropanolamine and β-phenylethylamine produce slight cross-reactivity with radioimmunoassays, but the concentrations of these drugs in urine usually are too low to produce false-positive results except following a severe overdose of these compounds.[101] The excretion of amphetamine is highly pH dependent, and amphetamine abusers may alkalinize their urine to reduce the concentration of amphetamines present in the urine or they may acidify their urine to increase amphetamine elimination.

### *Confirmatory*

Gas chromatography, high performance liquid chromatography, and gas chromatography/mass spectrometry are the most common methods to confirm and to quantify positive results of screening tests for amphetamine.[102,103] The US National Institute on Drug Abuse (NIDA) guideline requires that positive urine samples contain amphetamine concentration exceeding 200 ng/mL. Positive screening tests for amphetamine require confirmation by more specific methods (e.g., gas chromatography/mass spectrometry, high performance liquid chromatography), which separate amphetamine from methamphetamine and other structurally similar compounds. In contrast to gas chromatography/mass spectrometry, liquid chromatography/tandem mass spectrometry does not require sample derivation or hydrolysis. The interassay, interday variability (coefficient of variation) of liquid chromatography/tandem mass spectrometry for amphetamine was approximately 10–12%.[104] Detection limits for amphetamine in serum samples using a solid-phase microextraction method combined with liquid chromatography/electrospray ionization/tandem mass spectrometry was 0.3 μg/L.[105] The use of gas chromatography/mass spectrometry does not necessarily differentiate the illicit use of methamphetamine or amphetamine from the use of prescription drugs that contain these compounds or are metabolized to amphetamine and/or methamphetamine.[106] Interpretation of drug-testing results that include the alleged use of amphetamine/methamphetamine precursor drugs requires analysis of the following factors: detection of parent drug or unique metabolite, ratio of *d*- and *l*-enantiomers of methamphetamine and amphetamine, and methamphetamine and/or amphetamine concentrations relative to the history of prescription drug use (see Confirmatory Methods under Methamphetamine).

### *Street Sample Analysis*

In addition to the presence of impurities from the clandestine synthesis of amphetamine compounds, drug samples contain many adulterants. Analysis of street samples suggests wide variation in the potency of samples including the absence of amphetamine derivatives in up to 40% of purported samples. These illicit drugs contain varying amounts of phencyclidine, lysergic acid diethylamide (LSD), 2,5-dimethoxy-4-methylamphetamine (STP), cocaine, atropine, mescaline, and strychnine, as well as additives (e.g., cornstarch, maltose, lactose, magnesium silicate, quinine, fibrous material).

### *Storage*

Animal studies and examination of exhumed material indicate that amphetamine is fairly stable in the blood and bone marrow over several years of burial.[107] *In vitro* studies indicate that amphetamine is stable in urine samples stored at –20°C in 1% sodium fluoride for 2 years.[108] In a study of amphetamine concentrations in gray-top Vacutainer® (Becton, Dickinson, & Co., Franklin Lakes, NJ) tubes containing 100 mg sodium fluoride and 20 mg potassium oxalate, the mean decrease of the amphetamine concentration at 6 months and 1 year was 31% and 77%, respectively.[109] Amphetamine was less stable than methamphetamine. *N*-ethylbenzamide (CAS RN: 614-17-5) is a thermal decomposition product of the vulcanizing agent zinc ethylphenyldithiocarbamate (CAS RN: 3037-20-2) used in rubber production. The presence of this compound in glass containers sealed with a natural rubber septum may cause false-positive results for amphetamine as measured by gas chromatography,[110] but gas chromatography/mass spectrometry accurately identifies the contaminant.

## Biomarkers

### *Blood*

Antemortem. Toxicologic analyses of blood and urine confirm amphetamine ingestion, but these assays are not usually available to guide clinical management; extrapolation of these amphetamine concentrations to expected clinical effects must be done cautiously.

Paranoid delusions, disorganization of thoughts, hallucinations, and poor concentration occurred in a group of 18 patients evaluated for amphetamine psychosis.[111] The peak amphetamine concentration in plasma samples drawn from 15 of these psychotic patients within 24 hours of admission ranged from 0.08–0.64 mg/L. Although these patients received ammonia chloride for urine acidification (pH 5.1–6.1), the timing of the urine acidification in relation to the plasma sample was not reported. There was no correlation between psychiatric symptoms and plasma amphetamine concentrations. The mean peak plasma amphetamine concentration in plasma samples from 8 of the 18 chronic amphetamine abusers administered 200 mg amphetamine sulfate IV followed by urinary acidification (urine pH 5.1–5.4) was approximately 0.4 mg/L (range, 0.36–0.45 mg/L) compared with 0.43 mg/L (range, 0.31–0.60 mg/L) for 10 addicts receiving 160 mg amphetamine IV (urinary pH 5.2–6.4), as measured by gas chromatography/flame ionization detection. No psychotic symptoms occurred in these patients following the administration of these 2 amphetamine doses. The ingestion of approximately 1 g amphetamine chronically by tolerant users produces whole blood concentrations in the range of 2–3 mg/L with little obvious acute signs of intoxication.[112] In a study of amphetamine abusers hospitalized for psychotic behavior, the plasma amphetamine concentration ranged from 0.161–0.530 mg/L in admission peripheral blood samples.[111]

Postmortem. There are limited data on postmortem blood concentrations of amphetamine; therefore, the interpretation of the significance of a specific postmortem concentration of amphetamine requires careful analysis of the circumstances surrounding the death, the behavior of the user, the autopsy, prescription medications, anatomic site of postmortem sample collection, and the reliability of the sample integrity. In particular, the lower ranges of amphetamine concentrations must be interpreted with caution because of tolerance and the subjectivity associated with the determination of the contribution of amphetamine to the cause of death.[113] Consequently, the postmortem amphetamine concentration should not be used alone to determine the cause of death. Postmortem *d*-amphetamine blood concentrations in a case series of amphetamine-related fatalities ranged from 0.5–41 mg/L with an average of 8.6 mg/L.[114] Separation of the enantiomers by chiral derivatization may assist in the determination of the timing of ingestion (i.e., late vs. early) because of the more rapid metabolism of the (*S*)-enantiomer of amphetamine. A (*S*)-/(*R*)-enantiomer ratio of approximately 1 suggests the recent ingestion of amphetamine.[115] The use of some prescription medications (selegiline) may produce small, but detectable amounts of amphetamine and methamphetamine in postmortem blood samples.

### *Urine*

Urine amphetamine immunoassays detect the presence of these compounds following occasional use for

approximately 1–3 days depending on several factors including the dose, duration of use, urine pH, hydration (i.e., urine creatinine, specific gravity), analytic method (sensitivity, specificity, cutoff), and individual metabolic and excretion rates.[93] Because of structural similarities, phenylpropanolamine may cross-react with some amphetamine reagents. The potential for cross-reactivity depends on a variety of factors including the assay, the drug concentration, the extraction procedure (e.g., sodium periodate), and the metabolic products of the drug. At therapeutic concentrations, the cross-reactivity of these drugs to most immunoassays are relatively low, and false-positive results are unusual.[95] Drugs that produce amphetamine as a metabolite include amphetaminil, benzphetamine, clobenzorex, dimethamphetamine, *N*-ethylamphetamine, fenethylline, fenproporex, and mefenorex. High concentrations of other drugs that cause potential false-positive results on amphetamine immunoassays include the following: deprenyl, famprofazone, fencamine, furfenorex, mesocarb, phenothiazines (trifluoperazine, chlorpromazine, thioridazine),[116] prenylamine, trazodone,[117] bupropion,[118] and quinolones.[119]

## Abnormalities

Acute renal failure may develop secondary to acute tubular necrosis (as a result of hypotension), rhabdomyolysis, intravascular coagulation, hypovolemia, or hyperpyrexia. Hypoxemia may result from seizures, noncardiac pulmonary edema, or acute cardiac failure. Pulmonary function tests, except the carbon dioxide diffusing capacity, usually remain normal during chronic amphetamine use. Leukocytosis occurs frequently after amphetamine use; a leukemoid reaction may occur. Case reports associate microangiopathic hemolytic anemia with IV polydrug use including the abuse of amphetamine.[120] In patients with amphetamine-induced intracranial hemorrhages, computed tomography (CT) may reveal intracerebral hematomas, hemorrhage of the thalamus, cerebral edema, or transtentorial herniation. Intracranial hemorrhages are usually located in the cerebral white matter rather than abnormalities in the sites (i.e., basal ganglia, pons, cerebellum) commonly associated with chronic hypertension.

## Driving

The primary benefit of low doses of amphetamines is the variable reduction of fatigue.[121] The administration of 5–15 mg of dextroamphetamine to healthy, alert (i.e., nonfatigued) adults does not produce substantial improvement of fatigue[122] or psychomotor skills.[123,124] In a study of 30 student volunteers given 15 mg *d* -amphetamine, objective measures of reaction times increased about 10% above pretreatment values.[125] However, the report did not include the actual data or any statistical analysis. Improvement occurs in some selected tasks that require rapid responses or increased alertness (vigilance, simple reaction time, motor coordination, physical endurance), particularly in restoring baseline performance by fatigued volunteers.[126,127] Enhancement of performance is most likely to occur under conditions of boredom and low intellectual demand, and the positive effects of amphetamines decrease as the complexity of the task increases.[128] Saccadic eye movements are rapid conjugate shifts of gaze that allow changes in visual fixation from 1 object (e.g., pedestrian) to another (e.g., stoplight). Smooth pursuit eye movements stabilize visual images on the retina to optimize visual acuity. Studies in volunteers indicate that 15 mg *d*-amphetamine orally does not alter saccadic or smooth-pursuit eye movements, whereas the IV administration of the same dose abolishes the effect of fatigue on saccadic movements and reduces saccadic reaction time.[129]

Amphetamine users frequently abuse other drugs including ethanol. The interaction of *d*-amphetamine and ethanol on psychomotor tasks is complex with volunteer studies demonstrating contradictory results.[130,131] The Simulator Evaluation of Drug Impairment (SEDI) task is a measure of the skills (attention, memory, recognition, decision making, reaction time) required to operate machinery with precision. Although the administration of 10 mg *d*-amphetamine to 12 healthy volunteers did not alter their scores on the SEDI, this dose of *d*-amphetamine did attenuate the decrement produced by ethanol on accuracy and reaction time performance.[132] The mean peak ethanol concentration in these volunteers was approximately 100 mg/dL.

A driving stimulation study of healthy volunteers 2 hours after receiving 0.42 mg *d*-amphetamine/kg body weight indicated some impairment during daytime driving, but not during nighttime driving.[133] The mean dexamphetamine blood concentration was 83 ng/mL immediately prior to testing. The behaviors primarily contributing to this impairment included "failing to stop at a red traffic light," "slow reaction times," and "incorrect signaling." However, there were a large number of the control drivers judged impaired, and there was decreased visual acuity of the left (but not the right) eye of the volunteers receiving the *d*-amphetamine. There is some evidence that moderate doses (up to 30 mg) of amphetamines increase self-confidence and the acceptance of greater risk. However, these effects are neither strong nor consistent among different individuals.[134] In a study of 36 healthy volunteers, the administration of 10–20 mg *d*-amphetamine reduced scores on several psychologic measures of impulsivity,[135] whereas

other studies suggested increased impulsivity after *d*-amphetamine administration.[136] The use of *d*-amphetamine doses up to 25 mg is difficult to detect by standardized sobriety tests of motor coordination and observation of behavior.[137] Standard field sobriety tests (horizontal gaze nystagmus, walk and turn test, one leg stand test) are not sensitive measures of the effect of dexamphetamine as measured in adult volunteers receiving 0.42 mg/kg *d*,*l*-dexamphetamine or placebo.[138]

Impairment of driving skills also may develop during the withdrawal phase from chronic amphetamine abuse because of the presence of exhaustion, fatigue, depression, or agitation. Neuropsychologic testing of paid volunteers did not detect rebound effects following the administration of pharmacologic doses of *d*-amphetamine.[139] Consequently, impairment may occur even at low blood amphetamine concentrations. A study of 11 amphetamine abusers suggested that their accident rate was about 3–4 times higher than the rate expected based on age, sex, and driving exposure.[140] In a retrospective study of Norwegian drivers apprehended on the suspicion of driving under the influence, medical evaluation after the arrest indicated that 73% of the drivers with blood amphetamine concentrations exceeding 0.27 mg/L (2.0 μ*M*) were severely impaired.[141] American pilots selectively used dextroamphetamine during long flights (about 17 h and 35 h) during Operation Iraqi Freedom without obvious side-effects as evaluated by retrospective interviews within 4 weeks of the 94 sorties.[142]

There are few data on the blood amphetamine concentrations associated with driving impairment. Similar to the interpretation of postmortem amphetamine concentrations in blood samples, interpretation of the significance of specific amphetamine concentrations requires careful consideration of surrounding circumstances, behavior, tolerance, and the time of the sample. In a study of 6,094 drivers suspected of driving under the influence (moving traffic violations, sobriety checkpoints, traffic accidents), the mean blood amphetamine concentration was 1.01 mg/L (median 0.80 mg/L) with a range up to 11.9 mg/L.[143] There were no other drugs detected by gas chromatography/mass spectrometry in these blood samples.

### TREATMENT

The treatment of amphetamine, methamphetamine, and cocaine intoxication is similar; there are fewer clinical data on the specific treatment of amphetamine or methamphetamine intoxication than cocaine intoxication. There are no unique features of amphetamine intoxication that require treatment different than methamphetamine intoxication (see Treatment under Methamphetamine). Because amphetamine is a weak base, urinary acidification increases the excretion of unchanged drug and causes a decrease of the plasma half-life. However, the clinical efficacy of this therapeutic maneuver on clinical outcome remains doubtful, especially because cardiovascular and renal complications may develop during the use of this procedure during amphetamine intoxication. The treatment of the hallucinations and paranoia associated with amphetamine-induced psychosis typically involves the administration of dopamine agonists (e.g., haloperidol, chlorpromazine). Newer generation antipsychotic medications (e.g., olanzapine) also reduce the symptoms associated with amphetamine-induced psychosis and these medications may be better tolerated than the older antipsychotics (e.g., haloperidol).[144]

## METHAMPHETAMINE

### HISTORY

While attempting to synthesize ephedrine in Japan, Ogata synthesized methamphetamine in 1919.[145] Later, he sold the license for this process to Burroughs Wellcome Company, which sold methamphetamine in the United States as Methedrine® until this drug was withdrawn from the US market in 1968. During World War II, the Japanese government widely distributed amphetamine compounds in the form of over-the-counter stimulants (philopon, shabu) to their civilian workers as a method to increase worker productivity. After the war, the distribution of large legal stockpiles of methamphetamine ampules contributed to widespread parenteral abuse of methamphetamines in Japan. Between 1945 and 1955, the epidemic of methamphetamine (wake-amine) addiction involved over 2 million Japanese citizens, beginning with writers, musicians, and artists. Later, the abuse of methamphetamine extended to the Korean minorities in Japan.[146] Tight production controls of methamphetamine in Japan began with the Stimulants Control Law of 1951. A massive education program and strict penalties in Japan sharply reduced the abuse of methamphetamine by the mid-1950s. Although drug addiction in the Japanese culture was rare prior to the methamphetamine epidemic, other forms of drug abuse (heroin, methaqualone, 1,2-diphenyl-1-dimethylaminoethane [SPA]) appeared after the initial methamphetamine epidemic.

During the 1960s, one of the treatments of heroin addiction was a liquid form of methamphetamine. Although abuse of methamphetamine initially involved

the diversion of pharmaceutic products, illicit production of methamphetamine began in the early 1960s in San Francisco, a process largely controlled by motorcycle gangs in the California Bay area. Illicit production spread along the Pacific Coast of the United States during the 1960s.[147] Initially, oral methamphetamine was listed as schedule III drugs; however, in 1971, methamphetamine was added 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 methamphetamine to illicit markets. During the 1950s and 1960s, methamphetamine was a common prescription medication for the treatment of depression and obesity with a peak of 31 million prescriptions in the United States during 1967.[147] Parenteral methamphetamine was always listed as a schedule II drug.

During the 1980s, illicit production of a smokable form of (+)-methamphetamine hydrochloride (Ice) began in Japan and Korea. Abuse of Ice spread to Taiwan, the Philippine Islands, Hawaii, and to the mainland United States by the late 1980s. Although the abuse of Ice never reached epidemic proportions similar to freebase cocaine, illicit use and manufacture of methamphetamine spread from California to the Midwest.[147] A third epidemic of methamphetamine abuse via IV and pulmonary routes occurred in Japan during the 1990s following the importation of illicit methamphetamine from China and North Korea.[148] Since the 1980s, clandestinely manufactured methamphetamine replaced legal supplies as the primary source of methamphetamine; Mexican-based distributors and so-called superlabs in California and the southwestern United States replaced local manufacture of methamphetamine. More recently, exports from large Mexican methamphetamine laboratories replaced regional sources as the main supplier of methamphetamine in the United States.[149] Recent data from the US Substance Abuse and Mental Health Services Administration suggest that the current methamphetamine epidemic may have peaked around 2004–2005 with the use of methamphetamine reaching a plateau.

## IDENTIFYING CHARACTERISTICS

### Structure

Methamphetamine (CAS RN:537-46-2) is the common name for *N*,α-dimethylphenethylamine (desoxyephedrine, methylamphetamine, phenylisopropylmethylamine). The structures of methamphetamine ($C_{10}H_{15}N$) and amphetamine are similar, but the amino nitrogen in methamphetamine has a methyl group as demonstrated in Figure 1.1. The configuration at the chiral center of methamphetamine results in a dextrorotatory isomer [*d*-methamphetamine, *S*-(+)-methamphetamine] and a levorotatory isomer (*l*-methamphetamine, *R*-(–)-methamphetamine] with respect to plane-polarized light.[150] The [α]D25 (specific notation) of pure *d*-methamphetamine is +14–20°. Metabolism of the antiparkinson drug, selegiline, produces the *l*-(–) enantiomer of methamphetamine. Dimethylamphetamine is a pyrolysis product of methamphetamine and an illicit stimulant sold in Japan with no medical applications.[151] Although dimethylamphetamine has abuse potential, animal models suggest that this tertiary amino compound is substantially less potent than methamphetamine.[152]

The 2 enantiomers of methamphetamine demonstrate some differences in biologic effects. In volunteer studies of methamphetamine abusers administered IV methamphetamine doses of 0.5 mg/kg, the psychodynamic effects produced by *l*-methamphetamine and *d*-methamphetamine are similar; however, the effects of the former are shorter and less desirable as reported by the participants.[153] The abuse liabilities of racemic methamphetamine and *d*-methamphetamine are similar. Therapeutic doses of methamphetamine produce more prominent central than peripheral effects compared with similar doses of amphetamine as a result of the increased lipophilicity and enhanced CNS penetration of methamphetamine resulting from the *N*-methyl substitution.

### Physiochemical Properties

The addition of a methyl group to amphetamine increases lipid solubility and transport of methamphetamine across the blood–brain barrier. The molecular weight of methamphetamine (freebase) is 149.24 g/mol. Freebase methamphetamine is a lipophilic weak base with a $pK_a$ of 9.87 that is a dark liquid at room temperature; however, methamphetamine hydrochloride (molecular weight 185.74 g/mol) is a white to translucent crystalline solid at room temperature (melting point 170–175°C/338–347°F). Unlike most methamphetamine salts, the vapor pressure of methamphetamine hydrochloride is sufficiently high to allow the efficient smoking of this salt, regardless of the size of the crystals.[154] This hydrochloride salt of methamphetamine is soluble in water, chloroform, and ethanol, but not soluble in ether; extraction of methamphetamine from biologic samples occurs easily following the use of organic solvents at alkaline pH. Both methamphetamine and methamphetamine hydrochloride easily volatilize with heat; consequently, methamphetamine may volatilize during the dry-down or evaporation phase of extraction. Unlike cocaine hydrochloride, methamphetamine hydrochloride volatilizes at 300–305°C (572–581°F) without pyrolysis. Therefore, methamphetamine hydrochloride can be smoked in the salt form, whereas the smoking of cocaine

hydrochloride requires the complicated conversion of this salt to the freebase.

Because of the presence of protonated nitrogen and a chloride nucleophile, the hydrochloride salt of methamphetamine undergoes *N*-demethylation to amphetamine more easily than the methamphetamine base decomposes to amphetamine. The heating of methamphetamine hydrochloride salt to 400°C (752°F) and to 600°C (1,112°F) converts about 5% and 10%, respectively, of the methamphetamine dose to amphetamine.[155] Experimental studies indicate that demethylation and methylation reactions are the major pyrolysis processes at temperatures below 358°C (676°F).[156] At temperatures above 315°C (599°F), amphetamine and dimethylamphetamine form from demethylation and methylation reactions, respectively. Benzyl ethyl trimethylammonium is also a pyrolysis product, and the thermal degradation of this compound produces allylbenzene, *cis*-β-methylstyrene, and *trans*-β-methylstyrene. Above 445°C (833°F), the *l*-isomers of amphetamine and methamphetamine form from the respective *d*-isomer.[156]

Smoking methamphetamine in a tobacco mixture substantially reduces the recovery of methamphetamine compared with the recovery of methamphetamine using a smoking apparatus. In a study of the pyrolysis products from smoking methamphetamine mixed with tobacco in a smoking apparatus, the amount of methamphetamine transferred to tar ranged from 6% to 17%.[154] Major pyrolysis products of a 10- or 20-mg dose of methamphetamine present in mainstream smoke included methamphetamine, amphetamine, phenylacetone, dimethylamphetamine, and *N*-formyl, *N*-acetyl-, *N*-propionyl, and *N*-cyanomethyl methamphetamine compounds. Other minor pyrolysis products include *N*-acetylmethamphetamine, phenyl ester of propanoic acid, and furfuryl methamphetamine (*d*,*l*-furfenorex).[157] Mainstream smoke from the smoking apparatus contained 14.5% of the initial dose of 50 µg methamphetamine as measured by gas chromatography/mass spectrometry.[158] Other major products of pyrolysis present in the mainstream smoke included phenylacetone (3.1%), *N*-cyanomethylmethamphetamine (1.9%), *trans*-β-methylstyrene (1.7%), and *N*-formyl methamphetamine (1.5%).

## Terminology

The street names Speed and Crank typically refer to forms of methamphetamine hydrochloride that contain either pure *d*-methamphetamine or a racemic mixture of *d*- and *l*- methamphetamine enantiomers depending on the process used to produce the illicit methamphetamine.[159] Other names for the solid form of methamphetamine include Base, Fast, Meth, P, Point, Pure, Rabbit, Tail, Wax, and Whiz.[14] Trade names for methamphetamine compounds include Desoxyn® (Ovation Pharmaceuticals, Inc., Deerfield, IL) and the discontinued product, Methampex®. Based on the appearance of methamphetamine crystals, this form of methamphetamine hydrochloride is known as Batu (Hawaii), Crystal Meth, Crystal, Ice, Glass, and Shabu.

# EXPOSURE

## Epidemiology

Methamphetamine is the second most popular illicit drug (i.e., after cannabis) worldwide with annual global prevalence of about 0.4%; amphetamine is relatively more common than methamphetamine in Europe compared with Asia, Oceania, and North America.[160] Crystalline methamphetamine is one of the most prevalent illicit drugs in the United States; use began in the western United States in the early 1990s and subsequently spread across the United States. The prevalence of methamphetamine use has stabilized since 2000 with a decrease in new methamphetamine users aged 12 years and older beginning around 2005.[161] Based on weighted Internet surveys, the overall prevalence of current nonmedical methamphetamine use in 2005 was 0.27% among 18- to 49-year-olds; the estimated lifetime (i.e., at least once) was 8.9%.[162] The use of methamphetamine is also common in Taiwan and other parts of Asia. Southeast and East Asia are major global sources for methamphetamine production and trafficking, particularly Cambodia, Indonesia, Malaysia, Philippines, and the Mekong region of Vietnam.[163] In a retrospective study of autopsy cases performed in Taiwan between 1991 and 1996, methamphetamine-*related* deaths as defined by a postmortem blood methamphetamine concentration exceeding 0.1 mg/L accounted for 3.4–12.1% of the total autopsy cases.[164] Reviews of drug use in Australia indicate an increase in both importation and local manufacture of methamphetamine.[165] National household surveys of drug use in New Zealand indicate the increased use of crystal methamphetamine between 2003 and 2006 as a result of fewer respondents stopping the use of methamphetamine and more respondents reporting the increased frequency methamphetamine use.[166] The use of methamphetamine in North America varies with geographical location, type of methamphetamine, route of administration, and type of user. Furthermore, the form of methamphetamine changed from nonmedical use to the use of powder methamphetamine, and now to the use of the more potent crystal methamphetamine (Ice) with high purity.[167] The prevalence of methamphetamine use among young adults in

San Francisco has traditionally been high, particularly among homosexual males and IV drug users. In a cross-sectional study of young (median age 22 years) IV drug users in San Francisco, about 50% reported IV drug use within the last 30 days. The IV use of methamphetamine was higher in homosexual males with 60% of homosexual male, IV drug users reporting recent injection of methamphetamine compared with 47% of heterosexual male, IV drug users.[168]

## Sources

Therapeutic uses of methamphetamine include the treatment of attention deficit disorder (ADD) and narcolepsy. *d*-Methamphetamine is a prescription drug (Desoxyn®, Abbott Laboratories, Abbott Park, IL) available in the United States as a schedule II drug.

### *Origin*

In contrast to the synthesis of *d*-amphetamine, the production of methamphetamine is relatively simple. Methamphetamine synthesis involves the following general steps: 1) collection and storage of chemicals, 2) isolation of precursors and catalysts from commercial products, 3) cooking (mixing, heating, filtering), 4) extraction of methamphetamine base into organic solvent, and 5) salting (precipitation and drying of water-soluble salt).

Methamphetamine Powder. The most common methods of the illicit manufacturing of methamphetamine are phenylacetone (P2P or phenyl-2-propanone), red phosphorus/hydrogen iodide (hydroiodic or hydriodic acid ) reduction (Yankee Dope, Red P, or Red, White, and Blue), and ammonia/alkali metal reduction (Nazi Dope). Methamphetamine was originally synthesized in illicit laboratories primarily by reductive amination using the Leuckart reaction, which involved the condensation of phenylacetone (phenyl-2-propanone, P2P) with methylamine in the presence of formic acid and an aluminum amalgam catalyst. This forms an intermediate imine. As the geometry of the imine is flat, the reduction of the imine to methamphetamine proceeds without stereochemical preference. Therefore, the end-product of this synthetic approach is the racemic mixture of *d,l*-methamphetamine, which frequently contains the nonreacted starting material (phenylacetone). The legal restriction placed on phenylacetone in the early 1980s and substantial differences in the pharmacologic activity of the 2 methamphetamine enantiomers resulted in a search for alternative methods of methamphetamine synthesis.

Currently, the most popular methods of illicit methamphetamine synthesis involve the reduction of *l*-ephedrine or *d*-pseudoephedrine either with red phosphorus and hydriodic acid (the "red, white, and blue" method) or with sodium or lithium metal in condensed liquid ammonia (the Birch reduction or the "Nazi" method). The latter method is more common in rural areas. Both these methods produce *d*-methamphetamine with the former process yielding 54–82% of this enantiomer.[150] The substitution of phenylpropanolamine as the precursor in either synthetic process yields amphetamine.

The advantages of the synthetic approach to illicit methamphetamine production include the following: 1) the stereochemistry of the α-carbon is fixed in the starting material, so the reduction yields a pure product containing only the more desirable *d*-methamphetamine, and 2) the reagents and precursors are inexpensive, easily purchased on the commercial and retail level. The legitimate medical and commercial uses of these methamphetamine precursors severely limit attempts to restrict access to these chemicals; *smurfing* is the process whereby criminal individuals and groups attempt to circumvent state and federal pseudoephedrine sales restriction by purchasing small quantities of pseudoephedrine at multiple retail outlets. Alternatives for drug trafficking cartels are importation of ephedrine and pseudoephedrine from Southeast Asia and South America. Figure 1.5 displays both the Leuckart reaction and the reduction of ephedrine to yield methamphetamine. Although extremely uncommon, other synthetic processes for methamphetamine include "dry reduction" using hydriodic acid/red phosphorus with small amounts of water and the reduction of phenylacetone (phenyl-2-propanone) by the mercury-aluminum amalgam reduction.[169]

Crystal Methamphetamine Hydrochloride (Ice). The slow cooling of hot solutions of saturated solutions of methamphetamine hydrochloride in certain organic solvents produces large, glass-like crystals. In contrast to freebase cocaine, crystal methamphetamine is not the freebase form of methamphetamine. The smokable form of methamphetamine contains relatively pure *d*-methamphetamine in contrast to the racemic mixture of methamphetamine produced by the condensation of phenylacetone and methylamine.[170] The terms Ice, Batu (Hawaii), or Crystal refer to the relatively pure, smokable form of *d*-methamphetamine hydrochloride because this synthetic product appears as transparent, sheet-like crystals.[159] Typically, the production of Ice involves the crystallization of methamphetamine hydrochloride from a saturated solvent solution using the ephedrine- or pseudoephedrine-reduction method. This

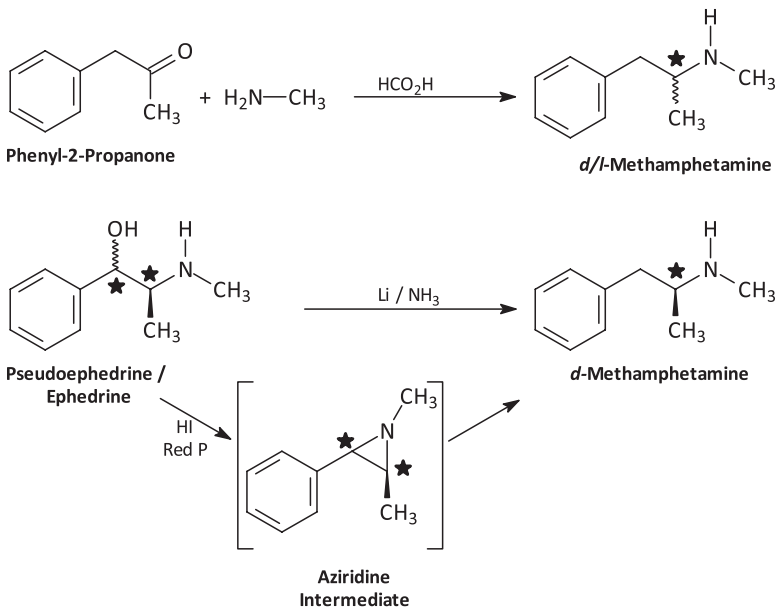



**FIGURE 1.5.** Synthetic routes to methamphetamine. The top scheme is the Leuckart reaction using phenyl-2-propanone (P2P) as a starting material. Reduction of the planar imine intermediate (not shown) results in a racemic mixture of *d*- and *l*-methamphetamine. The lower scheme depicts the reduction of ephedrine or pseudoephedrine (dictated by the stereochemistry of the benzylic hydroxyl) to form methamphetamine directly. Any one of a number of reductive techniques may be used for the reduction of ephedrine or pseudoephedrine to methamphetamine. However, the stereochemistry at the carbon alpha to the amine is maintained with these reductions yielding only the *d*-methamphetamine product.

process crystallizes sheets of *d*-methamphetamine hydrochloride crystals from the cooling of supersaturated, heated solutions of relatively pure *d*-methamphetamine as a result of the separation of the *d*- and *l*-isomers of ephedrine during the reduction process. Using ephedrine or pseudoephedrine as the starting material for Ice generates a more potent mixture that contains pure *d*-enantiomer rather than a racemic 50-50 mixture. The *d*-enantiomer of methamphetamine is several times more active pharmacologically than the *l*- enantiomer.[171]

### *Methamphetamine Laboratories*

Retrospective, cross-sectional studies based on self-administered questionnaires suggest that symptoms experienced by law-enforcement personnel during investigations of clandestine methamphetamine laboratories include headache, sore throat, respiratory tract and mucous membrane irritation, nausea/vomiting, skin irritation, and various CNS symptoms.[172,173] Dermal burns are usually limited to persons directly involved in the production of illicit methamphetamine.[174] These injuries develop following spills, uncontrolled reactions, and/or fires during the manufacturing of methamphetamine. Phosphine gas is a by-product of the red phosphorous method (Red P) method for the clandestine manufacturing of methamphetamine along with hydrochloric acid and iodine. In a study of a simulated red phosphorous cook, the airborne hydrogen chloride concentration during a 4-hour cooking period was 0.27 ppm; however, peak concentrations during the salting phase of the cook may substantially exceed this concentration.[175] The respirable methamphetamine concentration in this area during the cook was 720 μg/m$^3$. The anhydrous ammonia method generates ammonia and hydrochloric acid. Fatal concentrations of phosphine gas may form during the use of these types of manufacturing processes.[176] The increased popularity of methamphetamine and the proliferation of clandestine methamphetamine laboratories has caused an increasing incidence of burn injuries associated with laboratory accidents.[177] In a retrospective case-control study of 660 patients aged ≥16 years of age admitted to a burn center in the Midwestern United States, 10% of the 410 patients tested for drugs of abuse were positive for methamphetamine.[178] Burn injuries associated with the volatile process of methamphetamine synthesis are frequently more severe than other burn center patients including a higher incidence of third-degree burns, large burn areas, and inhalation injury.[178,179]

Children are often found during raids on homes with methamphetamine laboratories. The majority of the children display no overt clinical symptoms; however,

clinical features may range from respiratory irritation to agitation, seizures, and fatal sulfuric acid ingestion.[180] These children usually lack supervision and frequently have issues with school performance, criminal behavior, and social isolation. Protocols for the evaluation of these children include the following: 1) decontamination if external contamination is present, otherwise a bath/shower; 2) complete history, mental health, and physical examination within 48–72 hours, unless the presence of symptoms necessitates a medical evaluation earlier; 3) methamphetamine testing for legal purposes (urine drug screen with confirmation, hair samples), and placement in a safe environment.[181]

## Methods of Abuse

The pattern of methamphetamine abuse is more frequent and more continuous during the daytime than cocaine abuse, which usually involves episodic use during the evening.[182] Because of the easy synthesis and available supplies of methamphetamine, users typically spend substantially less (i.e., 25%) money than cocaine users.[183] Methamphetamine is listed as a prohibited substance by WADA.[25]

### *Chronic Oral Abuse*

"Parachuting" describes an oral method of methamphetamine abuse involving the swallowing of a methamphetamine-containing, sealed plastic bag with a hole cut on one end to dispense the amphetamine slowly during transit along the GI tract. Alternately, crushed methamphetamine tablets are rolled in a paper wrapper and swallowed. Severe, delayed (i.e., up to at least 42 h) methamphetamine toxicity can occur when the delayed release of large amounts of methamphetamine occurs during transit through the intestines.[184]

### *Intravenous Abuse*

Intravenous methamphetamine abusers represent a subgroup of long-term, chronic drug abusers with a high prevalence of high-risk sexual and antisocial behaviors, comorbid psychiatric disorders, and multiple drug use.[185,186] A "speed freak" is a compulsive methamphetamine abuser, who uses the drug continuously for days during a "run." During this phase, the intense methamphetamine use substantially reduces food consumption, sleep, and personal hygiene. High methamphetamine doses produce extreme suspiciousness, hyperactivity, poor impulse control, or an overt paranoid psychosis that can be associated with unpredictable violent behavior.[187] Stereotyped behavior during these runs includes skin picking, bead stringing, pacing, repetitive actions, and interminable chattering. Repeated IV injections (1–10 per day) prolong the run until exhaustion, disorganization, paranoia, severe anxiety, confusion, irritability, insomnia, or loss of drug supply terminates use, usually within several days to 1 week.

During the initial phase following cessation of methamphetamine use, exhaustion develops with the methamphetamine abuser sleeping deeply for 24–48 hours and then eating ravenously. Severe depression often occurs after the methamphetamine abuser becomes satiated. The methamphetamine abuser may resume IV drug use to relieve the depression, beginning another run.[188] To relieve anxiety, some methamphetamine abusers combine other IV drugs (e.g., heroin) with IV methamphetamine ("speedballing"). Particularly in the Pacific Northwest, methylphenidate (Ritalin®, Novartis, Basel, Switzerland) is a substitute for methamphetamine.

Occasionally, the rapid escalation of IV methamphetamine doses produces a condition called "overamped." During this situation, elevated blood pressure, temperature, and pulse, along with chest discomfort develop. Additionally, altered consciousness occurs, manifest by the inability to speak or move despite apparent awareness of the environment. Death from overdose is infrequent in tolerant individuals. In fact, habitual high-dose users commonly exhibit no apparent physical signs of dependence other than the obvious signs of economic, social, and emotional deterioration. The chronic abuser becomes unreliable, irritable, paranoid, and unstable, resulting in physical, social, and economic problems. Suicide may occur from either loss of impulse control or severe depression during the exhaustion phase. Adverse psychologic reactions from chronic methamphetamine abuse include anxiety reactions, psychosis, withdrawal reactions (e.g., exhaustion syndrome, biogenic amine depletion syndrome or [BADS]), prolonged depression, and persistent hallucinations.[189]

### *Smoking*

The smoking of methamphetamine hydrochloride does not require conversion to the freebase in contrast to cocaine hydrochloride because of the relatively high volatility of methamphetamine hydrochloride. Typically, the methamphetamine hydrochloride crystals are heated in the base of a glass pipe and the vapors are inhaled ("chasing the white dragon"), *without* drawing the vapors through a coolant liquid that is common during the freebasing of cocaine.

Figure 1.6 displays a methamphetamine pipe. The crystallization of methamphetamine to the hydrochloride salt (Ice) is necessary because the lipid soluble, pure base form of methamphetamine evaporates easily

**FIGURE 1.6.** Methamphetamine pipe. (Photo courtesy of the US Drug Enforcement Agency).

at room temperatures. All crystals of methamphetamine are "smokable" regardless of the size of the crystal. In a pharmacokinetic study of chronic methamphetamine smokers, the average dose inhaled was approximately 22 mg.[190] Animal and human studies suggest that the pharmacologic effects of methamphetamine by inhalation and by IV route are similar.[191,192]

## DOSE EFFECT

### Illicit Use

The response to methamphetamine depends on a variety of factors including the percentage of active isomers, the setting, tolerance, and expectations. In a study of volunteers familiar with the effects of methamphetamine, the inhalation of 20–25 mg methamphetamine produced minimal subjective and cardiovascular effects, whereas a 30-mg dose of methamphetamine caused more pronounced and sustained effects.[193] The use of 40 mg methamphetamine produced extreme subjective effects characterized by feelings of omnipotence as well as decreased appetite, difficulty concentrating, insomnia, memory lapses, and intense craving for further doses. Anecdotal reports suggest that the IV use of methamphetamine begins with the injection of 20- to 40-mg doses, but as tolerance develops the dose increases substantially. The typical daily methamphetamine abuser smokes or insufflates 0.5–1 g during a 24-hour period beginning in the morning and continuing every 2–4 hours until sleep ensues. In a case series of 65 current methamphetamine abusers, the estimated mean daily dose of methamphetamine was 720 mg with a range up to 3.5 g.[194] A binge involves the use of methamphetamine every few hours until the user can no longer stay awake (i.e., usually 3–4 d). After the binge, the user sleeps for a prolonged period (e.g., 24–48 h) and may resume daily methamphetamine use or start on another binge. Experienced IV methamphetamine users typically inject from 100–300 mg per use with maximum doses exceeding 1 g during binges.[27] As much as 1 g may be injected every 2–3 hours by a speed freak during a binge up to a daily dose of 5–8 g for several days until exhaustion, psychosis, or loss of drug access terminates the "speed run."

### Pharmaceutic Use

Medical use of methamphetamine includes the administration of daily doses up to 15 mg for obesity, up to 20–25 mg for ADD, and up to 60 mg for narcolepsy. Most methamphetamine analogues have been voluntarily removed from over-the-counter inhalants. However, the Vicks® inhaler (Procter & Gamble, Cincinnati, OH) is a nasal decongestant containing 50 mg of (*l*-methamphetamine (*l*-desoxyephedrine), menthol, camphor, methyl salicylate, and bornyl acetate. *l*-Methamphetamine has approximately 10% of the central nervous system potency of *d*-methamphetamine.[195]

### Fatalities

Determination of a fatal human dose is complicated by interindividual variation including tolerance and variations in purity of illicit drugs.[196] Death from methamphetamine overdose is relatively rare compared with the prevalence of methamphetamine abuse. The minimal lethal methamphetamine dose varies with age and animal species.

#### *Animal*

Experimental studies indicate that the IV $LD_{50}$ of methamphetamine in adult, nontolerant monkeys maintained in primate chairs was approximately 15–20 mg/kg.[197] Young monkeys ($LD_{50}$ = 5 mg/kg) and adult monkeys in open cages ($LD_{50}$ = 2–3 mg/kg) were more vulnerable, particularly when hyperactivity and elevated body heat occur. Chronic administration of escalating doses of IV methamphetamine does not produce toxicity in some animal models. Methamphetamine is twice as toxic in animal models as amphetamine.

#### *Human*

A 22-year-old man died 5 days after the ingestion of 140 mg methamphetamine hydrochloride.[198] He developed hyperthermia, hypotension, renal failure, and

hyperkalemia. Chronic methamphetamine users tolerate high doses of methamphetamine. Methamphetamine addicts can inject 1–5 g IV methamphetamine without developing severe complications as a result of the development of tolerance. A 27-year-old man survived after the injection of 75 mg methamphetamine with intensive supportive care after developing DIC, hypocalcemia, and rhabdomyolysis with myoglobinuria.[199] The estimated leakage of 20 g methamphetamine in a body packer caused his death (postmortem cardiac blood, 63.5 mg methamphetamine/L; admission blood, 8.6 mg methamphetamine/L), whereas a fellow body packer survived the estimated leakage of 18 g methamphetamine (admission blood, 7.6 mg methamphetamine/L) following intensive support for severe intoxication.[200]

## TOXICOKINETICS

### Absorption

#### *Oral*

The pattern of methamphetamine absorption is similar to amphetamine, including absorption from mucosal surfaces.[32] Studies in volunteers indicate that the bioavailability of methamphetamine following ingestion is approximately 60–70%.[190] The average time between ingestion and peak plasma methamphetamine concentration was approximately 2–2.5 hours.[201] Ingestion of an 18-mg dose of methamphetamine hydrochloride by volunteers produced peak plasma concentrations of 0.035–0.038 mg/L with an average lag time from ingestion of about half an hour.[155]

#### *Insufflation*

Methamphetamine easily crosses the alveolar and nasal membranes after smoking and insufflation. In a study of 11 methamphetamine abusers receiving up to 50 mg/70 kg body weight intranasally, peak cardiovascular and subjective effects occurred within 15 minutes of administration.[202] However, peak plasma methamphetamine concentrations occur about 4 hours after insufflation. Volunteer studies indicate that the bioavailability of intranasal doses of methamphetamine is near 80%.[203]

#### *Smoking*

Absorption of methamphetamine hydrochloride (Ice) by the lungs is rapid with peak effects occurring within 15–20 minutes of the initiation of smoking.[190] Studies in volunteers indicate that the plasma methamphetamine concentration rises rapidly and then increases slowly over the next 4 hours before declining. Following the smoking of approximately 22 mg methamphetamine hydrochloride by 6 volunteers familiar with the effects of methamphetamine, the peak plasma methamphetamine concentration ($0.047 \pm 0.0056$ mg/L) occurred at $2.5 \pm 0.5$ hours after initiation of smoking.[193] The peak plasma *amphetamine* (i.e., active metabolite) concentration of 0.003–0.006 mg/L in these volunteers occurred 10–24 hours after smoking began.[193] In a study of 8 experienced methamphetamine users, the mean bioavailability of the delivered doses of methamphetamine via intranasal administration and smoking were similar (i.e., 79% and 67%, respectively), depending on technique.[203] However, the absolute bioavailability of methamphetamine after smoking was substantially less (mean, 37%) than intranasal administration, primarily as a result of the amount of drug retained in the smoking apparatus.

Smoking of methamphetamine in a pipe reduces the bioavailability of the drug both by deposition of active compound in the pipe apparatus and through thermal decomposition. Following insertion of a pipe in an aluminum block heated to about 300°C, approximately 25% of the dose remained in the pipe after the completion of the smoking of a 30-mg dose of methamphetamine hydrochloride by healthy volunteers.[155] During this *in vitro* study, the recovery of intact methamphetamine base from pipes at temperatures of 400°C (752°F), 600°C (1,112°F), and 800°C (1,472°F) was approximately 98%, 88%, and 62%, respectively. The amount of amphetamine formed as a result of the complete pyrolysis methamphetamine was about 1%. The recovery of intact methamphetamine hydrochloride was slightly less than methamphetamine base with the recovery being 81%, 62%, and 38% for these temperatures, respectively.

#### *Mucosal Surfaces*

Case reports suggest that serious methamphetamine intoxication can develop following the concealment of methamphetamine-containing bags in the vagina. After inserting a bag of methamphetamine that leaked in her vagina, a 20-year-old woman developed seizures and apnea.[204] She recovered after intubation without obvious sequelae; however, her clinical course was complicated by aspiration pneumonia and mild rhabdomyolysis without renal dysfunction.

### Distribution

Methamphetamine distributes widely to most parts of the body. The volume of distribution ($V_d$) of methamphetamine is approximately 3–4 L/kg, which is smaller than the $V_d$ of phencyclidine, but higher than the $V_d$ of cocaine. In a study of volunteers given an average

inhaled dose of 22 mg *d*-(+)-methamphetamine and an IV dose of 15.5 mg *d*-(+)-methamphetamine, the volume of distribution in the elimination phase was 3.24 ± 0.36 L/kg and 3.73 ± 0.59 L/kg, respectively.[190] Animal studies suggest that methamphetamine accumulates in the brain following distribution from the plasma. There are substantial differences in the protein binding of methamphetamine between most animal species and humans. The range of protein binding in a study of various animal species (bovine, rat, rabbit, guinea pig, horse, mouse, chicken) ranged from about 61–98%. Therefore, the pharmacokinetics of methamphetamine in animal studies must be extrapolated with caution to humans.[205]

## Biotransformation

The metabolism of methamphetamine involves aromatic hydroxylation of the benzene ring at the 4-position, aliphatic hydroxylation of the β-carbon position (minor), *N*-demethylation to amphetamine, oxidative deamination, *N*-oxidation, and conjugation of nitrogen.[206,207] The 2 primary metabolites of methamphetamine biotransformation are 4-hydroxymethamphetamine and amphetamine. Amphetamine is both a minor metabolite of methamphetamine and a product of the pyrolysis of methamphetamine. Figure 1.4 demonstrates the biotransformation pathways of methamphetamine. Other minor oxidative metabolites in the urine include norephedrine, 4-hydroxynorephedrine, benzoic acid, and benzyl methyl ketoxime.[37] The metabolism of *N*-dimethylamphetamine also produces the active metabolite, amphetamine. Aromatic hydroxylation (4-hydroxylation) and *N*-demethylation of methamphetamine probably involves the cytochrome P450 isoenzyme, CYP2D6.[208] Additionally, other cytochrome P450 subfamilies (CYP2C, CYP3A) also catalyze the demethylation of methamphetamine along with cytochrome P450-independent pathways.[209] Hydroxyclobenzorex is a metabolite of illicit amphetamine that does not occur following the ingestion of therapeutic doses of amphetamines; consequently, the presence of this metabolite indicates illicit drug use.[210] The biotransformation methamphetamine varies substantially between animal species; humans metabolize a relatively smaller portion of methamphetamine and excrete a relatively larger portion of unchanged methamphetamine compared with rats and guinea pigs.[211]

## Elimination

Methamphetamine is a highly basic drug with primarily renal elimination; therefore, the renal excretion of methamphetamine is dependent on urine pH, urine flow, and dose.[212] The plasma methamphetamine concentration rises rapidly after smoking and then reaches a plateau after several hours. The geometric mean plasma methamphetamine half-life in volunteers administered methamphetamine by smoking (30 mg in pipe bowl, 21.8 ± 0.3 mg estimated delivered dose) and IV injection (15.5 mg) was approximately 11 hours and 12 hours, respectively, with a range of about 8–18 hours.[190] The plasma elimination half-life of *d*-methamphetamine is longer than the corresponding *l*-enantiomer. In a study of 12 methamphetamine abusers administered IV doses of 0.5 mg/kg or 0.25 mg/kg, the plasma elimination half-life for *l*-methamphetamine ranged from 13.3–15.0 hours comparedwith10.2–10.7hoursfor*d*-methamphetamine.[153] The difference between the half-life of the 2 isomers was statistically significant at $P < .0001$. Metabolism of these 2 methamphetamine doses accounted for 58% and 55%, respectively, of the total clearance.

The renal excretion of amphetamine represented about 3–8% of the total methamphetamine clearance, whereas the renal excretion of unchanged methamphetamine accounted for most of the remaining clearance (i.e., about 40% of the total). Figure 1.7 displays the average urinary concentration of methamphetamine and amphetamine during the 60 hours after the administra-

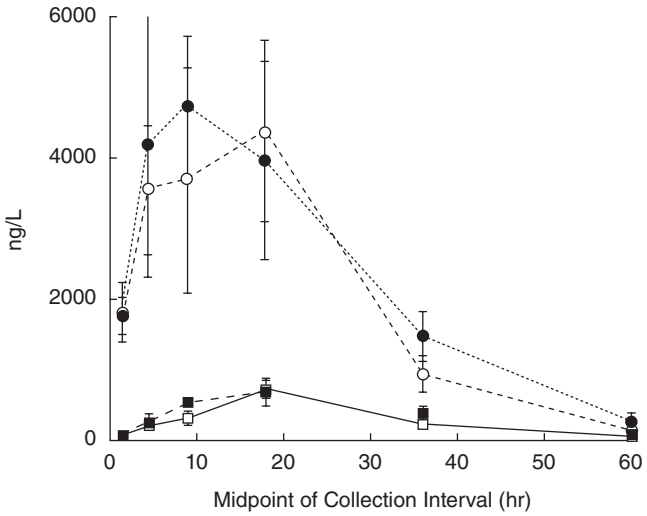



**FIGURE 1.7.** Urinary concentrations of amphetamine and methamphetamine after smoking 30 mg methamphetamine and the intravenous administration of 15.5 mg methamphetamine.[190] Solid circle = urine methamphetamine concentration after smoking; solid box = urine amphetamine concentration after smoking; open circle = urinary methamphetamine concentration after IV administration; open box = urinary amphetamine concentration after IV administration. (Reprinted with permission from CE Cook, AR Jeffcoat, JM Hill, DE Pugh, PK Patetta, BM Sadler, WR White, M Perez-Reyes, Pharmacokinetics of methamphetamine self-administered to human subjects by smoking S-(+)-methamphetamine hydrochloride, Drug Metabolism and Disposition, Vol. 21, p. 717, copyright 1993.)

tion of methamphetamine via smoking (30 mg in a pipe) and IV (15.5 mg) injection. Under normal conditions (urine pH 6–8), the kidney excretes about 37–54% of an absorbed methamphetamine dose as unchanged methamphetamine within the first 24 hours, 15% as *p*-hydroxymethamphetamine, and 4–7% as amphetamine. In very acidic urine (pH ≤ 5.0) the percentage of unchanged methamphetamine excreted in the urine increases up to 76%, whereas this percentage decreases in very alkaline urine (pH ≥ 8.0) to as little as 2% of the absorbed dose. In a study of 8 volunteers receiving 4 daily 10 mg (low dose) or 4 daily 20 mg (high dose) doses of *sustained-release* (*d*)-methamphetamine, the urinary terminal elimination half-life was approximately 24 ± 7 hours compared with 21 ± 7 hours for amphetamine.[213] Urinary pH was not controlled in this study and about 12% of the urine samples had a pH in excess of 8.0. Analysis of the urine data indicated that more biotransformation and less excretion of unchanged methamphetamine occurred following the high dose than the low dose. Within the first 24 hours after the *first* methamphetamine doses, the mean peak urinary excretion rate for methamphetamine was about 300 ± 200 μg/h (range, 141–600 μg/h) at about 9 ± 8 h after the last dose. In comparison, the mean peak urinary excretion rate for the low methamphetamine dose was 674 ± 571 μg/h (range, 107–1,379 μg/h) at about 10 ± 7 hours after the last dose. Consequently, the fraction of methamphetamine excreted in the urine decreases with increasing doses of methamphetamine, and the amount of urinary methamphetamine is not proportional to the absorbed dose of methamphetamine. During the course of the study from the initial administration of the 4 daily methamphetamine doses to 8 days after the last methamphetamine dose, the peak urinary methamphetamine concentrations for the low-dose and high-dose regimens were approximately 6.14 ± 2.40 μg/mL (range, 3.1–10.9) and 11.3 ± 5.1 μg/mL (range, 5.1–18.5 μg/mL), respectively. Although low amphetamine/methamphetamine ratios (<5%) suggest recent use (i.e., <3–6 h), high intra- and interindividual variability limits the use of this ratio *alone* to determine the time of methamphetamine use.

## Tolerance

The progressive decline in subjective and cardiovascular effects despite the presence of high and sustained methamphetamine plasma concentrations indicates the development of tolerance.[193] This tolerance is pharmacodynamic rather than related to changes in the methamphetamine metabolism.[214] Experimental studies indicate that the administration of low doses (10 mg) of methamphetamine for 2 weeks does not alter the pharmacokinetics of methamphetamine.[215] In a 15-day residential study, healthy volunteers received oral methamphetamine 5 or 10 mg twice daily on days 4–6 and 10–12; the volunteers received placebo on the other days.[216] Compared with baseline placebo effects, positive subjective effects of methamphetamine occurred only on day 4; however, adverse effects persisted through day 12.

## Interactions

Case reports suggest that the ingestion of ethanol can potentiate the side effects of methamphetamine.[217] In volunteer studies of methamphetamine addicts, the pattern of alcohol use altered the metabolism of methamphetamine. Simultaneous ingestion of ethanol inhibited the *p*-hydroxylation and *N*-demethylation of methamphetamine.[218] However, in a double-blind, double-placebo, within-subject study of methamphetamine addicts, the administration of ethanol (1 g/kg) did not alter the subjective effects following the IV administration of 30 mg methamphetamine.[219] Case reports associate fatal serotonin syndrome with the use of methamphetamine and moclobemide.[220]

## Maternal/Fetal Kinetics

Methamphetamine crosses the placenta following use by the mother during pregnancy. An infant weighing approximately 2.5 pounds died 4 hours after birth via a cesarean section for partial abruption of a low lying placenta.[221] The mother ingested methamphetamine as a diet pill during the entire pregnancy. The postmortem concentration of methamphetamine in the blood, liver, and lungs of the neonate was 0.355 μg/g, 0.246 μg/g, and 0.857 μg/g, respectively. A postmortem case series included positive methamphetamine samples from two 1-month old infants and 5 fetuses dying between the fifth and eighth month of pregnancy.[222] The postmortem fetal blood concentrations of methamphetamine and amphetamine ranged from 0.18–1.2 mg/L and from 0–0.08 mg/L, respectively. In a study of pregnant sheep, methamphetamine crossed the placenta within 30 seconds of IV administration; fetal blood pressure increased 20–37% above baseline along with a drop in fetal oxyhemoglobin saturation and arterial pH.[223] Because of the longer elimination half-life of methamphetamine in the fetal circulation, the fetal methamphetamine concentration eventually exceeded the maternal methamphetamine concentration. Pharmacokinetic studies indicate that methamphetamine diffuses into breast milk following the recreational use of methamphetamine by lactating mothers. The absolute daily infant dose of methamphetamine and amphetamine in methamphetamine equivalents in 2 infants of lactating mothers using methamphetamine was

17.5 μg/kg and 44.7 μg/kg.[224] The mothers self-administered a single IV dose of methamphetamine from their usual source (purity/dose unknown). The authors recommended withholding breast feeding 48 hours after a recreational dose of methamphetamine.

# HISTOPATHOLOGY AND PATHOPHYSIOLOGY

## Mechanism of Action

Methamphetamine stimulates the release of catecholamines from sympathetic nerve terminals, particularly dopamine in the mesocortical, mesolimbic, and nigrostriatal pathways; these structures influence emotions, motivation, reward systems, and motor output.[225] Methamphetamine enters the cytosol via passive diffusion and the membrane-bound catecholamine-uptake transporters, disrupting the pH gradient and facilitating the redistribution of monoamines in the cytosol. This process reverses the normal reuptake mechanism of the catecholamine transporters, resulting in increased movement of catecholamines into the synapses and the central and peripheral α- and β-adrenergic postsynaptic receptors.[1] Both the physiologic effects and mechanisms of action of methamphetamine and amphetamine are similar. The physiologic effects of methamphetamine result from the enzymatic inactivation, release, and uptake of catecholamine neurotransmitters (dopamine, norepinephrine), and to a lesser extent, the indoleamine, 5-hydroxytryptamine (serotonin) neurotransmitters. *In vitro* studies indicate that release of norepinephrine by methamphetamine is about twice as great as dopamine release and about 60-fold greater than serotonin release.[226] The effects of methamphetamine on the brain are complex and include dopaminergic, serotonergic, and GABAergic activity. Animal models suggest that methamphetamine stimulates the release of dopamine via several mechanisms including inhibition of monoamine oxidase and increased efflux of methamphetamine by displacement of storage vesicles. The dopamine transporter (DAT) is the primary site of action of methamphetamine as reflected by the absence of methamphetamine-induced effects in experiments with DAT knockout mice that lack the dopamine transporter.[227] Effects at monoaminergic synapses include the following: inhibition of monamine oxidase (MAO), blockade of uptake, and promotion of neurotransmitter release into the synaptic cleft. The prolonged action of methamphetamine at the synapse depletes available neurotransmitters and results in acute tolerance or tachyphylaxis. In part, this acute tolerance explains the use of escalating doses of methamphetamine during methamphetamine runs or binges.

### *Cardiovascular*

Methamphetamine produces cardiovascular effects only in large doses, but it displays more prominent CNS effects at low doses when compared with amphetamine. A study of 2 champion cyclists demonstrated that the ingestion of 10 mg methamphetamine did not increase the capacity for aerobic exercise as measured by heart rate, minute ventilation, blood lactic acid concentration, and maximum oxygen consumption.[228] However, the administration of 10 mg methamphetamine increased their endurance of anaerobic metabolism and resulted in the ability to maintain higher levels of exercise for longer periods compared with placebo.

### *Central Nervous System*

Experimental data indicate that at least some of the CNS effects of methamphetamine result from the alteration of pre- and postsynaptic dopamine activity in the brain. Animal data suggest an adaptive upregulation of nucleus accumbens dopamine $D_1$ receptor function during chronic methamphetamine administration.[229] G proteins are the intracellular messengers that link dopamine receptors to the effector enzyme, adenylyl cyclase. Dopamine receptor types are classified based on the ability to stimulate ($D_1$ receptors, also $D_5$) or inhibit ($D_2$ receptors, also $D_3$ and $D_4$) adenylyl cyclase through the mediation of the stimulatory or inhibitory G proteins. Although methamphetamine is usually considered more addictive than amphetamine, there are few data on the neurobiologic differences between these 2 structurally similar drugs. In a locomotor activity study of rats, methamphetamine and amphetamine similarly increased dopamine concentrations in the nucleus accumbens and the prefrontal cortex, but the dopamine concentrations in the prefrontal cortex were lower following methamphetamine than amphetamine administration.[230] The administration of amphetamine increased glutamine concentrations in the nucleus accumbens, whereas methamphetamine did not.

## Mechanism of Toxicity

### *Cardiovascular System*

Similar to amphetamine, methamphetamine causes excessive sympathetic nervous system activity and vasoconstriction, resulting in tachycardia and potentially, in susceptible patients, myocardial ischemia and cardiac arrhythmias. Dilated cardiomyopathy and congestive heart failure develops in some methamphetamine abusers, but the exact role of methamphetamine and the route of exposure require further clarification.[231] Experimental studies in animals indicate that chronic

methamphetamine administration causes myocyte atrophy, hypertrophy, cellular edema, eosinophilic degeneration, fibrosis, contraction bands, and vacuolization.[232] Ultrastructural changes include myofibrillar hypercontraction, loss of myofilaments, and mitochondrial degeneration.[233]

### *Central Nervous System*

The administration of high doses of methamphetamine to animals causes long-term depression of both dopamine and serotonin synthesis in various regions of the brain.[234,235,236] In studies of rodents, the chronic parenteral administration of methamphetamine produces marked alteration of nigrostriatal dopaminergic neurons at doses lower than those required to produce damage by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[237] A study of gerbils administered 2 subcutaneous doses of methamphetamine at 35 mg/kg demonstrated morphologic alteration of mesocortical dopamine nerve fibers and their postsynaptic structure in the frontal cortex 1 week after administration.[238] *d*-Methamphetamine is a positive reinforcer under controlled laboratory condition in both animals and humans.[239,240]

In humans, chronic abuse of high doses of methamphetamine can produce a psychosis that simulates schizophrenia. Following termination of methamphetamine administration, recurrence of the psychotic symptoms may occur after the single use of amphetamine compounds or other drugs (e.g., ethanol).[241] Although the increased release of dopamine at the synaptic vesicles and the blockade of uptake are part of the effect of methamphetamine,[242] the exact mechanism of this neurotoxic effect is unclear. Postmortem examination of chronic methamphetamine users suggests that partial desensitization of dopamine stimulation of adenylyl cyclase activity occurs in the stratum following chronic methamphetamine use (caudate, putamen, nucleus accumbens);[243] however, autopsies of brains from chronic methamphetamine users do not indicate that methamphetamine distributes preferentially to dopamine-rich areas in the brain.[244]

In a study of methamphetamine abusers, positron emission tomography (PET) scanning detected moderate reduction of dopamine transporter concentrations in the caudate and putamen averaging 27.8% and 21.1%, respectively, when compared with controls.[245] A study of former methamphetamine abusers demonstrated a reduction in the density of dopamine transporter in the nucleus accumbens and caudate/putamen, but there was no difference in the density of striatal dopamine $D_2$ receptors as measured by PET scanning.[246] The long-term functional and pathologic consequences of chronic depletion of dopamine and serotonin (i.e., neuroadaptation) requires further clarification to understand the effects of age, genetics, and duration of use on catecholamine reuptake transporters and presynaptic receptors.[247]

### *Hyperthermia*

Animal models indicate that intrabrain heat production is the primary cause of functional brain hyperthermia; the cerebral circulation dissipates potentially dangerous heat from brain tissue by bringing relatively cooler blood and subsequently removing warmed blood.[248] Although physiologic and behavioral activation is a transient phenomenon, brain temperature may exceed physiologic limits under severe conditions. Methamphetamine stimulates brain metabolism in a dose-dependent pattern while strongly diminishing heat dissipation as a result of peripheral vasoconstriction. The combination of neural activation in the setting of strenuous physical exercise in a hot, humid environment may cause serious elevation of brain temperatures and fatal hyperthermia.

## Postmortem Examination

The most common postmortem findings include pulmonary edema, intense visceral congestion, petechial hemorrhages, relatively increased core body temperature, and increased heart weight.[249] Edema and/or congestion typically occurs in multiple organs, particularly the lung and brain.[250] Mechanisms of sudden death include ruptured berry aneurysms and aortic dissection with cardiac tamponade.[251] Hyperpyrexia with subsequent rhabdomyolysis and hepatorenal failure commonly occurs during fatal methamphetamine intoxication.[252]

### *Heart*

Postmortem examination of hearts from methamphetamine abusers may or may not demonstrate structural abnormalities. A 31-year-old woman, who smoked methamphetamine regularly, developed diffuse systemic vasospasm, an acute myocardial infarction and fatal cardiogenic shock.[253] Postmortem examination revealed diffuse transmural myocardial ischemia with patchy interstitial fibrosis and focal acute infarction of the posterior left ventricle and lateral papillary muscle. There was no histologic evidence of an active myocarditis. Histologic examination of methamphetamine addicts, who died suddenly, reveal hemorrhage and congestion of the lungs with either no changes[254] or relatively minor cardiac abnormalities.[255,256] These cardiac abnormalities included both hypertrophy and atrophy

of myocytes, disarray of myofibrils, endocardial hemorrhage, eosinophilic changes, small round cell infiltration, and degeneration of myofibrils including myolysis and contraction band necrosis.[257] Histologic examination of cardiac tissue may reveal varying degrees of coronary arteriosclerosis, but pathologic changes of a myocardial infarction are rare.[258]

#### *Central Nervous System*

Intracranial abnormalities on postmortem examination of methamphetamine abusers include intracerebral hematoma with cerebral edema and uncal herniation,[259] subarachnoid hemorrhage with or without cerebral aneurysm, and necrotizing angitis.[62] Intraventricular hemorrhage following methamphetamine use is relatively rare compared with intracerebral or subarachnoid hemorrhage.[260] The pathologic changes of the cerebral vasculitis associated with methamphetamine abuse are similar to the changes of polyarteritis nodosa, but these changes involve primarily the large arteries in contrast to the vascular changes associated with typical hypersensitivity angiitis.[261] Postmortem examination of the brains of methamphetamine users indicates that methamphetamine is distributed relatively evenly throughout the brain rather than concentrating in dopamine-rich areas.[262]

## CLINICAL RESPONSE

### Illicit Use

Methamphetamine, amphetamine, and cocaine produce similar clinical effects with the major distinguishing feature being the prolonged effect of methamphetamine or amphetamine compared with cocaine. Agitation and sinus tachycardia were the most common effects in a retrospective review of 47 methamphetamine exposures in children under the age of 6 years as reported to the California Poison Control System.[263] Seizures occurred in 2 cases (9%). Following the ingestion of large doses of methamphetamine, CNS symptoms begin within 30–60 minutes and persist for 4–6 hours. The onset of symptoms following the inhalation of methamphetamine is much more rapid than ingestion. Unusual complications associated with methamphetamine toxicity include decreased visual acuity secondary to retinal vasculitis[264] or hemorrhage.[265] Methamphetamine abuse is a common cause of rhabdomyolysis. In a retrospective study of 367 emergency department patients with rhabdomyolysis (serum creatine kinase ≥1000 U/L), 43% of the patients had positive urine drug screens for methamphetamine.[266] Case reports document rhabdomyolysis with myoglobinuria, hyperpyrexia, leukemoid reaction, disseminated intravascular coagulation, and acute renal failure following IV administration of phenmetrazine and methamphetamine.[199] Headache, myalgias, lightheadedness, paresthesias, weakness, and delirium can occur along with hyperthermia.

Suggestive signs of chronic methamphetamine abuse include involuntary repetitive movements (rocking, fidgeting), multiple crusts on the skin (skin picking), extensive dental caries at base of anterior maxillary teeth, cachexia, fatigue, forgetfulness, agitation, and irritability. Case reports associate chronic amphetamine abuse with choreoathetoid movements that typically resolves with 12–24 hours.[267] Rampant dental caries often occur following the chronic abuse of methamphetamine.[268] The characteristic pattern of tooth decay involves the buccal smooth surface of the posterior teeth and the interproximal of the anterior teeth.[269] These caries often progress to complete destruction of the coronal portion of the tooth. The etiology of this pattern is unclear, but contributing factors include xerostomia, bruxism, and lack of oral hygiene.[270] Rare case reports associate methamphetamine abuse with transient visual loss, retinal vasculitis, and retinal hemorrhage.[271,272]

#### *Behavioral Abnormalities*

Most methamphetamine users do not display overt signs of methamphetamine use. An acute anxiety reaction characterized by dysphoria, agitation, and muscle tremors was the most common acute psychiatric complaint of patients presenting to the Haight-Ashbury Clinic (San Francisco, CA) during the epidemic of methamphetamine use during the 1960s.[188]

#### *Mental Disorders*

The prevalence of psychotic symptoms is substantially higher in methamphetamine users than the general population, particularly in dependent methamphetamine abusers. In a cohort of 309 recruited individuals using methamphetamine at least monthly, 13% of the participants screened positive for psychosis with 23% experiencing at least 1 clinically significant symptom of suspiciousness, unusual thought content, or hallucinations in the previous year.[273] Psychotic reactions occur in methamphetamine abusers with or without a prior history of a psychiatric disorder, but premorbid schizoid/schizotypal personality and early, heavy methamphetamine abuse predispose users to methamphetamine-related psychosis.[274] Separating the effects of drug abuse and comorbid psychiatric disorder is difficult because over 50% of individuals with a history of schizophrenia have a coexisting substance

abuse disorder.[275] Furthermore, about 50% of individuals with methamphetamine dependence have comorbid psychiatric disorders other than substance abuse, particular anxiety disorders (e.g., phobias, social/generalized anxiety), mood disorders (major depression), and antisocial personalities.[276] Experimental studies indicate that a single dose of methamphetamine can cause brief (i.e., few hours) increases in psychotic features in schizophrenic patients.[277] In a experimental study of 14 psychotic patients with a history of methamphetamine abuse, the IV administration of methamphetamine in doses up to 640 mg over 1 hour produced psychotic symptoms that persisted up to 5–6 days in 2 patients.[278] The persistence of psychotic symptoms longer than a week in 1 patient was associated with recurrent methamphetamine use.

The clinical presentation of methamphetamine-induced and amphetamine-induced psychoses is similar. In a select population of 31 incarcerated, chronic IV methamphetamine abusers with psychosis, common symptoms included auditory and visual hallucinations, delusions of persecution and reference, thought broadcasting, depression, and suicidal ideations.[279] Orientation, memory, and sensorium usually remain clear, but transient, fluctuating disturbances of consciousness may occur during periods of florid psychosis after heavy methamphetamine use.[280]

Although the acute psychosis induced by methamphetamine resembles paranoid schizophrenia, several characteristics other than the clearing of psychotic symptoms with abstinence separate drug-induced psychoses from paranoid schizophrenia.[281] For example, paranoid schizophrenics typically manifest more clouding of consciousness, auditory hallucinations, thought disorders, flat affect along with less sexual stimulation and stereotyped repetitive behavior than patients with methamphetamine-induced psychoses.[282] About 29% of 31 incarcerated, chronic IV methamphetamine abusers with psychosis suffered from recurrent episodes of psychosis (flashbacks).[279] In this population of methamphetamine users, psychologic stress, cessation of antipsychotic medication, or recurrent drug use precipitated these flashbacks.[283,284]Cocaine- and methamphetamine-induced psychoses are too similar to distinguish based on presenting signs and symptoms. Other drugs associated with psychoses include bromide, alcohol, hallucinogenic drugs, L-dopa, monoamine oxidase inhibitors, and tricyclic antidepressants.

In contrast to the psychosis associated with schizophrenia, the methamphetamine-induced psychosis typically resolves shortly after cessation of drug use; occasionally, the psychotic symptoms are persistent and refractory to pharmacologic treatment despite abstinence. Most patients with methamphetamine-induced psychosis improve within hours to a week of abstinence, but the psychosis may persist over 3–6 months in some patients, particularly after prolonged methamphetamine abuse.[285,286] Spontaneous recurrence of methamphetamine-induced psychoses occasionally develop in patients with a previous history of drug-induced psychosis, particularly during periods of psychologic stress that involve fear of other people.[287,288] The acute relapse into psychosis may occur after an extended asymptomatic period during abstinence from methamphetamine use. The relapse is similar to the previous psychotic episode with typical clinical features including bizarre delusions, auditory hallucinations, delusions with jealous or persecutory content, and incoherence or loosening of association.[289] Ethanol or small doses of methamphetamine (i.e., 50 mg over 5 days) may reactivate the extreme paranoia along with negativistic and suspicious attitudes.[290] Case reports suggest that the use of stimulant drugs can exacerbate the presence of chronic fluctuating somatic and vocal tics (e.g., eye blinking, jaw jerks, hip turning, humming, panting, muscle jerks).[291] Parkinsonism is not a prominent clinical feature of methamphetamine use despite the reduction of dopamine concentrations in the caudate of chronic methamphetamine users.[292]

### *Medical Complications*

Central Nervous System. Cerebrovascular complications associated with methamphetamine abuse include ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, particularly in the anterior circulation.[293] Frequently, these patients have underlying vascular pathology including atherosclerosis, stenosis, and/or aneurysms. Case reports associate the IV use of methamphetamine with the development of necrotizing angiitis and both ischemic and hemorrhagic stroke including fatal pontine hemorrhage.[294] Cerebral embolism may result from endocarditis complicating IV methamphetamine abuse. Fatal spontaneous intracranial hemorrhage and subarachnoid hemorrhages can occur without evidence of vasculitis or structural abnormalities.[295] Occasional intracerebral hemorrhages occur in the basal ganglia following methamphetamine inhalation.[28,296] Although an ischemic stroke is less common than a hemorrhagic stroke following drug abuse, ischemic strokes do occur after methamphetamine abuse by oral, IV, or pulmonary routes.[297] The cause of these strokes is multifactorial.[298] Although most of the patients with subarachnoid hemorrhages had cerebral aneurysms,[299] most of the cases of thrombosis and intracerebral hemorrhage were not associated with documented vasculitis, vascular malformations, or vasospasm.[78]

Cardiopulmonary System. A few case reports associate acute myocardial infarction with the inhalation of methamphetamine.[300] Although these patients frequently have coronary artery disease, some reports associate the inhalation of methamphetamine with the development of myocardial injury and pulmonary edema without the presence of significant coronary artery disease.[253] Epidemiologic data suggests that methamphetamine use modestly increases the risk of acute myocardial infarction. In a study of 11,011 acute myocardial infarctions identified in a quality indicators database from Texas, the adjusted odds ratio for acute myocardial infarction in methamphetamine users was 1.61 (95% CI: 1.24–2.04, $P = 0.0004$).[301] The adjusted confounders included cocaine, alcohol, and tobacco use, hypertension, diabetes mellitus, lipid disorders, obesity, congenital defects, and coagulation abnormalities. Noncardiogenic pulmonary edema following methamphetamine use is very rare. A case report associated the development of pulmonary edema following methamphetamine inhalation with normal pulmonary artery pressures.[302] No cardiac catheterization was performed. Case reports associate the development of acute aortic dissection with hypertensive crises following the use of methamphetamine. In a case series of 109 patients presenting to an urban hospital with aortic dissection, patients with methamphetamine abuse accounted for 5.5% of patients of all ages and 20% of the patients in this series under 50 years of age.[303]

Case studies of cardiomyopathies following the abuse of methamphetamine are rare; the contribution of drug impurities and predisposing factors to the development of these cardiomyopathies remains unclear. Case reports suggest that a cardiomyopathy may develop following the chronic ingestion of methamphetamine without evidence of myocardial necrosis, and the cardiomyopathy typically resolves with cessation of methamphetamine use.[304] A retrospective review of patients ≤45 years of age hospitalized for congestive heart failure suggested that a history of methamphetamine use was associated with a more severe cardiomyopathy.[305] The reduction in left ventricular ejection fraction was statistically significant at $P = 0.004$. However, there was no documentation of a dose response.

Peripheral Vascular. Perivascular infiltration of methamphetamine can produce local necrosis, cellulitis, granulomas, and abscess formation. Intra-arterial injection causes intense vasospasm with distal cyanosis, ecchymosis, petechiae, edema, paresthesias, pain, weakness, necrosis, and decreased capillary filling. Immediate intense vasospasm is obvious after intra-arterial injections. Rarely, case reports associate ischemic colitis with methamphetamine use via exposure routes other than IV (e.g., smoking, oral).[306,307]

## Fatalities

Death from methamphetamine use alone without underlying cardiac and/or vascular pathology is relatively rare except following intentional ingestion of massive amounts of methamphetamine. In one case series of postmortem examinations with detectable quantities of methamphetamine, two-thirds of fatalities involved with methamphetamine use resulted from violence, including accidents, suicide, and, less often, homicide.[254] The most common nontraumatic, nonoverdose causes of death associated with methamphetamine use include cerebrovascular hemorrhage and heart disease.[308] Rarely, hallucinations and sudden death occur during strenuous exercise in warm environments, particularly in chronic, heavy methamphetamine abusers. Persistent seizures, hyperthermia (>39–40°C/102.2–104°F), coma, severe tachycardia (>160–170 beats/minute), shock, renal failure, severe rhabdomyolysis, and focal weakness are poor prognostic signs.[309,310] Sudden death may occur during restraint of an agitated, chronic methamphetamine abuser in the same manner as the chronic use of high doses of cocaine causes excited delirium with hyperthermia, severe lactic acidosis, and sudden death during restraint occurring in both the hospital setting and police custody.[311,312]

## Abstinence Syndrome

As a binge progresses, unpleasant side effects ("tweaking") replace the pleasurable effects of using methamphetamine including dysphoria, depression, fatigue, paranoia, akathisia, anxiety, irritability, confusion, insomnia, and drug craving.[313] The intensity of these symptoms usually peaks 1–3 days after cessation of methamphetamine use. The acute phase of amphetamine withdrawal initially involves increased sleeping ("nod off") and eating followed by anhedonia, irritability, poor concentration, anxiety, and craving-during the depressive phase ("crash"). Typically, these symptoms are mild and most symptoms resolve within several days to 1 week.[314] Although some symptoms may last several weeks, the persistence of severe symptoms beyond 1 week suggests an underlying disease process.[315]

## Reproductive Abnormalities

Based on animal studies and limited human data, potential adverse effects of methamphetamine abuse during pregnancy include low birth weight,[316] prematurity, and malformations (cleft palate, cardiac anomalies);[317]

however, multiple sociologic and economic variables as well as polydrug use complicate the interpretation of the effect of methamphetamine on fetal outcomes.[92,318] In general, studies of mothers using illicit drugs (i.e., methamphetamine) demonstrate higher rates of prematurity and intrauterine growth retardation (reduced body weight and length, smaller head circumference) in the drug-exposed group compared with groups of mothers without a history of illicit drug use.[319,320] Case reports also associated methamphetamine use by pregnant women with fetal death and maternal complications (eclampsia, HELLP syndrome, amnionic emboli, death).[321] Follow-up studies of children from mothers using methamphetamine during pregnancy indicate a high rate of behavioral problems (aggressive behavior, problems with peers) and poor school performance (delayed development in math and language achievement), but the psychosocial effects associated with maternal drug use are difficult to separate from the effects of methamphetamine use during the prenatal period.[322] Many of these studies suffer from small sample size, inadequate control groups, poor exposure data, and confounding with other prenatal drug use.

## DIAGNOSTIC TESTING

### Analytic Methods

#### *Screening*

Immunoassays are sensitive methods for screening urine samples for the presence of methamphetamine, but these techniques lack specificity. Newer immunoassays (e.g., EMIT II®) are more specific than older assays (e.g., EMIT d.a.u.®), but some assays cross-react with high concentrations of phenmetrazine, phentermine, benzphetamine, illicit hallucinogenic derivatives (MDA, MDEA, MDMA), antidepressants (bupropion),[323] and some phenothiazine compounds (chlorpromazine, promethazine).[324,325] Gas chromatography is a popular method for screening methamphetamine because of the lack of native fluorescence, significant oxidative electrochemical properties at low voltage, and good ultraviolet absorption characteristics. Methamphetamine elutes early in underivatized samples; some methamphetamine may be lost during the time the detector is turned off for the elution of the solvent front.[150] High concentrations of ephedrine or pseudoephedrine may result in the formation of methamphetamine at the injector port of the gas chromatograph.[326]

#### *Confirmatory*

Illicit Use. The NIDA guideline requires that positive urine samples contain amphetamine and methamphetamine concentrations exceeding 200 ng/mL and 500 ng/mL, respectively. Positive screening tests for methamphetamine require confirmation by more specific methods (e.g., gas chromatography/mass spectrometry), which provide structure-specific information. Human studies suggest that the requirement for the presence of >200 ng amphetamine/mL may result in substantial numbers of false-negative samples because of the relatively small amount of amphetamine excreted after the use of methamphetamine as a result of variations in dose and dosing frequency of methamphetamine. The pharmaceutic preparation of methamphetamine in the United States is the *d*-enantiomer; therefore, the presence of both *d*- and *l*-enantiomers suggests the use of illicit methamphetamine unless the individual ingested prescription drugs (e.g., ethylamphetamine, famprofazone, fencamine, fenproporex, prenylamine) that are metabolized to methamphetamine and contain both enantiomers.[327] Separation of these 2 enantiomers requires special chiral columns or derivatizing reagents. High performance liquid chromatography retention time data are not compound-specific like the data obtained by gas chromatography/mass spectrometry methods; therefore, more interference occurs during high performance liquid chromatography procedures compared with gas chromatography/mass spectrometry.[93] In contrast to gas chromatography/mass spectrometry, liquid chromatography/tandem mass spectrometry does not require sample derivation or hydrolysis. The interassay variability (coefficient of variation) of liquid chromatography/tandem mass spectrometry between days for methamphetamine was approximately 10–12%.[328] Detection limits for methamphetamine in serum samples using a solid phase microextraction method combined with liquid chromatography/electrospray ionization/tandem mass spectrometry was 0.04 ng/mL.[105] Enhanced polymer column extraction with gas chromatography/mass spectrometry in scan mode is a simple, reliable method to determine the presence of structurally related amphetamine compounds (e.g., MDMA, MDA, PMA) that cross-react with the methamphetamine immunoassays.[329] The lower limits of detection of these compounds ranges between 5–50 ng/mL. Excessively high temperatures in the injector can cause a confirmed positive for methamphetamine when ephedrine is present in the sample and heat-catalyzed reduction of the ephedrine to methamphetamine occurs. However, the sample should not contain the required 200 ng/mL amphetamine. Phentermine is a structural isomer of methamphetamine; consequently, the similar mass spectrum for these 2 structurally similar drugs requires careful analysis of the retention times and mass spectra for consistency. Derivatization resolves the lack of specificity of methamphetamine mass spectrum.

Medicinal Use. The use of gas chromatography/mass spectrometry does not necessarily differentiate the illicit use of methamphetamine or amphetamine from the use of prescription drugs that contain these compounds or compounds that are metabolized to amphetamine and/or methamphetamine.[106] The interpretation of drug testing results involving the alleged use of amphetamine/methamphetamine precursor drugs requires analysis of the following factors: 1) detection of parent drug or unique metabolite, 2) ratio of *d*-/*l*-enantiomers of methamphetamine and amphetamine, and 3) methamphetamine and/or amphetamine concentrations relative to the history of prescription drug use. In a study of urine samples from 10 volunteers collected during the 12-hour period following the administration of 30 mg *d*-methamphetamine, about 90% of the methamphetamine-positive samples did not contain amphetamine concentrations above the 200 ng/mL standard.[330] Some biologic samples with high concentrations of methamphetamine may not contain detectable concentrations (>50 ng/mL) of *d*-amphetamine.[331] Gas chromatography/mass spectrometry with electro impact or chemical ionization separates amphetamine and methamphetamine from related amines including ephedrine, phenylpropanolamine, phentermine, and synthetic amphetamine analogues (e.g., methylenedioxymethamphetamine).[332]

Medicinal drugs that produce amphetamine or methamphetamine as metabolites include the following: amphetaminil, benzphetamine, clobenzorex, deprenyl, dimethylamphetamine, ethylamphetamine, famprofazone, fencamine, fenethylline, fenproporex, furfenorex, mefenorex, mesocarb, prenylamine, and selegiline. Medications with unique metabolites include 4-hydroxyclobenzorex (clobenzorex), famprofazone (3-hydroxymethylpyrazolone, *p*-hydroxydesmethylfamprofazone), fenethylline (7-carboxymethyltheophylline), fenproporex (dihydroxyfenproporex, hydroxyfenproporex), furfenorex (1-phenyl-2-[*N*-methyl-*N*-γ-valerolactonylamino]-propane), mefenorex (hydroxymethoxymefenorex, hydroxymefenorex), and prenylamine (diphenylpropylamine).[327] The Vicks® inhaler contains 50 mg of *l*-methamphetamine (desoxyephedrine). Therapeutic use of these inhalers does not usually produce positive results on currently available immunoassays, but excessive use of these inhalers potentially may produce false-positive results.[333] Although the Vicks® inhaler sold in the United States contains 50 mg *l*-methamphetamine, Vicks® inhalers from other countries may contain different concentrations of enantiomers.[334] Enantiomeric separation using chiral chromatography or derivatization techniques (e.g., chiral gas chromatography/mass spectrometry or high performance liquid chromatography) differentiate the use of Vicks® inhaler from the use of racemic methamphetamine.[335] Currently, the common reduction process for methamphetamine production yields enantiomerically pure *d*-methamphetamine. Consequently, the detection of essentially pure *l*-enantiomers of methamphetamine and amphetamine indicates the use of these inhalers. Metabolism of prescription drugs that produce only the *d*- and/or *l*-enantiomer include benzphetamine (*d*-enantiomer), deprenyl (*l*-enantiomer), dimethylamphetamine (*d*-enantiomer), ethylamphetamine (*d*- and *l*-enantiomer), famprofazone (*d*- and *l*-enantiomer), fencamine (*d*- and *l*-enantiomer), fenproporex (*d*- and *l*-enantiomer), prenylamine (*d*- and *l*-enantiomer).[327]

Hair. Methods for the quantitation of methamphetamine in hair samples include liquid chromatography/mass spectrometry and gas chromatography/mass spectrometry (gas chromatography/mass spectrometry). Liquid chromatography/mass spectrometry is highly sensitive and reproducible, whereas capillary gas chromatography produces a sharp peak and electron ionization produces highly reproducible mass spectra. Gas chromatography/mass spectrometry coupled with micropulverized extraction, aqueous acetylation and microextraction by packed sorbent allows the determination of methamphetamine in a 1 mg hair specimen with <20% deviation from the lower limit of quantitation (0.2 ng/mg).[336]

### *Street Sample Analysis*

Impurities appear during the illicit manufacture of methamphetamine as a result of incomplete reactions and inadequate purification of intermediate and final products. Methamphetamine may contain additives (e.g., methylsulfonylmethane or dimethyl sulfone) or adulterants (e.g., other stimulants) as a result of additions to the methamphetamine after the synthetic process. There are several routes of methamphetamine synthesis, and each route produces unique organic impurities. Methods for profiling impurities in illicit methamphetamine include gas chromatography with flame ionization detector,[337] high performance liquid chromatography using column switching,[20] and gas chromatography/mass spectrometry after liquid/liquid extraction with organic solvents,[338] headspace solid phase microextraction,[339] or thermal desorption.[340] Analysis of illicit samples with these methods provides useful information regarding drug sources and trafficking routes.[341]

The presence of nonreacted phenylacetone or the presence of a racemate in an illicit drug sample of methamphetamine suggests the use of the Leuckart

method of methamphetamine synthesis. α-Benzylphenethylamine derivatives are the most common contaminates of the reductive amination of phenylacetone using the Leuckart procedure to produce amphetamine and methamphetamine.[342] Side reactions and incomplete conversions during the Leuckart process result in a variety of impurities and intermediate products, including benzyl methyl ketone, dibenzyl ketone, formamide, di(1-phenylisopropyl) formamide, formic acid, methylamine, *N,N*-dimethyl amphetamine, *N*-formyl amphetamine, di(1-phenylisopropyl)amine, benzylamine, and several pyrimidine and pyridine compounds.[343,344] Benzaldehyde is a common contaminant of methamphetamine produced when phenylacetone (P2P) is synthesized from the reaction of benzaldehyde with nitroethane followed by hydrogenation with iron and hydrochloric acid. However, the presence of benzaldehyde is not specific for this type of reaction.

Impurities from the clandestine synthesis of methamphetamine from ephedrine or pseudoephedrine via hydriodic acid include 1-benzyl-3-methylnaphthalene and 1,3-dimethyl-2-phenylnaphthalene.[345] An aziridine is a potentially toxic intermediate of the reduction of ephedrine, probably through the intermediate formation of iodoephedrine with the Red P/HI method. The Birch reduction of ephedrine or pseudoephedrine to form methamphetamine involves treatment of the starting material with an alkali metal (e.g., lithium or sodium in liquid ammonia). During this process, an overreduction causes the partial reduction of the aromatic ring along with the production of small amounts of the cyclohexadienyl analogue of methamphetamine. Several of these impurities (e.g., α-benzyl-*N*-methylphenethylamine or BNMPA) are pharmacologically active, but the toxic effects of these impurities remains relatively unreported.[346,347] Rarely, lead contaminates illicit methamphetamine.[348] Although postproduction adulteration is the most likely cause of lead contamination in illicit methamphetamine, potentially lead can contaminate the methamphetamine syntheses when lead acetate and phenyl acetic acid are used to produce phenylacetone (phenyl-2-propanone).

### *Storage*

Methamphetamine is relatively stable in properly stored and frozen postmortem samples. Animal studies and examination of exhumed material indicate that methamphetamine is fairly stable in the blood and bone marrow over several years.[349] *In vitro* studies indicate that methamphetamine is stable in urine samples stored at –20°C in 1% sodium fluoride for 2 years.[108] In a study of methamphetamine concentrations in samples stored at ambient temperature in gray-top Vacutainer® (Becton Dickinson, Franklin Lakes, NJ) tubes containing 100 mg sodium fluoride and 20 mg potassium oxalate, the mean decrease in methamphetamine concentrations at 6 months and 3 years was 9.31% and 38.1%, respectively.[109]

## Biomarkers

The time course of the deposition of methamphetamine and amphetamine in oral fluids and plasma is similar, but the concentrations of these drugs are higher and the detection time shorter compared with urine. In a study of 5 volunteers receiving 10 mg or 20 mg methamphetamine daily for 4 days, the mean detection times were 0.02 and 4.8 hours, respectively, using the recommended cutoff (5 ng methamphetamine/mL, >2.5 ng amphetamine/mL).[350] The mean times to last positive specimen at this cutoff were 4.0 hours and 20.6 hours, respectively. Analysis of urine samples had higher detection times and rates compared with oral fluids.

### *Blood*

Therapeutic use. Following the ingestion of a liquid dose of 12.5 mg methamphetamine, the mean peak plasma concentration of methamphetamine was about 0.02 mg/L as measured by gas chromatography with flame-ionization detection.[201] Volunteer studies indicate that the central (arousal) and peripheral sympathomimetic effects (i.e., elevated heart rate and blood pressure) begin at plasma methamphetamine concentrations near 0.005 mg/L and 0.02 mg/L, respectively.[351] Doses of methamphetamine in clinical studies do not usually exceed 60 mg, which corresponds to a maximum blood methamphetamine concentration of approximately 0.1–0.2 mg/L.[352] The actual physical effects of methamphetamine are somewhat variable depending on the duration of drug use, psychiatric state, and the situation as well as the methamphetamine concentration. Moderate subjective effects, as defined by a mean score of 38% of the maximum "high" ever achieved, occurred in 6 experienced methamphetamine users following the smoking of 30 mg (inhaled dose of about 22 mg) methamphetamine hydrochloride.[193] The mean peak plasma concentration of methamphetamine was approximately 0.047 mg/L.

The clinical effects of methamphetamine decline more rapidly than the concentration of methamphetamine in the plasma as a result of acute tolerance to the effects of methamphetamine. Consequently, the acute subjective and cardiovascular effects of methamphetamine subside despite the presence of methamphetamine in the plasma. In a study of 8 experienced methamphetamine users, each volunteer received either a 50 mg intranasal dose of methamphetamine along with 10 mg deuterium-labeled methamphetamine

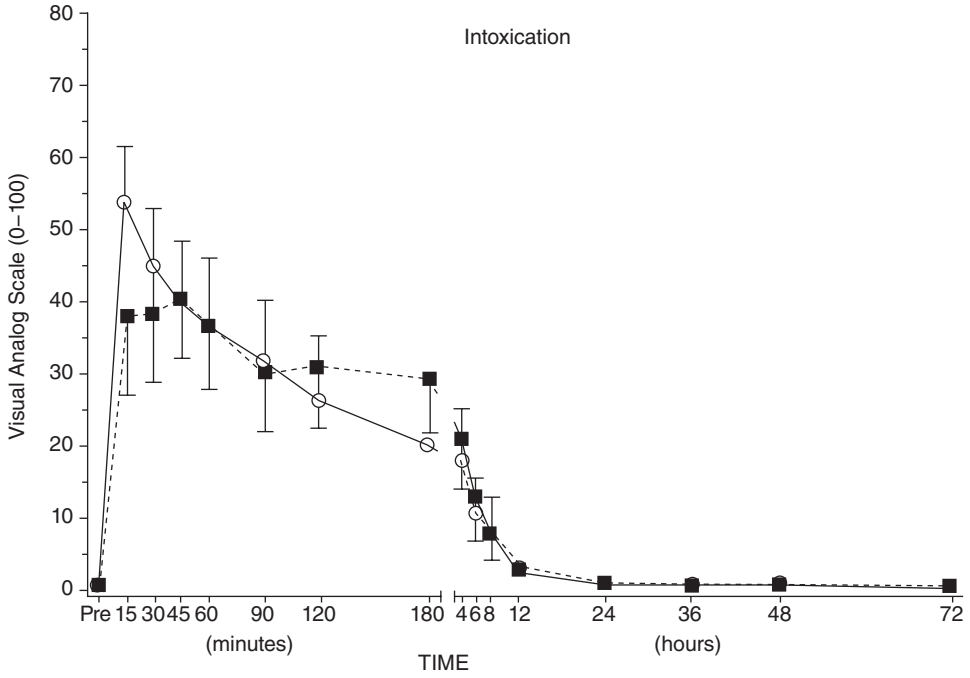



**FIGURE 1.8.** Subjective effects of intranasal (squares) and smoked (circles) methamphetamine based on Visual Analog Scale (0–100) over 72 hours.[203] Each participant also received 10 mg intravenous deuterium-labeled methamphetamine with the intranasal or smoked dose of methamphetamine. (Reprinted by permission from Macmillan Publishers Ltd: Clinical Pharmacology & Therapeutics, Vol. 74, DE Harris, H Boxenbaum, ET Everhart, G Sequeira, JE Mendelson et al., The bioavailability of intranasal and smoked methamphetamine, p. 484, 2003.)

intravenously or 40 mg of smoked methamphetamine along with 10 mg deuterium-labeled methamphetamine IV.[203] Subjective effects of methamphetamine were measured by a visual analog scale from 0–100 with zero being no effect and 100 being "most ever." Figure 1.8 displays the time course of the visual analog scale for intoxication following the administration of methamphetamine via smoking and intranasal administration.

Illicit Use. The clinical effects of methamphetamine depend, in part, on the presence of tolerance. In a case series of 7 chronic methamphetamine abusers exhibiting signs of violence and irrational behavior, the blood methamphetamine concentrations ranged from 0.15–0.56 mg/L as measured by gas chromatography with hydrogen-flame ionization detector.[353] Of 1,265 blood samples submitted for analysis from individuals involved in criminal activity (driving under the influence, rape, homicide, under influence of a controlled substance), about 12% (157 samples) tested positive for methamphetamine.[354] The methamphetamine concentrations ranged from 0.025–2.03 mg/L with a mean concentration of 0.308 mg/L.

Overdose. A review of animal and postmortem data suggested that mild, moderate, and serious intoxications occur at blood methamphetamine concentrations near 0.3 mg/L, 0.4–0.5 mg/L, and 3 mg/L, respectively.[355,356] Following a methamphetamine overdose, blood methamphetamine concentrations in the range of 1–2 mg/L are associated with severe methamphetamine intoxication (hyperthermia, DIC, renal failure, rhabdomyolysis) and death. A 33-year-old male was arrested for driving erratically, and his initial whole blood methamphetamine concentration was 0.23 mg/L.[357] About 3–4 hours after ingesting an unknown amount of methamphetamine, he developed confusion, agitation, and diaphoresis, followed by seizures, hyperthermia, and a marked sinus tachycardia. The serum methamphetamine concentration was 1.94 mg/L. He later developed hyperthermia and fatal DIC. Following a methamphetamine overdose, the plasma methamphetamine concentration 1 hour prior to death from hyperthermia and multiorgan failure was 6.74 μmol/dL (approximately 10 mg/L) with a blood ethanol concentration near 50 mg/dL.[358] A 41-year-old man presented to the emergency department with agitation, diaphoresis, marked sinus tachycardia (160 beats/min), hallucinations, and a temperature of 41.6°C (106.9°F).[359] The serum methamphetamine and amphetamine concentrations on admission 6 hours after the injection of methamphetamine were 0.3 mg/L and 0.04 mg/L, respectively. He recovered after a prolonged course of rhabdomyolysis and hepatorenal

failure. Rarely, survival occurs when the blood methamphetamine concentration exceeds 3–4 mg/L. A driver ingested a bag of methamphetamine following a routine traffic stop, and his serum methamphetamine concentration 1 hour later on arrival to the hospital was 9.46 mg/L.[360] He developed dysrhythmias and seizures, but he survived with supportive care. Details of his medical care were not reported. There are few data on the ratio of whole blood methamphetamine/plasma methamphetamine concentrations.

Postmortem. There are limited data on postmortem blood concentrations of methamphetamine; therefore, the interpretation of the significance of a specific postmortem concentration of methamphetamine requires careful analysis of the circumstances surrounding the death, the behavior of the individual, the autopsy, prescription medications, anatomic site of postmortem sample collection, and the reliability of the sample integrity. In particular, the lower ranges of methamphetamine concentrations must be interpreted with caution because of tolerance and the subjectivity associated with the determination of the contribution of methamphetamine to the cause of death.[164,361]

A study of 413 autopsy reports of cases with detectable methamphetamine in postmortem blood did not find a statistically significant difference ($P = 0.65$) in the mean methamphetamine concentration (2.08 mg/L) between deaths related to the medical effects of methamphetamine and the mean methamphetamine concentration (1.78 mg/L) in deaths not related to the medical effects of methamphetamine.[249] The use of some prescription medications may produce small, but detectable amounts of amphetamine and methamphetamine in postmortem blood samples. The concentration of methamphetamine and amphetamine in postmortem heart blood samples from a 72-year-old woman, who was found dead with a suicide note, was 0.28 mg/L and 0.08 mg/L, respectively.[362] Her list of prescribed medications included selegiline, desipramine, trazodone, and bromocriptine. The source of the methamphetamine and amphetamine was probably the metabolism of selegiline. Consequently, the postmortem methamphetamine concentration should not be used alone to determine the cause of death.

*Concentrations.* Most deaths related to methamphetamines are associated with postmortem methamphetamine concentrations exceeding 0.5–1 mg/L. In a series of 13 autopsies in which methamphetamine was the only drug present in toxicologically significant quantities, the methamphetamine concentration in postmortem blood samples (site not reported) ranged from 0.09–18 mg/L with a median of 0.96 mg/L.[363] There is a wide range of methamphetamine concentrations in blood samples from methamphetamine-related deaths, and the range of methamphetamine concentrations in blood samples from homicides and accidental overdoses usually overlap.[364] In a case series of 23 homicides and 9 accidental overdoses involving only methamphetamine use, the mean (± standard deviation) methamphetamine concentrations in postmortem blood from the 23 homicides and 9 accidental overdoses was 0.66 (±1) mg/L and 0.980 (±1) mg/L, respectively.[365] Amphetamine is a metabolite of methamphetamine, and case reports indicate that the amphetamine concentrations in postmortem blood from fatal cases of methamphetamine overdose are approximately 4–5% of the blood methamphetamine concentration.[366]

*Redistribution.* Some postmortem redistribution of methamphetamine likely occurs because of the basic $pK_a$ and the diffusion of methamphetamine from the sites in the pulmonary veins to the left side of the heart.[367] Additionally, failure to ligate the femoral vein during aspiration of postmortem blood may cause an increase in redistribution of methamphetamine from central to peripheral blood in cases involving the ingestion of large amounts of methamphetamine.[311] In postmortem samples from 4 methamphetamine abusers, blood samples from the left heart were 1.9–2.6 times higher than blood samples from the right heart.[368] The methamphetamine concentrations in samples from the femoral veins were closer to the concentrations in the right heart than to the left heart. In a case series of 3 fatalities, the left/right heart blood ratio was 1.0, 1.59, and 2.06 with the highest ratio occurring in autopsy blood containing the highest concentration of methamphetamine.[367] In a case series of 20 autopsies, the heart/femoral blood ratios of methamphetamine averaged 2.1 with a range of 1.2–5.0.[369] The presence of large amounts of methamphetamine in the stomach may result in the postmortem diffusion of significant amounts of methamphetamine to cardiac blood.[200] Stomach fluid and saliva may contain small amounts of amphetamine (i.e., about 0.1% of the blood methamphetamine concentration) as a result of the diffusion of amphetamine from surrounding blood vessels.[252]

### Urine

The absorption of methamphetamine is rapid with the appearance of the parent compounds in the urine beginning about 20 minutes after ingestion. The concentration of methamphetamine depends on a number of variables including dose, duration of use, urine pH, urinary excretion rates, and individual pharmacokinetics. Figure 1.7 demonstrates urine methamphetamine

and amphetamine concentrations in urine samples from volunteers receiving 15.5 mg methamphetamine intravenously or 30 mg methamphetamine via a glass pipe. The mean methamphetamine concentration in urine samples from 30 outpatients presenting for treatment of methamphetamine abuse was 18.1 ± 26.2 mg/L (range, 0–101.5 mg/L).[370] In 16 urine samples from methamphetamine addicts sent to a Japanese criminal science laboratory, the median urine methamphetamine concentration was about 21 mg/L (range, 0.7–157.5 mg/L).[371] The median methamphetamine concentration in 30 forensic urine samples from Japanese users arrested for methamphetamine use was about 6.7 mg/L (range, 0.77–154.2 mg/L).[372]

Urine amphetamine immunoassays detect the presence of these compounds following occasional use for approximately 1–3 days depending on several factors including the dose, duration of use, urine pH, hydration (i.e., urine creatinine, specific gravity), analytic method (sensitivity, specificity, cutoff), and individual metabolic and excretion rates.[373] The normal urinary pH range is about 4.5–8.0 with urine creatinine concentration below 20 mg/dL and specific gravity <1.003 suggesting dilution of the urine specimen. The US DOT Regulations (49 Code of Federal Regulations Part 40) defines a substituted urine specimen as containing ≤5 mg creatinine/dL *and* a specific gravity of ≤1.001 or ≥1.020. Other criteria for an adulterated specimen include nitrite ≥500 μg/mL, urine pH ≤3 or ≥11 or the presence of substances (e.g., glutaraldehyde, chlorochromate, hydrogen peroxide, bleach, anionic surfactant, hydrochloric acid) normally absent in human urine. Studies of volunteer methamphetamine users indicate that under extreme circumstances the urine drug screen for amphetamine/methamphetamine may remain positive for approximately 1 week.[374] Current US workplace drug testing for methamphetamine requires the presence of urinary methamphetamine and urinary amphetamine concentrations above 500 ng/mL and 200 ng/mL, respectively. Because of interindividual variation and low urinary concentrations of amphetamine, the detection rate for urine specimens collected within 12 hours of ingestion and analyzed using these cutoffs is relatively low. In a volunteer study of 8 volunteers ingesting daily doses of 10 mg methamphetamine for 4 days, about 16% of the urine specimens collected within 12 hours of the dose of amphetamine were positive based on the current cutoff.[375] Final detection times after the 4 doses averaged 55.0 ± 18.7 hours with a range of 31–92 hours. Reducing the methamphetamine cutoff to 250 ng/mL extends the detection time to approximately 24 hours. In a study of 5 healthy volunteers receiving 10 mg or 20 mg methamphetamine daily for 4 days, the mean detection times for methamphetamine in urine samples based on current cutoffs were 43.6 and 66.9 hours, respectively.[350] Lowering the cutoff to 250 ng methamphetamine/mL and 100 ng amphetamine/mL increased the mean detection times to 59.5 and 79.7 hours, respectively. Although detectable concentrations of *d*-amphetamine (i.e., >50 ng/mL) are usually present in urine samples containing methamphetamine, the absence of detectable concentrations of *d*-amphetamine does not necessarily confirm the lack of methamphetamine abuse.[376]

α-Benzyl-*N*-methylphenethylamine (BNMPA) is an impurity that contaminates illicit methamphetamine produced by the Leuckart reaction using phenylacetone (phenyl-2-propanone) synthesized from phenylacetic acid. The presence of BNMPA or its major metabolite, *p*-OH-BNMPA, indicates the illicit use of methamphetamine.[377] Additionally, the presence of the (*d*)-enantiomer or a racemic mixture of methamphetamine enantiomers *suggests* the illicit use of methamphetamine in contrast to licit drugs, which contain only the (*l*)-enantiomer.[378,379] When calibrated at 0.3 mg *d*-amphetamine/L, excessive use (i.e., >twice recommended dose) of Vicks® nasal inhaler (*l*-methamphetamine) may produce false-positive results on some immunoassays, but false-positive results are unlikely during the use of a 1000 ng/mL cutoff.[380] The metabolism of the anti-parkinson drugs, selegiline and deprenyl produces *l*-amphetamine and *l*-methamphetamine, resulting in positive urine drug screens for methamphetamine. Detection of these metabolites requires chiral chromatography; routine gas chromatography/mass spectrometry does not separate the *d*- and *l*-enantiomers. Additionally, the ratio of methamphetamine/amphetamine is much lower (i.e., 2.5) following selegiline ingestion than following methamphetamine ingestion (i.e., about 10).[98] Because of structural similarities, ephedrine and pseudoephedrine may cross-react with some immunoassay screening reagents for methamphetamine.

### *Hair*

Sensitive methods for detecting amphetamine and methamphetamine in hair include gas chromatography/mass spectrometry[381,382] and liquid chromatography/tandem mass spectrometry liquid chromatography/tandem mass spectrometry.[383] Multiple factors complicate the interpretation of the results of hair analysis including hair growth rates, analytic techniques (washing, sample preparation), drug incorporation rates, sectional differences in drug concentrations, hair color and melanin content (increased incorporation in dark hair), life-style differences (shampooing, dyeing, bleaching), sunlight

exposure, and limited data on the correlation between chronic drug use and hair concentrations.[384] In general, the methamphetamine and amphetamine concentrations in axillary and pubic hair are somewhat higher than scalp hair. In a study of 5 methamphetamine users, the mean methamphetamine concentrations in scalp and axillary hair were 13.49 μg/g (range, 2.7–22.7 μg/g) and 18.68 μg/g (range, 2.9–53.35 μg/g), respectively.[385] There is substantial variation in the metabolite/parent drug ratio (amphetamine/methamphetamine) ratio in hair samples. The methamphetamine and amphetamine concentrations in 2,444 positive forensic samples submitted for methamphetamine abuse ranged from 0.51–193.75 μg/g and 0.13–13.39 μg/g, respectively, in head hair.[386] The amphetamine/methamphetamine ratio was 0.004–1.16. A 12-week study of 6 methamphetamine users admitted to a drug treatment program demonstrated peak methamphetamine concentrations in hair samples ranging from 1–7 cm from the root over the course of the study.[387] The incorporation of basic drugs into hair is relatively high compared with acidic and neutral drugs.[388] Consequently, the use of hair analysis to detect methamphetamine use requires further validation.

## Abnormalities

### *Rhabdomyolysis*

Rhabdomyolysis may develop after the administration of large methamphetamine doses, particularly in association with hyperthermia.[389] Potential laboratory changes in patients with rhabdomyolysis include elevated serum muscle enzymes (creatine kinase, aldolase), myoglobinuria, hyperbilirubinemia, hyperuricemia, hypocalcemia, hyperkalemia, renal failure, hyperphosphatemia, and hypokalemia. Coagulopathies associated with hyperthermia and DIC may cause intramuscular hemorrhage, elevated compartment pressures, and rhabdomyolysis.

### *Blood*

Leukocytosis occurs frequently after methamphetamine use. Disseminated intravascular coagulation (thrombocytopenia, hypofibrinogenemia, hypoprothrombinemia, reduced partial thromboplastin levels, elevated fibrin split products) can occur after IV or oral amphetamine use, especially in association with rhabdomyolysis and hyperthermia. Hypoglycemia is a rare complication of severe methamphetamine intoxication, probably as a result of the depletion of glycogen stores during prolonged hyperadrenergic state.[310] Elevated serum hepatic aminotransferases complicate the IV abuse of methamphetamine, but the frequency of direct drug hepatotoxicity is unclear in the absence of rhabdomyolysis and end organ failure.

### *Central Nervous System*

Acute. Intracranial hemorrhages in methamphetamine abusers are usually located in the cerebral white matter rather than the sites commonly associated with chronic hypertension (i.e., basal ganglia, pons, cerebellum). These intracranial hemorrhages may occur in association with aneurysms or arteriovenous malformations. Other pathologic findings associated with amphetamine use include subarachnoid hemorrhage, subdural hematoma, and drug-induced vasculitis.[390,391] Angiographic studies of involved vessels demonstrate beading of the anterior or middle cerebral arteries with partial or complete occlusion of small-caliber vessels (<1 mm).[392]

Chronic. Neuropsychologic testing suggests that high-dose methamphetamine/amphetamine abuse reduces scores on the Wechsler Memory Scale-Revised tests on attention/concentration, delayed recall indices, and verbal memory compared with controls who do not use illicit drugs.[393] There were no statistical differences in neuropsychologic scores between controls ($n = 9$) and low-dependence methamphetamine/amphetamine users as defined by the severity of dependence scale (i.e., intensity of use rather than cumulative dose). Total lifetime street-use of methamphetamine/amphetamine was not significantly different between the high-dose ($n = 11$) and low-dose methamphetamine/amphetamine ($n = 15$) groups. About 68% of the drug users used methamphetamine/amphetamines intravenously; the study did not separate amphetamine users from methamphetamine users. A study of cognitive function in chronic methamphetamine users demonstrated statistically significant differences in test scores on visual discrimination learning and shifting as well as smaller differences in visuospatial memory, when compared with age- and IQ-matched controls.[394] In a meta-analysis of 18 studies on neuropsychologic testing in chronic methamphetamine abusers, moderate to large deficits occurred in domains of learning ($d = –0.66$), executive functions ($d = –0.63$), and memory ($d = –0.59$).[395] These results suggest detrimental effects on the limbic and frontostriatal circuits. The most prominent effects on memory occurred in episodic memory, which is a multifactorial ability (e.g., encoding, consolidation, retrieval) dependent on multiple regions in the brain (e.g., frontal, temporal). Slightly smaller effects were observed in attention/working memory, language, and

visuoconstruction. The relationship between these deficits and characteristics of methamphetamine use (e.g., route, duration of use, abstinence) and confounders (e.g., premorbid psychologic conditions, comorbid diseases) are not well defined.

Although there are limited data, human studies suggests that chronic methamphetamine abuse produces permanent alteration of brain chemistry and function. PET scans detected a reduction in dopamine transporters in the caudate nucleus and putamen of 6 abstinent methamphetamine users.[396] However, none of these former methamphetamine abusers had clinical signs of parkinsonism. The reported mean period of abstinence for these former methamphetamine users was 3 years. A brain proton magnetic resonance spectroscopy (MRS) study of 26 abstinent methamphetamine abusers demonstrated an approximate 5% reduction in the concentration of the neuronal marker, *N*-acetylaspartate, in the basal ganglia and in frontal white matter.[397] The median time from the imaging study to the last reported use of methamphetamine was about 4 months.

## Driving

There are limited data on the causal relationship between methamphetamine use and trauma, including traffic accidents. In general, the increasing prevalence of methamphetamine in postmortem samples from drivers in fatal accidents reflects the increasing abuse of this drug. A retrospective study of patients admitted to a California trauma center indicated that the percentage of urine samples positive for amphetamines (presumably mostly methamphetamine based on prevalence of use) and for cocaine was 13.2% versus 6.2%, respectively.[398] Studies of postmortem blood from fatal traffic accident victims demonstrated that the rate of methamphetamine use ranged from 1.8%–8.0%.[352,399,400] In a study of 17 drivers involved in fatal traffic accidents, the postmortem methamphetamine concentration ranged from 0.05–2.6 mg/L with a median of 0.35 mg/L.[363] Accident investigation of these fatal accidents indicated that 16 of the 17 drivers were responsible for the fatal accident. Drifting out of the lane of travel and reckless (high speed) driving were the most prominent causal factors. In a study of postmortem blood samples from 370 fatally injured drivers, detectable concentrations of methamphetamine occurred in 18 (4.9%). The methamphetamine concentrations ranged from <0.01–1.08 mg/L with mean and median concentrations of 0.73 mg/L and 0.26 mg/L, respectively.[401] Culpability for the accidents was not reported.

A study of 26 positive blood samples from drivers apprehended for driving under the influence of methamphetamine demonstrated a mean methamphetamine concentration of 0.55 mg/L with a range up to 1.88 mg/L.[352] Two additional drivers developed irrational, agitated, violent behavior after ingesting methamphetamine during their apprehension. The methamphetamine concentrations were 2.58 mg/L and 9.46 mg/L. The latter driver developed seizures. Driving abnormalities associated with methamphetamine intoxication includes tailgating, rapid lane changes without signaling, and speeding.[402]

The effect of methamphetamine on driving is complex and dose-related. In general at low doses, methamphetamine is a stimulant, but psychomotor skills, reasoning, and cognition deteriorate as the dose and duration of use increases.[150] Furthermore, CNS depression during the withdrawal phase and psychotic symptoms from chronic abuse of high doses of methamphetamine may impair driving skills. The intensity of effects at a specific methamphetamine concentration depends in part on the amount of tolerance to amphetamines. Studies of volunteers given methamphetamine indicate that the effects of methamphetamine on the psychomotor skills required to operate machinery effectively are similar to the effects of *d*-amphetamine. The administration of 15–20 mg methamphetamine to healthy volunteers slightly improves performance on some simple tasks (reaction times, vigilance, attention), particularly in fatigued subjects. However, the positive effects of methamphetamine on psychomotor skills is neither consistent or without adverse effects. In study of 70 college-age volunteers receiving IV methamphetamine (0.2 mg/kg or 0.3 mg/kg) or placebo, methamphetamine alone produced subjective arousal and a small improvement in recall of recently learned words; however, the number of incorrect responses increased substantially.[403] In a study of 36 male college students receiving 15 mg methamphetamine/150 pounds intravenously, there was slightly improved speed on some repetitive motor tasks when compared with baseline.[404] However, there were no differences between methamphetamine and placebo on several tests of reaction time. Standard field sobriety tests (horizontal gaze nystagmus, walk and turn test, one leg stand test) are not sensitive measures of the effect of methamphetamine as measured in adult volunteers receiving 0.42 mg/kg *d*,*l*-methamphetamine or placebo.[138]

# TREATMENT

## Stabilization

The treatment of amphetamine, methamphetamine, and cocaine intoxications are similar; however, there are fewer clinical data on the specific treatment of methamphetamine intoxication compared with cocaine. The

major life-threatening complications of acute methamphetamine intoxication include hyperthermia, hypertension, seizures, cardiovascular instability, and trauma. Coma, shock, acute renal failure, severe hyperthermia (i.e., temperature >41°C/105.8°F), and seizures are poor prognostic indicators.[405] Severely intoxicated patients require IV access, cardiac monitoring, pulse oximetry, an electrocardiogram (ECG), and supplemental oxygen. Respiratory depression does not usually occur during mild to moderate methamphetamine intoxication, but pulmonary edema (cardiogenic shock, acute respiratory distress syndrome) can develop during severe methamphetamine poisoning. Most patients tolerate sinus tachycardia without pharmacologic intervention. Both hypertension and tachycardia often respond to IV benzodiazepines (adult: lorazepam 2 mg or diazepam 5 mg bolus titrated to effect). Core body temperatures should be measured in any agitated patient. Patients with suspected myocardial ischemia should be managed with nitrates, morphine, benzodiazepines, aspirin, and benzodiazepines. Hypotension may respond to fluid challenges, but often a vasopressor is needed. Shock is a poor prognostic sign that indicates the need for monitoring of cardiac output to determine the most efficacious combination of fluid and vasopressors.

### *Hypertension*

Elevated blood pressure during methamphetamine intoxication does not usually require treatment unless the hypertension contributes to myocardial ischemia. Benzodiazepines can be administered for agitation. Treatment for severe hypertension includes IV sodium nitroprusside (0.5–8 μg/kg/min) or phentolamine (2.5–5 mg initial IV bolus). Phenothiazine compounds reduce amphetamine-induced hypertension in animal models, but there are inadequate clinical data to determine the efficacy of these drugs during methamphetamine toxicity. Theoretical concerns about potential reduction in the seizure threshold have limited the administration of phenothiazine compounds in clinical practice. Beta blockers should be avoided because the blockade of $\beta_2$-mediated vasodilation can cause vasoconstriction and paradoxical worsening of the hypertension associated with the methamphetamine.

### *Seizures*

Seizures usually respond to benzodiazepines (lorazepam, diazepam). Therapeutic options for the treatment of status epilepticus include phenobarbital and anesthetic agents (e.g., propofol). Hyperthermia, acidosis, hypoxemia, and rhabdomyolysis may complicate the clinical course during status epilepticus; these patients should be evaluated for the presence of these complications.

### *Agitation*

Diazepam (5–10 mg IV in adults or 0.1–0.3 mg/kg in children) or lorazepam (1–2 mg IV in adults) are the safest drugs for agitation; IV midazolam (initial starting dose, 0.03 mg/kg/h) titrated to effect is a short-acting alternative to IV lorazepam or diazepam, particularly in critical patients. Lorazepam is preferred to diazepam when IV access is unavailable.[66] Benzodiazepines should be titrated to the desired clinical effect. Intravenous droperidol (2.5–5 mg) is an alternative to diazepam or lorazepam for the treatment of acutely agitated methamphetamine-intoxicated patients. In a prospective clinical study of adult patients, the administration of IV droperidol (2.5–5 mg) produced more rapid and profound sedation compared with IV lorazepam (2–4 mg) in a group of 146 patients with methamphetamine intoxication.[406] More repeat doses of lorazepam were administered during the first hour of treatment than repeat doses of droperidol. A study of 18 pediatric patients with methamphetamine intoxication suggested that IV haloperidol is a safe adjunctive therapy with benzodiazepines for the treatment of acute methamphetamine intoxication in children.[407] The starting dose of haloperidol was 0.025–0.05 mg/kg, repeated every 15–30 minutes as necessary for the treatment of delirium. Hypotension, respiratory depression, and dystonic reactions are potential complications of butyrophenone use. A calm environment and familiar faces may also help alleviate agitation.

### *Hyperthermia*

Severe temperature elevation (i.e., >40–42°C/104–107.6°F) is a poor prognostic sign, and hyperthermia frequently occurs with evidence of end-organ failure (hypotension, hyperkalemia, metabolic acidosis, rhabdomyolysis, elevated serum creatinine kinase, coagulopathy).[309] Elevated core body temperature should be treated aggressively, especially when temperatures exceed 39–40°C (102.2–104°F). Cooling measures include removal of clothing, cool rooms, cool mist spray to the skin, liberal use of fans, ice baths, and sedation (benzodiazepines). Ice-bath immersion produces the most rapid response, but technical difficulties frequently limit the use of this modality. The use of hypothermic blankets or the application of ice packs often does not produce sufficient cooling for these patients. Neuromuscular paralysis, sedation (midazolam, continuous propofol infusion), and mechanical ventilation may be necessary to reduce the muscle rigidity and

hyperactivity associated with refractory hyperthermia.[408] Vital signs should be followed closely (i.e., every 15–20 minutes) and cooling measures continued until core temperatures are below 38.5–39°C (101.3–102°F). Less severe temperature elevations (<38–40°C/100.4–104°F) can be treated by placement in a cool room, removal of clothes, minimization of physical activity (sedation), tepid sponging, or evaporative methods (cool mist spray, fans).

## Gut Decontamination

There are few data on the effect of decontamination procedures on the clinical outcome of methamphetamine intoxication. Most patients requiring treatment for ingesting methamphetamine are "body stuffers," who attempted to conceal evidence by swallowing variable quantities of methamphetamine. Animal studies indicate that the administration of activated charcoal within 1 minute after the oral administration of a lethal dose of methamphetamine reduces early mortality in mice, but mortality at 48 hours was similar between the treated and untreated groups of mice.[409] All animals demonstrated signs (piloerection, tremor, agitation) of methamphetamine toxicity within 9 minutes of oral administration of the methamphetamine. The administration of activated charcoal, sedation as needed, and supportive care are treatment options for body stuffers. More aggressive decontamination (polyethylene glycol electrolyte lavage solution) is necessary for body packers; however, the ingestion of methamphetamine by body packers is unusual compared with cocaine because of the ease of local clandestine manufacture of methamphetamine.

## Elimination Enhancement

Currently, the use of forced diuresis with urinary acidification is not recommended. There are inadequate clinical data on the efficacy of hemodialysis, peritoneal dialysis, and hemoperfusion during amphetamine intoxication to recommend the use of these procedures. The large volume of distribution of methamphetamine suggests that these measures will not significantly increase the elimination rate of methamphetamine. Animal studies do not support the use of multiple-dose activated charcoal as a means of enhancing methamphetamine elimination.[410]

## Antidotes

There are no specific antidotes for methamphetamine intoxication.

## Supplemental Care

Most methamphetamine body stuffers with serious methamphetamine intoxication present to the emergency department with a pulse >120 bpm and/or body temperature ≥38.0°C (100.4°C).[411] Delayed symptoms may occur following the ingestion of well-wrapped baggies or rolled plastic baggies that simulate sustained release packaging ("parachuting methamphetamine"). Monitoring of these patients may be necessary up to 24 hours after ingestion.

### *Ancillary Tests*

Depending on clinical judgment and severity of poisoning, laboratory examination includes complete blood count, serum electrolytes, calcium, phosphorus, uric acid, creatine kinase, hepatic transaminases, creatinine, glucose, blood urea nitrogen (BUN), coagulation profile (platelet count, fibrin split products, fibrinogen, prothrombin time, partial thromboplastin time), urinalysis including myoglobin, arterial blood gases, chest x-ray, ECG, cardiac monitoring, and appropriate diagnostic neurologic testing (i.e., CT of the brain with or without angiography, lumbar puncture). The use of the urine dipstick is a convenient method to detect the presence of hemoglobin or myoglobin at concentrations above 5–10 mg/L.[412] After the cessation of the myoglobin formation, hepatic metabolism and renal excretion clear plasma myoglobin within 1–6 hours. The presence of myoglobinuria necessitates generous fluid replacement, but alkalinization of the urine is not routinely recommended because the excretion of amphetamine compounds decreases substantially in alkaline urine and there are inadequate data to support the efficacy of alkalinization in this setting.

### *Methamphetamine Psychosis*

Fulminant psychosis in chronic methamphetamine abusers requires hospitalization to provide a protective environment, particularly when suicidal ideations are present. There are limited clinical data on the treatment of methamphetamine psychosis.[413] Empirical treatment includes the use of chlorpromazine at dosages of 50 mg orally or intramuscularly every 4 hours. Depending on adverse effects (sedation, orthostatic hypotension) and clinical response, the total daily dose varies up to 200–800 mg divided in 4–6 doses. The administration of oral or intramuscular doses (2–5 mg) of haloperidol every 6 hours is an alternative to chlorpromazine. Newer antipsychotic medications include olanzapine; limited clinical data suggest that olanzapine is as effective as

haloperidol for methamphetamine psychosis with lower risk of adverse effects.[414] Long-term management of the habitual methamphetamine user is difficult because of frequent relapses. Treatment of these patients involves group therapy and restructured lifestyles. Gradual withdrawal with methamphetamine is unnecessary. Heavy abusers become irritable and depressed during this period; antidepressants and suicide precautions are often required. In addition to behavioral group therapy, experimental pharmaceutic treatment of underlying methamphetamine abuse include the use of bupropion or risperidone.[415,416] Other experimental pharmacologic agents for the treatment of methamphetamine abuse include baclofen, mirtazapine, and topiramate.[417] The concomitant use of antipsychotic drugs does not necessarily prevent the exacerbation of psychotic symptoms in patients, who continue to use methamphetamine.

### *Complications*

Severe methamphetamine intoxication may be complicated by a variety of problems, including acute renal failure, rhabdomyolysis, acute compartment syndrome, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral edema with transtentorial herniation, DIC, and acute respiratory distress syndrome/acute lung injury. Laboratory examinations and repeat physical examinations are necessary to diagnose these conditions early. Management is primarily supportive, but surgery may be required for intracranial lesions or compartment syndrome.

Distal ischemia is usually an isolated problem resulting from inadvertent intra-arterial administration of methamphetamine compounds; there are few clinical data on outcomes to guide treatment of the distal ischemia. Therapeutic options for the treatment of ischemia include intra-arterial tolazoline (12–25 mg/limb), IV nitroprusside infusions (0.5–8 μg/kg/min), dextran 40 (80 mL/h), local nerve blocks, and axillary nerve block. Other therapeutic measures include the use of heparin, thrombolytics, and papaverine. Monitoring of intra-arterial pressure during these infusions is mandatory. Supportive care for compartment syndrome includes analgesics, elevation of extremities, and elimination of methamphetamine exposure. Fasciotomies are usually unnecessary unless there is clear evidence of high compartment pressures and associated distal ischemia.

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