PowerPoint Assignment

Prior to beginning work on this discussion, read the required chapters from the text and review the required articles for this week.

Taking on the role of the expert in the treatment of schizophrenia or depression, you will prepare a presentation for a group of physicians who are seeking your opinion on the treatment of patients with these disorders. For this interactive assignment you will create and upload a 5- to10-slide PowerPoint presentation as well as a five-minute screencast of the presentation to share with your peers.

For this presentation, select either schizophrenia or depression as the basis for your presentation. Begin by creating your PowerPoint presentation. In the presentation, include information which explains the neurotransmitter theory behind the disorder and how the drugs used to treat the disorder affect those neurotransmitter systems. Evaluate the risk and benefits of treating a patient with the most common type of medication and of not using drugs to treat the patient. In your evaluation, examine issues such as the rate of success with the most common drugs used as well as the incidence of side effects with these same drugs, including mortality associated with drug use. Then consider not using medications to treat the disorder. Take into account the natural course of the illness, the rate of spontaneous recovery, and the rate of mortality when untreated. You may also incorporate the use of other modes of treatment into your evaluation.

Your PowerPoint must include your presenter notes in the notes field to indicate what you intend to say during the screencast and well-chosen images to enhance the understanding of your audience. Remember that your screencast will be a maximum of five-minutes, and use your speaker notes to ensure that you will be able to present your materials within this time limit. (You may access Garr Reynolds's Top Ten Slide Tips (Links to an external site.) for additional assistance in creating an effective visual presentation.) Once you have created your PowerPoint you will create a screencast presentation of up to 5 minutes in length using any screencasting software you choose. (Quick-Start Guides are available for Screencast-O-Matic (Links to an external site.) for your convenience.) Attach your PowerPoint file to your intial post and include the URL for your screencast in the body of the post before submitting it.

Assignment (4)

Select a psychoactive drug that is of pharmacological interest to you, but not one you will review as part of your Critical Review or one that was included in your previous Rapid Review. For this paper, you may choose drugs of abuse; however, the paper must focus on the pharmacology of the drug and not on the social or addictive aspects. If you focus on addiction and social impact, your paper will not receive credit.

In addition to the text, research a minimum of three peer-reviewed articles published within the last five years on your selected drug. Prepare a three-page summary of the drug using the PSY630 Rapid Review Example paper (Links to an external site.) as a guide.

In your Rapid Review, analyze and explain the pharmacological aspects of the drug as they relate to the following: neurotransmitters affected, receptors, route of administration, half-life, doses, side effects, drug interactions, contraindications, and other important facets of the drug. Explain these aspects of the drug in terms of the psychiatric disorders indicated for the drug and the issue(s) associated with that use. If there is no accepted therapeutic use for the drug, evaluate and describe the actions of the drug with regard to the abuse process.

The paper:

- Must be three to five double-spaced pages in length, excluding title page and references page, and it must be formatted according to APA style as outlined in the Ashford Writing Center. (Links to an external site.)
- Must include a title page with the following:
  - Title of paper
  - Your name
  - Course name and number
  - Your instructor's name
  - Date submitted
- Must address the topic of the paper with critical thought.
- Must use at least three peer-reviewed sources in addition to the text.
- Must document all sources in APA style as outlined in the Ashford Writing Center.
- Must include a separate references page that is formatted according to APA style as outlined in the Ashford Writing Center.

COCAINE is the Psychoactive Drug To Do Paper ON. Please use The Book reference (attached) then 3 More peer-reviewed Sources

Book Resource ✳

Advokat, C. D., Comaty, J. E., & Julien, R. M. (2018). *Julien's primer of drug action: A comprehensive guide to the actions, uses, and side effects of psychoactive drugs* (14th ed.). Retrieved from https://vitalsource.com

CHAPTER 7

Cocaine, the Amphetamines, and Other Psychostimulants

The psychostimulants are drugs that exert their primary behavioral effects by augmenting the action of the monoamine (biogenic amine) neurotransmitters, the most important of which is dopamine. Sometimes these drugs are referred to as *sympathomimetics* because they activate the transmitters that stimulate the sympathetic nervous system and mimic sympathetic arousal.

In addition to cocaine and amphetamines (including methamphetamine), the psychostimulants include the naturally occurring plant products, such as ephedrine and cathinone, as well as the synthetic drugs methylphenidate and modafinil (and its active isomer, armodafinil). Although these latter substances have approved medical uses, this chapter primarily concerns their recreational use as drugs of abuse. Most recently, recreational use of the group of synthetic stimulants, colloquially known as "bath salts," has become a serious public health concern and this development has received the greatest attention among the drugs in this category.

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COCAINE

History

Cocaine is derived from the leaves of the *Erythroxylon coca* plant, grown in the high altitude of the Peruvian and Bolivian Andes of South America. In fact, methodology has been developed that can identify which of the 19 known coca-growing regions in Bolivia, Colombia, and Peru is the origin of a sample of cocaine (Mallete et al., 2016). It has been suggested that this substance may have arisen naturally because it is toxic to insects that eat the leaves of the plant and therefore protects it from damage. Nevertheless, at least 5000 years ago, humans discovered the psychoactive properties of the plant, and its ability to reduce fatigue, thirst, and hunger was

appreciated for many centuries by the indigenous Indian population. In fact, the practice of chewing the leaves or brewing a tea from the leaves persists even today. When chewed, the leaves are usually mixed with lime (often from sea shells), which interacts with saliva to release the cocaine and reduce its bitter taste, resulting in a daily dose of about 200 milligrams. When the Incas conquered the region in about the tenth century C.E., they adopted it as a sacred substance, restricted to the priests and nobility for special ceremonies. When the Spanish conquered the Incas in the sixteenth century, they initially banned coca use, but then realized how useful it was as a form of money and as a way of increasing the productivity of the native workers.

The Spanish sent samples of the plant to Europe, where eventually Carl Linnaeus classified it in its own family (*Erythroxylaceae*) and the most important species was named *Erythroxylon coca* by Jean-Baptiste Lamarck. Europeans, however, were unaware of the psychoactive properties of the plant, perhaps because its potency deteriorated during the long trip from South America to Europe. It was not until 1857 (or 1859) that the compound was isolated and named cocaine by the chemist Albert Nieman, who noted its anesthetic effect on his tongue.

Cocaine soon became very popular as an additive to drinks and elixirs, most famously when added to wine by Angelo Mariani in 1863. This product, Vin Mariani, was extremely successful and was endorsed by a long list of celebrities, including presidents, kings, and even the Pope. In the United States, a Georgia pharmacist, John Pemberton, developed a similar product called "French Wine of Cola, Ideal Tonic." But when the city of Atlanta prohibited the sale of alcohol, he changed the formulation, removing alcohol, adding soda water, and combining the coca (about 60 milligrams in 8 ounces) with syrup of the kola nut, containing 2 percent caffeine. This drink, named Coca-Cola, was promoted as a health drink and is one reason why soda fountains in the United States were located in drug stores, that is, with other medicinal products.

At the same time, the introduction of the syringe and hypodermic needle prompted many attempts to use cocaine to produce local anesthesia for surgery. Perhaps the first medical report of cocaine's local anesthetic action was made in 1880[4] and cocaine became widely used for topical anesthesia, spinal anesthesia, and nerve blocks from about 1884 until about 1918, when *procaine* (Novocaine) was developed as the first synthetic local anesthetic. Procaine is devoid of psychological and dependence-producing effects.

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In 1884, Sigmund Freud advocated the use of cocaine to treat depression and to alleviate chronic fatigue. He described cocaine as a marvelous drug with the ability even to cure opioid (morphine and heroin) addiction. While using cocaine to relieve his own depression, Freud described the drug as inducing exhilaration and lasting euphoria that was no different from the normal euphoria of the healthy person. Unfortunately, he did not immediately perceive its side effects—tolerance, dependence, a state of psychosis, and withdrawal depression. But eventually, in his later writings, Freud called cocaine the "third scourge" of humanity, after alcohol and heroin.

Around the end of the nineteenth century in the United States, there were no restrictions on the sale or consumption of cocaine, and it became popular with writers and other artists. Robert Louis Stevenson is said to have conceived of Dr. Jekyll and Mr. Hyde with cocaine in mind, and some of the behavioral effects of the drug were exhibited by Sir Arthur Conan Doyle's character Sherlock Holmes, under the supervision of his companion, Dr. Watson. In the late 1800s, however, concern about cocaine's toxicities increased, with several hundred reports of cocaine intoxication and several reported deaths. About 1910, President Taft proclaimed cocaine to be "Public Enemy Number One," and in 1914, the Harrison Narcotic Act banned the incorporation of cocaine into patent medicines and beverages. With the enforcement of the Narcotic Act, cocaine use decreased during the 1930s, largely replaced by the newly available amphetamines, which were cheaper and produced longer-lasting yet similar effects. Cocaine all but disappeared until the late 1960s, when tight federal restrictions on the distribution of amphetamines raised the cost, once again making cocaine attractive.

In the 1980s, a new epidemic of cocaine use began with the widespread availability of crack cocaine, intended for use by inhalation (smoking) rather than injection. This stimulant epidemic continues today, although the relatively inexpensive and widely available methamphetamine is currently more commonly encountered. With the increased availability of lower-cost methamphetamine, the number of cocaine users has stabilized (for more historical information, see Doweiko, 2012; Levinthal, 2012; McKim and Hancock, 2013).

Forms of Cocaine

The leaf of *E. coca* contains about 1 percent cocaine. When the leaves are soaked

The leaf of *E. coca* contains about 1 percent cocaine. When the leaves are soaked and mashed, cocaine is extracted in the form of coca paste (60 to 80 percent cocaine). *Basuco* is a residual paste that is a by-product of cocaine production. It produces a very brief (2-minute) "high" when smoked. This induces binge, which results in rapid addiction. Coca paste is usually treated with hydrochloric acid to form the less potent, water-soluble salt *cocaine hydrochloride* before it is exported. The powdered hydrochloride salt can be absorbed through the nasal mucosa ("snorted," that is, by nasal insufflation) and, because this salt form is water soluble, it can be injected intravenously. In the hydrochloride form, however, cocaine decomposes when it is heated and is destroyed at the temperature of smoke, making it unsuitable for use by inhalation. In contrast, cocaine base, also known as *freebase*, is insoluble in water, but is soluble in alcohol, acetone, or ether. Heating the freebase converts cocaine to a stable vapor that can be inhaled, allowing the drug to reach the brain within less than 10 seconds, a very potent, addictive characteristic. Unfortunately, this process can be dangerous and there is considerable risk of fire or an explosion. It was appreciated that it might be very profitable to offer a safer smokeable form of cocaine. This product, called *crack cocaine*, or simply *crack*, is essentially cocaine base that is prepared for smoking before it is sold to the user. In illicit factories, cocaine hydrochloride is mixed with baking soda and water and heated until cocaine crystals precipitate. The name *crack* is derived from the sound of the crystals popping when smoked. (Interestingly, this is a variant of the method used by the Incas. By mixing the coca leaves with lime, they made saliva more basic, which enhanced absorption.)

Cocaine hydrochloride ("crystal" or "snow"), when snorted as a line of drug, provides a dose of about 25 milligrams; a user might sniff about 50 to 100 milligrams of drug at a time. The smoking of crack cocaine yields average doses in the range of 250 milligrams to 1 gram (Table 7.1).

TABLE 7.1 Pharmacokinetics of cocaine administration

Administration route	Mode	Initial onset of action (sec.)	Duration of "high" (min.)	Average acute dose (mg)	Peak plasma levels (ng/mL)	Purity (%)
Oral	Coca leaf chewing	300–600	45–90	20–50	150	0.5–1
Oral	Cocaine HCl	600–1800		100–200	150–200	20–80

can also cause "spontaneous abortion, probably due to an increase in maternal plasma norepinephrine, which increases uterine contractility, constricts placental vessels, and decreases blood flow to the fetus." Spontaneous abortions are more likely to occur if the drug is ingested in binges rather than in typical fashion. Malek also notes that congenital anomalies, such as brain malformation and cardiovascular abnormalities, are common with maternal cocaine use and " have been reported to occur in 7 to 40 percent of infants exposed to cocaine in utero." Withdrawal symptoms may occur in about one-third of babies born to cocaine-using mothers. These include seizures, lethargy, hyperactive reflexes, vomiting, diarrhea, high-pitched crying, and restlessness. Such babies have a harder time feeding and are more likely to be sick in their first year of life. Prenatal cocaine exposure may impair attentiveness and emotional expressivity in offspring, producing a condition that resembles attention deficit/hyperactivity disorder (Thompson et al., 2009). Although one study found that intrauterine cocaine was not a strong predictor of adolescent delinquent behaviors (Gerteis et al., 2011), another group of researchers reported that adolescents between the ages of 14 and 17 exposed to cocaine in utero had lower gray matter volume in brain regions involved in emotion, reward, memory, and executive function compared with nonexposed adolescents. Amazingly, each 1 milliliter decrease in gray matter volume increased the probability of initiating substance use by 69 to 83 percent (Rando et al., 2013).

In addition to suffering the deleterious direct effect of the drug, the infant born of a cocaine-using mother is more likely to be abused and neglected. Prenatal care is often poor and tobacco and alcohol use is prevalent. Because of the decreased appetite produced by cocaine, both the mother and the fetus are at risk of malnutrition (Keegan et al., 2010). Many negative effects of cocaine on offspring are due to psychiatric problems of the mothers, which may be mediated by depression. Cocaine-using mothers are less attentive and interactive with their infants during the first six months. As the number of environmental risk factors (depression, domestic abuse, psychiatric symptoms, and absence of a significant other) increases, a substance-abusing mother may be overwhelmed and have little time for effective parenting. High levels of cocaine use are strongly associated with failure to maintain custody of children due to neglect and/or abuse (Nephew and Febo, 2012).

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AMPHETAMINES

Like cocaine, the amphetamines (Figure 7.3) produce a variety of sympathomimetic effects on both the CNS and the autonomic nervous system.[2] The amphetamine molecule has two isomers. The more potent one is *dextroamphetamine*, or *d-amphetamine* (Dexedrine, DextroStat); the less potent is the levo- or l-amphetamine isomer. The two isomers are combined in the medication Adderall, approved for treatment of ADHD (see Chapter 15). A modified version of d-amphetamine is formed by substituting CH_3 (called a *methyl group*) for the H at one end, producing methamphetamine (see Figure 7.3). This change allows the drug to cross the blood–brain barrier much faster.

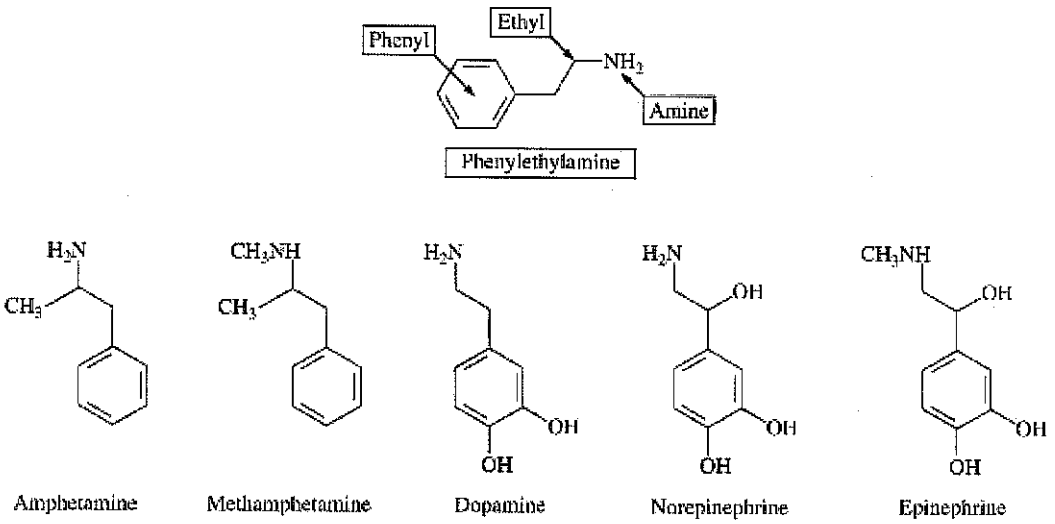

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FIGURE 7.3 The basic sympathomimetic amine nucleus (phenylethylamine), the neurotransmitters dopamine, norepinephrine, and epinephrine, and the structures of amphetamine and methamphetamine.

History

The Romanan chemist Lazar Edeleanu first developed the drug amphetamine—which he called *phenylisopropylamine*—in 1887. Its structure was similar to the natural substance ephedrine, which had been separated from the herb *ma-huang* source around the same time by Nagayoshi Nagai. But the actions of amphetamine were not studied until 1910, when the pharmacologists Barger and Dale wrote about its effects. Because there was no therapeutic use for amphetamine at that time, it was not developed further. In 1918, over 30 years after Edeleanu's work, the chemist Akira Ogata developed the related agent, methamphetamine, from the same plant source *ma-huang*.

In 1924, ephedrine's structure was determined and it was found to have an effect similar to our transmitter epinephrine. Epinephrine was already being used to treat asthma, but it was short-lived and had to be injected. Ephedrine was better because it could be taken orally and was longer-lasting. Being a natural plant product, however, there were concerns that supplies would run out, and intense efforts were made to find an alternative.

When looking for a synthetic alternative to ephedrine, Gordon Alles, a seminal figure in psychopharmacology, recalled amphetamine. He not only reproduced it in his laboratory, but took it himself and suggested it as a cheaper replacement. As the volatile base form, amphetamine is an effective decongestant and was sold for that indication under the brand name Benzedrine by the company Smith, Kline & French in the early 1930s, particularly for treating asthma. In ampule formulation, amphetamine was easily usable for nonmedical purposes and the drug began to be abused.

During World War II, the United States, Germany, and Japan gave amphetamines to their soldiers to fight battle fatigue and enhance performance. Hitler was said to be addicted to amphetamines. Between 1935 and 1946, a list of 39 conditions for which amphetamines could be used in treatment included schizophrenia, morphine addiction, tobacco smoking, head injury, radiation sickness, hypotension, seasickness, severe hiccups, and caffeine dependence. In 1935, amphetamine was found to be effective in promoting wakefulness, for the treatment of the neurological disorder *narcolepsy*, and in 1937 it was first reported to have a "calming" effect on hyperactive children. Large-scale abuse (usually oral ingestion of amphetamine tablets) began in the late 1940s, primarily by students and truck drivers to maintain wakefulness, temporarily increase alertness, and delay sleep. In the 1960s, amphetamines were also used as diet pills and as antidepressants. Their anorexic and antidepressant actions, however, become tolerant within weeks, and they are no longer approved for those uses. Today, legitimate use is largely restricted to the clinical treatment of ADHD and occasionally in the treatment of narcolepsy.

In the late 1960s, the abuse pattern changed with the advent of injectable forms of the drug. During the next decades there was an epidemic of abuse (especially in Japan) that saw the appearance of the "speed freak"—users who took IV doses continuously for days.

After decades of reported abuse, the Food and Drug Administration (FDA) restricted amphetamine to prescription use in 1965, but nonmedical use remained widespread. Amphetamine became a Schedule II drug under the Controlled Substances Act in 1971. Eventually the epidemic receded for several reasons. First, users saw the dangers of compulsive use and this understanding was expressed in the phrase "speed kills." Second, at the same time, the government exerted pressure on drug companies to decrease their legal production of the drug; medical use was inhibited and unethical physicians were prosecuted. Third, more effective and legal medical alternatives to depression were discovered. And fourth, cocaine reappeared. During the 1970s and 1980s, more people could afford cocaine. In 1974, 5 million people said they had tried it; by 1985, 25 million people had done so. Although cocaine use began leveling off in the mid-1980s, it rose again after "crack" appeared—the smokeable version of cocaine. And then, in the mid-1990s, amphetamine abuse resurfaced, becoming even more of a scourge when the smokeable form of methamphetamine, "ice," was developed.

Currently, there is much concern about the abuse of prescription stimulants by college students and young adults. It is especially difficult to get reliable data about how many nonstudent adult workers misuse stimulants, although substance abuse treatment facilities report seeing an increase in adults in the age range from 25 to 45 years (Schwarz, 2015). A survey released in November 2014 (*Under Pressure: College Students and the Abuse of Rx Stimulants: Partnership for Drug-Free Kids*) found that 20 percent of college students and 17 percent of young adults (ages 18 to 25) reported the abuse of stimulants at least once in their lifetime. The most common reason for taking the drugs was to improve their performance in school or on the job while pursuing an active social life. A substantial proportion of young people are using these drugs in an effort to balance their academic or professional work and time with friends and family. (For a discussion of this issue, see Gerlach et al., 2014.)

In January 2015, the drug *lisdexamfetamine* (Vyvanse), which is already approved for ADHD, became the first drug approved for binge-eating disorder. Lisdexamfetamine is a combination of the stimulant dextroamphetamine and the amino acid L-lysine. In this form, the drug is inactive. When swallowed, the amino acid is metabolically separated from dextroamphetamine in the gut, which activates the stimulant. Doses of 50 or 70 milligrams per day reduced the number of binge-eating days per week, with body weight reductions between 5.2 percent and 6.25 percent. Most common adverse effects were dry mouth, decreased appetite, insomnia, and headache (Citrome, 2015). Although the FDA had previously forbidden the promotion of this drug for obesity (which is common in cases of

binge-eating disorder), the administration said Vyvanse was granted priority approval because there was no other drug treatment available for the disorder. And it did not ask an advisory committee to review the issue because Vyvanse is already sold as an ADHD drug and its safety profile is well known.

Pharmacokinetics of Amphetamine Compared with Cocaine

Most of the pharmacokinetic differences between cocaine and amphetamine are minor. Both are very lipid soluble and well absorbed from all sites in the body. Amphetamine has a longer duration of effect than cocaine. The half-life of cocaine is short, 30 to 90 minutes, which promotes repeated use. Enzymes in the plasma and liver rapidly and almost completely metabolize cocaine. Amphetamine's half-life is in hours. Moreover, individuals differ in their pharmacokinetic response to oral amphetamine. About 20 to 25 percent are early peak responders (within 60 minutes), who have an earlier rise in plasma levels and more sustained heart rate elevation than late peak responders (more than 60 minutes; 50 to 55 percent) (Smith et al., 2016). Such differences in the temporal pattern of response might influence abuse potential.

Mechanism of Action

Similar to cocaine, amphetamine modifies the action of dopamine and norepinephrine in the brain (see Figure 7.4). But amphetamine does this in several ways. At low doses, (1) it binds to the presynaptic membrane of dopaminergic neurons and induces the release of dopamine from the nerve terminal; (2) it binds to the dopamine reuptake transporter, causing it to not only block reuptake, but also to act in reverse and transport free dopamine out of the nerve terminal; (3) at high doses, it interacts with dopamine containing synaptic storage vesicles, releasing free dopamine, perhaps into the nerve terminal, although exocytotic release has been questioned (Siciliano et al., 2014); and (4) also at high doses, amphetamine binds to monoamine oxidase (MAO) in dopaminergic neurons and prevents the degradation of dopamine, leaving free dopamine in the nerve terminal. It has further been shown that as few as five days of amphetamine self-administration reduced the ability of D_2 autoreceptors to inhibit dopamine release

in the nucleus accumbens (Calipari et al., 2014). This would also be expected to increase extracellular dopamine. High-dose amphetamine has a similar effect on noradrenergic neurons; it can induce the release of norepinephrine into the synaptic cleft and inhibit the norepinephrine reuptake transporter.

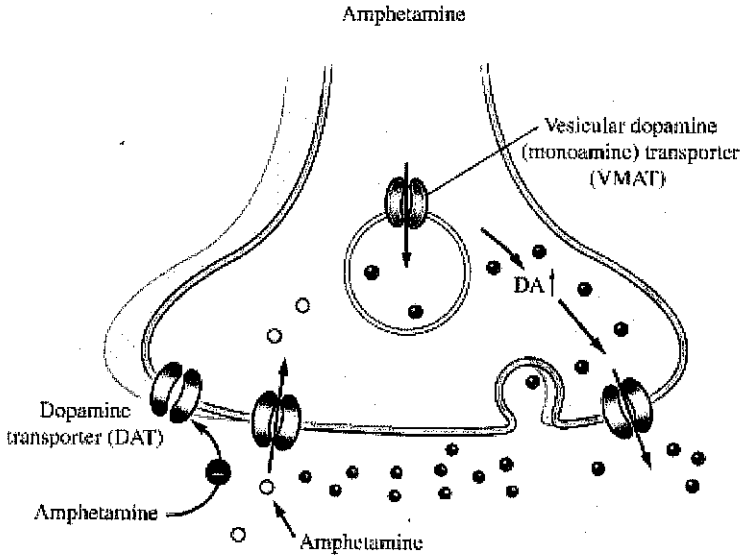

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FIGURE 7.4 Mechanism of action of amphetamine on dopamine nerve terminals. Amphetamine blocks the dopamine (DA) transporter (DAT), preventing the reuptake of dopamine. Amphetamine is also taken up into the terminal by the DAT, where it interferes with the dopamine transporter of the synaptic vesicles (VMAT). This depletes the vesicles and increases DA levels in the cytoplasm of the terminal. As a result, the direction of the DAT reverses, which means more dopamine is released into the synaptic cleft. Not shown is an additional effect of amphetamine, a weak block of the enzyme MAO. Amphetamine also has comparable effects on the norepinephrine transporter (NET).

Pharmacological Effects

Both cocaine and amphetamine have the net effect of increasing the amount of dopamine available (although through different mechanisms); therefore, cocaine abusers have difficulty distinguishing between the subjective effects of 8 to 10 milligrams of cocaine and 10 milligrams of dextroamphetamine when the doses are administered intravenously.

Pharmacological responses to amphetamines vary with the specific drug, the dose, and the route of administration. In general, with amphetamine itself, effects may be categorized as those produced by low to moderate doses (5 to 50

milligrams), usually administered orally, and those observed at high doses (more than approximately 100 milligrams), often administered intravenously. These dose ranges are not the same for all amphetamines. For example, dextroamphetamine is three to four times more potent than amphetamine; low-to-moderate doses range from 2.5 to 20 milligrams, while high doses are 50 milligrams or more. Amphetamine metabolites are excreted in the urine and are detectable for up to 48 hours. Methamphetamine is even more potent, although methamphetamine-dependent people who have developed a tolerance to the drug take massive doses.

At low doses, all amphetamines increase blood pressure and heart rate, relax bronchial muscle, and produce a variety of other actions that follow from the body's alerting response. In the CNS, amphetamine is a potent stimulant, producing alertness; euphoria; excitement; wakefulness; a reduced sense of fatigue; loss of appetite; increased mood, motor and speech activity; and a feeling of power. Interestingly, some subjective effects of amphetamine, such as "arousal" and "euphoria," are related to personality traits, such as "impulsivity" (Kirkpatrick et al., 2013). In fact, it has been reported that pathological gamblers had different blood pressure and cortisol responses to amphetamine than healthy controls (Zack et al., 2015), suggesting noradrenergic disturbances that may be more affected by the drug. During short-duration, high-intensity activity, such as an athletic competition, performance may be enhanced despite impairment of dexterity and fine motor skills.

At moderate doses (20 to 50 milligrams), additional effects of amphetamines include stimulation of respiration, slight tremors, restlessness, and a greater increase in motor activity, insomnia, and agitation. As doses increase, this reaction is accompanied by the worsening or de novo production of anxiety disorders, possibly progressing from restlessness and nonspecific anxiety to obsessive behaviors, panic disorders, paranoia, and eventually a paranoid psychosis. Recreational use of amphetamine is also associated with neuronal dopamine system dysfunction—such as less dopamine binding, blunted release, and blunted subjective response to an amphetamine challenge relative to nonusers (Schrantee et al., 2015).

Chronic high doses produce additional effects. Stereotypical behaviors include continual, purposeless, repetitive acts; sudden outbursts of aggression and violence; paranoid delusions; and severe anorexia. Weight loss, skin sores, infections from neglected health care, and a variety of other consequences occur both because of the drug itself and because of poor eating habits, lack of sleep, or the use of

the drug itself and because of poor eating habits, lack of sleep, or the use of unsterile equipment for intravenous injections. Most high-dose users show a progressive deterioration in their social, personal, and occupational affairs.

The toxic dose of amphetamine varies widely. Severe reactions can occur even from low doses (20 to 30 milligrams). On the other hand, people who have developed tolerance have survived doses of 400 to 500 milligrams. Even larger doses are tolerated by chronic users. The slogan "speed kills" refers not only to a direct fatal effect of single doses of amphetamine, but also to the deteriorating mental and physical condition of the addicted user.

Methamphetamine

It has been estimated that 35 percent of methamphetamine in the United States comes from clandestine laboratories (Talbert et al., 2012). It is easily synthesized from readily obtainable chemicals, including pseudoephedrine. Methamphetamine was originally an approved drug, effective in the treatment of ADHD. Today, however, it is rarely used legitimately and has clearly demonstrated neurotoxicity.

Like cocaine hydrochloride, methamphetamine (the hydrochloride salt) is broken down at temperatures required for smoking. But when converted to its crystalline form, methamphetamine can be effectively vaporized and inhaled in smoke. It also known as ice, speed, crystal, crank, and go, with considerable overlap in nomenclature with other amphetamines except for ice, which refers to the smokeable form. Thus, ice is to methamphetamine as crack is to cocaine: the crystalline, smokeable form of the parent compound. Unlike cocaine, however, methamphetamine has an extremely long half-life (about 12 hours), resulting in an intense, persistent drug action.

Pharmacokinetics

Smoking ice results in its near-immediate absorption into plasma, with additional absorption continuing over the next 4 hours. The blood level then progressively declines. The biological half-life of methamphetamine is more than 11 hours. After distribution to the brain, about 60 percent of the methamphetamine is slowly metabolized in the liver and the end products are excreted through the kidneys, along with unmetabolized methamphetamine (about 40 percent is excreted

along with unmetabolized methamphetamine (about 10 percent is excreted unchanged) and small amounts of its pharmacologically active metabolite, amphetamine.

Neurotoxicity

Methamphetamine produces acute delusional and psychotic behavior. Psychotic symptoms in one study were just over five times more likely to occur during episodes of methamphetamine use. The risk was dose dependent and doubled if the addict also used marijuana or alcohol (McKetin et al., 2013). More than 75 percent of methamphetamine-induced-psychosis inpatients exhibited some form of violence. The most common psychotic symptoms were persecutory delusions and auditory hallucinations. Recovery can take more than a month and, in addition to antipsychotics, electroconvulsive therapy was administered for patients with psychoses lasting more than a month (Zarrabi et al., 2016). Hsieh and colleagues (2014) suggest that methamphetamine-induced psychosis may be caused by damage to cortical interneurons. The process involves an overflow of dopamine in the striatum, leading to excessive cortical glutamate release, ultimately damaging interneurons. Interneuronal damage would impair thalamocortical signals, which would manifest as psychotic symptoms.

Methamphetamine users are also at risk for various types of cardiac toxicity, such as strokes, heart attack, and tears of the aorta (aortic dissection) (Huang et al., 2016; Westover and Nakonezny, 2010). Furthermore, methamphetamine abuse reduces immunity and increases the risk of acquiring numerous infectious diseases, such as AIDS, hepatitis, MRSA, STDs, and fungal diseases (Salamanca et al., 2015).

Neurotoxicity includes damage to serotonin and dopamine nerve terminals, neuronal death, and replacement with astroglial and microglial cells in the brain (Cadet and Krasnova, 2009; Sekine et al., 2008). Dopaminergic defects have been associated with slower motor function and memory deficits, perhaps with predisposition to future development of neurodegenerative disorders such as Parkinson's disease (Callaghan et al., 2012). In fact, Ares-Santos and colleagues (2014) showed that methamphetamine killed neurons in the striatum of mice within 30 days after administration. There was a partial recovery of dopamine terminals starting three days after treatment, and motor activity and coordination also showed some recovery in parallel with the dopaminergic terminals. Nevertheless, there was long-lasting loss and degeneration of dopaminergic cell bodies in the

substantia nigra and dopaminergic terminal destruction in the striatum.

Thompson and coworkers (2004) first identified the structural defects in the human brain associated with chronic methamphetamine abuse. The authors noted an 11 percent reduction in gray matter (neurons), a 7 percent increase in white matter volume (due to inflammation), and a 20 percent increase in ventricular (fluid chamber) volumes. These data indicate neuronal loss with scar replacement (white matter) and a compensatory increase in ventricle size. In brief, the limbic region, involved in drug craving, reward, mood, and emotion, lost 11 percent of its tissue. "The cells are dead and gone," Dr. Thompson stated. Addicts were depressed, anxious, and unable to concentrate. The 8 percent tissue loss in the hippocampus, the brain's center for making new memories, was comparable to the brain deficits in early Alzheimer's. Methamphetamine addicts also performed significantly worse on memory tests than healthy people of the same age. Nevertheless, whether or not abuse causes cognitive decline in humans is not certain and the evidence is mixed. Overall, most of the data argue for intellectual decline for some duration in some users (Dean et al., 2013).

The molecular basis of this neurotoxic effect includes "oxidative stress (metabolic activation), activation of genetically based transcription factors, DNA damage, excitotoxicity, blood–brain barrier (BBB) breakdown, glial cell activation, and neuronal degeneration" (Cadet and Krasnova, 2009, 101). Acute and chronic methamphetamine "induces robust, widespread, but structure-specific leakage of the blood–brain barrier, acute glial cell activation, and increased water content (edema), which are related to drug-induced brain hyperthermia (elevated temperature)" (Kiyatkin and Sharma, 2009, 65). The "leaky" blood–brain barrier ultimately increases the migration of reactive oxygen molecules, such as white blood cells, into the brain, initiating the neuronal damage. The increased brain temperature produced by methamphetamine potentiates these toxic effects (Kiyatkin et al., 2007; Kiyatkin and Sharma, 2012; Turowski and Kenny, 2015). This same action (and potential for brain injury) is also caused by methamphetamine derivatives, including MDMA ("ecstasy") and 5-MeO-DiPT ("Foxy") (Gouzoulis-Mayfrank and Daumann, 2009; Nakagawa and Kaneko, 2008).

The review by Northrop and Yamamoto (2015) describes the blood–brain barrier disruptions produced by methamphetamine as a starting point for developing treatments, which may improve the long-lasting neural and cognitive damage. It has even been suggested that because methamphetamine can break down the blood–brain barrier, it might be used to help transport other drugs into the CNS, especially considering that it is already an FDA-approved medication under the

trade name Desoxyn, for treating ADHD and obesity. The FDA, however, warns that prescribers must carefully weigh the inherent risks of Desoxyn against the limited therapeutic benefits. (For a thorough review of the history, epidemiology, pathophysiology, and clinical presentation and treatment of methamphetamine abuse and toxicity, see Richards et al., 2016.)

Effects in Pregnancy

As with cocaine, there is no clear-cut pattern of congenital abnormalities, although infants born to methamphetamine-abusing mothers exhibit growth retardation and lower birth weights (Smith et al., 2006), and an increased rate of intracerebral hemorrhage. Sowell and colleagues (2010) reported that brain structures known to be sites of neurotoxicity in adult methamphetamine abusers are more vulnerable to prenatal methamphetamine exposure than to alcohol exposure, and more severe cortical damage is associated with more severe cognitive deficits in offspring. Although there is some empirical evidence for amphetamine-induced neurotoxicity and neurodevelopmental deficits, the data are scarce and it is difficult to separate from the other factors of poverty, neglect, and other drug use (Behnke and Smith, 2013; Oei et al., 2012).

Good and colleagues (2010) reported on the demographic variables associated with pregnancy in methamphetamine-using mothers. While 17 percent of nonmethamphetamine users gave birth to preterm babies, that number jumped to 50 percent in drug users. More of the users gave birth via C-sections and suffered uncontrolled high blood pressure and placental abruption. The majority of pregnant methamphetamine users (about 66 percent) also had fewer prenatal care visits, and more of their babies died soon after birth (4 percent) or responded poorly on newborn health measures (6 percent) than the offspring of nonusers (1 percent). Almost 25 percent of the drug-using mothers had been abused during their pregnancy; and 40 percent of the babies born of methamphetamine using mothers were removed from their birth mother and placed in foster care, another care facility, or adopted.

The first study of behavioral effects of children born to methamphetamine-using mothers was published by LaGasse and colleagues in 2012. They found that at age 3, scores for anxiety, depression, and moodiness were slightly higher in children of methamphetamine users, with differences persisting at age 5. The older children who had been exposed to methamphetamine also had more aggression and

of positive effects and increases in negative feelings (dizziness, nausea, depression, and so on). (For a review, see Panenka et al., 2013.)

Amphetamines are prone to compulsive abuse and physical dependence is readily induced. Once drug use is stopped, a person experiences a withdrawal syndrome. Withdrawal symptoms include increased appetite, weight gain, decreased energy, and increased need for sleep. Paranoid symptoms may persist, but generally do not develop as a result of withdrawal. On the other hand, patients suddenly discontinuing amphetamine use may develop severe depression and become suicidal. Early in abstinence, chronic methamphetamine users have low brain levels of stored dopamine. In some abstinent users, dopamine levels recover, raising the question of whether users who cannot maintain abstinence have a more persistent dopamine depletion (Boileau et al., 2016).

Management of amphetamine withdrawal does not require detoxification, but it does require appropriate and cautious clinical observation of the patient, recognition of depression, and treatment with an appropriate antidepressant drug if clinically necessary. Antipsychotic drugs (see Chapter 11) may be necessary to treat paranoid or psychotic reactions or behaviors (Shoptaw et al., 2009).

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NONAMPHETAMINE BEHAVIORAL STIMULANTS

Nonamphetamine stimulants include ephedrine (found in nature in the Chinese herb ma-huang), pseudoephedrine, the herbal substance *khat,* the related cathinones ("bath salts"), DMAA, methylphenidate, pemoline, *modafinil* (Provigil), and *armodafinil* (Nuvigil).

Ephedrine today has little use in medicine other than intravenous use in anesthesiology to temporarily elevate blood pressure and heart rate when such action is needed. Ephedrine also transiently reduces appetite. Most use of ephedrine has been in herbal medicine, incorporated into herbal and dietary supplements for energy increase and weight loss. Unfortunately, the drug can be toxic or even fatal when combined with other stimulant drugs such as caffeine and was banned in dietary supplements by the FDA in 2004. Pseudoephedrine is used in cough and cold medicines to relieve nasal congestion. But as a compound used in

the illicit manufacture of methamphetamine, it has been placed under prescription-only restriction.

Catha edulis is a flowering shrub in East Africa. The leaves and fresh shoots are commonly known as *khat*. Khat can be chewed (like loose tobacco) or brewed as a tea at a daily dose of up to several hundred grams. Khat has stimulant properties and is said to cause excitement, loss of appetite, and euphoria, similar to the effects of amphetamine or cocaine. The active components of khat are cathinone (see Figure 7.5) and cathine (closely related in structure). Khat must be used fresh because cathinone, the pharmacologically more active substance, deteriorates within about 48 hours after harvest. The cathine appears to be a mild psychostimulant, comparable to caffeine in potency. Khat is being increasingly encountered as a substance of abuse in the United States and elsewhere.

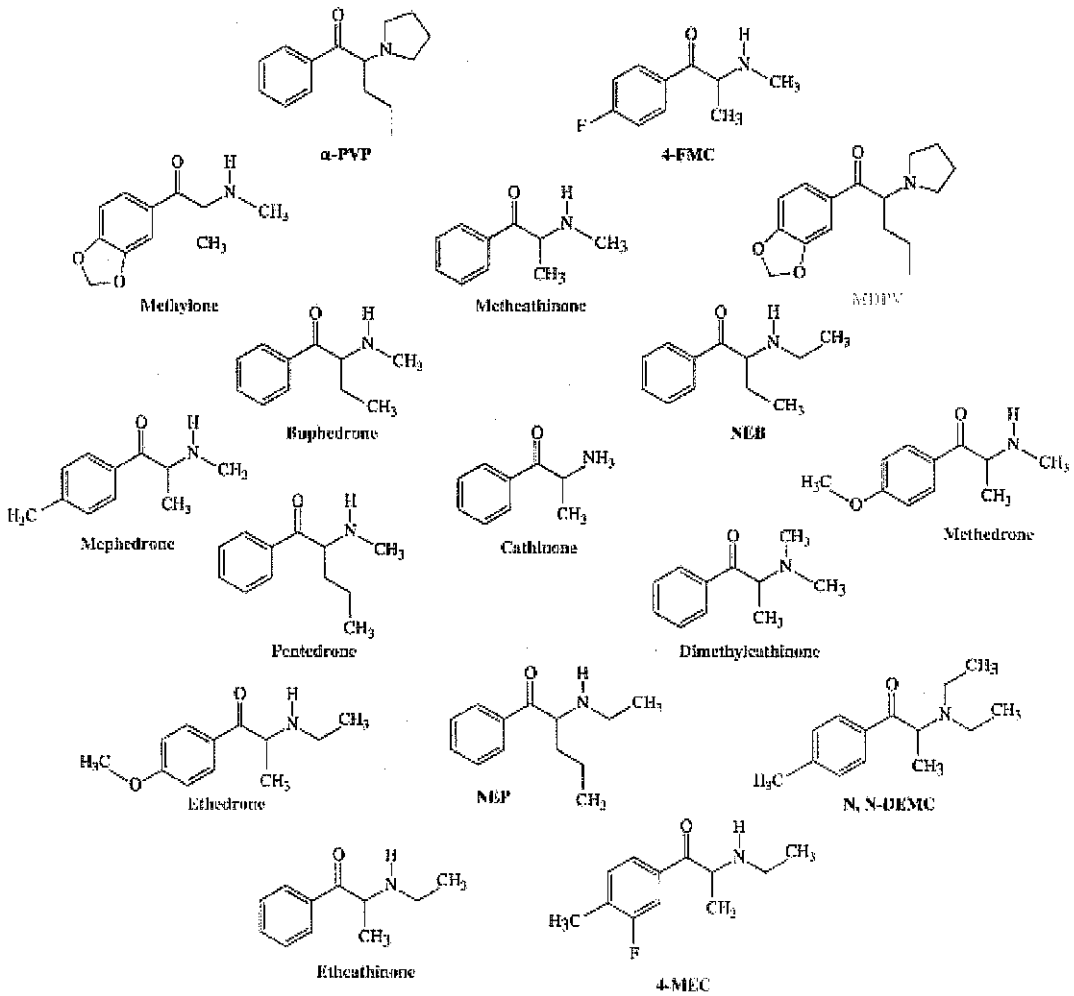


FIGURE 7.5 Chemical structures of a small sample of some synthetic cathinones.

Synthetic Cathinones (Bath Salts)

By far, the most concerning development in stimulant abuse in the past few years has been the increased use of derivatives of cathinone ((*S*)-2-amino-1-phenyl-1-propanone), the naturally occurring beta-ketone amphetamine analogue found in the leaves of the *Catha edulis* (khat) plant. Synthesis of cathinone derivatives (sometimes referred to as *bk-amphetamines*) has been reported since the late 1920s; for example, methcathinone was synthesized in 1928 and mephedrone in 1929 (Prosser and Nelson, 2012; Rosenbaum et al. 2012). By 1933, the League of Nations was already raising concerns about detrimental effects. But it was not until the 1990s that outbreaks occurred globally, eventually reaching the United States around 2009.

In early 2011, emergency rooms began to see an increase in admissions from ingestion of bath salts–synthetic cathinone that paralleled the sharp rise in reported overdoses (Aarde et al., 2015). In September of that year, the Drug Enforcement Administration (DEA) gave notice that it intended to temporarily "schedule" the three drugs that were the main synthetic cathinones. Mephedrone, methylone, and MDPV (methylenedioxypyrovalerone) were officially classified as Schedule I drugs on April 12, 2013. Legal regulation of bath salts is difficult because each compound has to be individually banned (Beaman and Hayes, 2013). Although some bath salt materials only contain a single compound, others contain two or more combinations of pure cathinone. In addition, they may be contaminated with other substances such as caffeine, lidocaine, and piperazines (Baumann, 2014).

Several routes of exposure are effective, including nasal insufflation, oral ingestion, rectal insertion, and intravenous and intramuscular injection. According to user input, mephedrone and methylone doses are 100 to 200 milligrams orally; effects begin about 30 to 45 minutes after ingestion and last about 2 to 5 hours. MDPV appears more potent, with effects elicited 15 to 30 minutes after a typical oral dose of 10 to 15 milligrams and lasting 2 to 7 hours. These drugs produce amphetamine-like or cocainelike subjective effects due to catecholaminergic activation in the central and peripheral nervous systems and MDMA-like ("ecstasylike") effects from serotonergic activation (Baumann, 2014). Papaseit and

colleagues (2016) have conducted the first human clinical trial (ClinicalTrials.gov, NCT02232789) comparing mephedrone and MDMA (mephedrone dose of 200 milligrams; MDMA dose 100 milligrams). Mephedrone produced a significant increase in blood pressure, heart rate, and pupillary diameter. It elicited stimulantlike effects of euphoria and well-being, and induced mild changes in perceptions with similar ratings to those observed after MDMA administration. But mephedrone blood levels peaked earlier and its duration of effect was briefer than MDMA, which might account for its more compulsive abuse liability.

Among the dangerous toxic reactions produced by high doses or long-term use of synthetic cathinones are hyperthermia and hallucinations, which may be associated with aggressive behaviors. Typical clinical effects include agitation and anxiety, paranoia, impaired concentration and memory, headache, rapid heart rate, hypertension, vertigo, abdominal pain, rhabdomyolysis (muscle damage), and convulsions, which can be lethal (for a review, see Karila et al., 2015).

In rat brain synaptosomes, mephedrone and methylone release dopamine, norepinephrine, and serotonin, similar to MDMA. MDPV, however, antagonizes the uptake of dopamine and noradrenaline, and minimally affects serotonin. Importantly, MDPV is 50 times more potent than cocaine as a blocker of DAT and 10 times more potent as a blocker of NET (Baumann et al., 2014). Compared with mephedrone or methylone, MDPV has been found to be anywhere from 3 to 10 times more potent in potentiating motor activity. Most of the fatal bath salt overdoses in the United States reported MDPV in either urine or blood. MDPV-specific urine and blood tests conducted on patients admitted to the emergency room showed a tenfold increase in overall dopamine levels compared with those who took cocaine (Islam et al., 2015).

Rats readily self-administer MDPV across a range of doses (0.05 to 0.5 milligram per kilogram infusion) and will increase their intake at certain concentrations, which is similar to what is seen with methamphetamine and other drugs of compulsive use in humans (such as cocaine and heroin). While rats will also self-administer methylone, they usually do not escalate their dosage over time. This observation implies that the addictive effects of the methylone may be mediated by its release of serotonin. Such data have led to the speculation that the actions of stimulant drugs in humans might be predicted by considering the inhibition ratio of the dopamine transporter to the serotonin transporter as well as the potency at which dopamine and serotonin are secreted by neurons, where "a relative

activation of the serotonin system would be linked to a reduction in abuse potential" (Miliano et al., 2016).

Repeated use of high doses of synthetic cathinones will result in tolerance, dependence, and craving. Sudden termination of chronic methcathinone, mephedrone, and MDPV may elicit symptoms of withdrawal (Miliano et al., 2016). No specific antidote is available. Bath salt–induced agitation often is treated with IV benzodiazepines. Mephedrone produces a delirious state in conjunction with psychotic symptoms. Antipsychotic therapy has been suggested for addressing ongoing agitation. Symptomatic treatment of tachycardia involves beta blockers, such as labetalol (Islam et al., 2015).

After mephedrone became illegal, it was replaced by several "second-generation" chemical formulations. These included 4-methyl-N-ethylcathinone (4-MEC), which releases serotonin and blocks dopamine reuptake, and 49-methyl-α-pyrrolidinopropiophenone (4-MePPP), which can block both dopamine and serotonin reuptake, although it is more potent at the dopamine transporter. This distinction is derived from rat studies that showed that the drug 4-MEC greatly increased serotonin while it only slightly raised dopamine levels and did not alter motor activity. In contrast, 4-MePPP produced selective increases in dopamine and robust motor stimulation (Saha et al., 2015). Concentrations of methylone, mephedrone, and MBPV are reportedly higher in placental blood and fetal brains of mice than they are in either maternal brains or plasma (Strange et al., 2017). Therefore, fetal risk from these compounds is a cause for concern. As yet, there are no reported studies of possible teratogenesis from use of these compounds.

Flakka (α-pyrrolidinovalerophenone)

Although reports of MDPV dropped precipitously after it was banned in 2011, at about the same time, DEA surveillance reports of a drug with the street name "flakka" (α-pyrrolidinovalerophenone, α-PVP) increased from about 20 to more than 3000. In 2013, Dr. Michael Baumann, the head of NIDA's drug analysis laboratory, found that it acted almost exactly like the banned drug—a finding that supported the DEA's decision to outlaw α-PVP in 2014 (Underwood, 2015).

The name "flakka" (from the Spanish word *flaca*) is a Hispanic colloquial expression that means either a slender woman or a beautiful, elegant woman "who

charms all she meets." Originally synthesized in the 1960s, flakka is a synthetic stimulant structurally related to other bath salts, such as 3,4-methylenedioxypyrovalerone (MDPV), and may be described as a "second-generation bath salt." It comes in the form of crystals of different colors that dissolve in the mouth, which gives it another nickname, "gravel," because of its similar appearance to white–pink aquarium gravel. Because it is cheap and may elicit some strange behaviors, flakka is sometimes called "$5 insanity." It can be taken by mouth, injected, snorted, or vaporized, and in this state, it may substitute for nicotine in e-cigarettes. Overdoses are more likely as a result of vaporization, because this approach increases the rate at which the drug enters the bloodstream. Flakka is more potent than cocaine or amphetamine in blocking dopamine and norepinephrine transporters. Heart rate and blood pressure might be dangerously elevated by the rapid increase in norepinephrine, while sudden increases in dopamine may elicit euphoria, along with delusions, hallucinations, and agitation. Other behavioral effects of flakka are comparable to those of stimulants, such as alertness and energy, and may progress to include delirium accompanied by paranoia and possibly delusions of great power and strength (Olson, 2015).

Intoxication due to flakka is treated with supportive care to reverse the effects and prevent further problems. Therapy includes intravenous benzodiazepines to sedate the patient and mitigate seizures until the effects of the drug wear off. Intravenous fluids are also administered, especially if rhabdomyolysis is evident. It is difficult to identify flakka intoxication with a laboratory assay because standard urine drug testing does not detect the substance. Flakka and its metabolites, however, may be recognized by special testing of blood or urine through the use of gas and liquid chromatographic mass spectrometric methods (Melton, 2015).

One agent that shares some structural components of ephedrine and amphetamine is *DMAA* (1,3-dimethylamylamine or methylhexaneamine). This drug was initially patented in 1944 and marketed as Forthane for decongestion. Forthane was withdrawn in the 1970s, but DMAA returned in 2004 after the FDA banned the sale of the stimulant ephedra in dietary supplements (because of thousands of adverse event reports). Supplement manufacturers used DMAA as a substitute for ephedra and claimed it was a natural component of the geranium plant (Gregory, 2013).

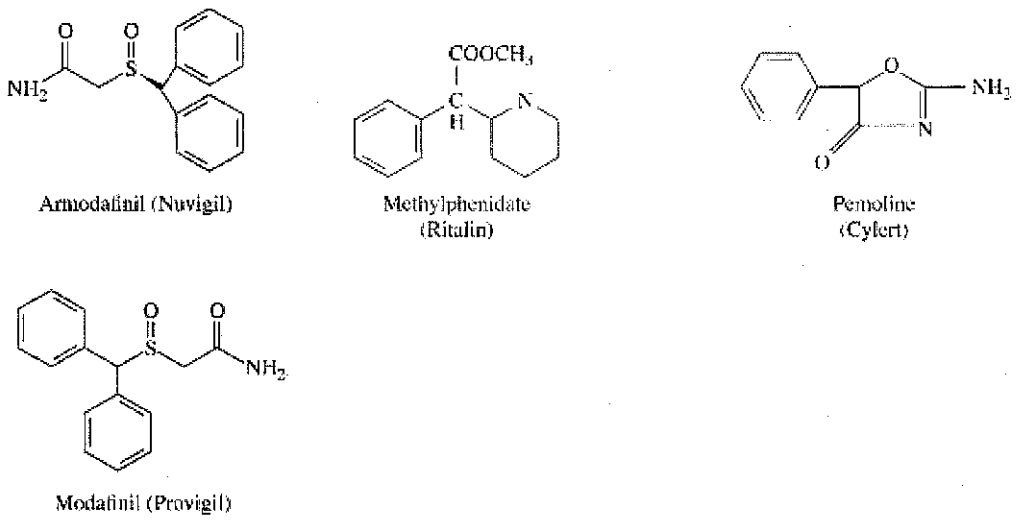
In April 2012, the FDA sent letters to ten companies that manufactured and distributed 16 dietary supplements containing DMAA, stating that it is not a "dietary ingredient." The FDA said it had received 42 adverse event reports on products

ingredient. The FDA said it had received 42 adverse event reports on products containing DMAA. It raises blood pressure and may cause a heart attack because it constricts blood vessels. The U.S. Army has pulled DMAA supplements from all of its on-base stores after the deaths of two soldiers were linked to its use. Several lawsuits regarding DMAA have also been filed and it has now been added to the group of banned substances by the World Anti-Doping Agency.

Some manufacturers have removed DMAA from their products, but others have insisted that the substance is a natural component of the geranium plant and is safe when used as directed. This is questionable, however, since the only study cited was a Chinese report from 1996 in a journal that is no longer in existence. Moreover, the authors simply speculated that it was a component, without any analyses to confirm their findings.

Armstrong and colleagues (as cited in Zhang et al., 2012) have found no detectable DMAA in eight different geranium oils and other studies have not been able to confirm its presence. DMAA is not accepted as an herbal substance by the American Botanical Council, and both DMAA and methylhexaneamine, are not permitted to be identified on labels as "geranium" by the American Herbal Products Association.

Methylphenidate (Ritalin) (Figure 7.6) is a nonamphetamine behavioral stimulant in which the regular-release formulation has a half-life of 2 to 4 hours. Its primary medical use is in the treatment of ADHD (see Chapter 15). Methylphenidate increases the synaptic concentration of dopamine by blocking the presynaptic dopamine transporter (a cocainelike action) and also perhaps by slightly increasing the release of dopamine (an amphetaminelike or ephedrinelike action). When methylphenidate is injected intravenously, experienced cocaine users report a cocainelike or amphetaminelike rush, an action not usually experienced with oral dosage. At clinically relevant doses, methylphenidate blocks more than 50 percent of the dopamine transporters 60 minutes after oral administration. A slow uptake of methylphenidate into the brain after oral administration accounts for its low level of positive reinforcement effects.



Advokat/Comaty/Julien, *Julien's Primer of Drug Action*, 14e, © 2019 Worth Publishers

FIGURE 7.6 Structures of four synthetic noncatecholamine psychostimulants—*methylphenidate* (Ritalin), *pemoline* (Cylert), *modafinil* (Provigil), and *armodafinil* (Nuvigil).

Pemoline (Cylert) is a CNS stimulant structurally dissimilar to either methylphenidate or amphetamine (see Figure 7.6). Its use for the treatment of ADHD is limited by reports of rare instances of hepatitis, necessitating close monitoring of liver function. Indeed, the risks of pemoline outweigh its usefulness and it has been removed from the market.

Modafinil (Provigil) (see Figure 7.6) is a nonamphetamine psychostimulant whose primary characteristic is "wakefulness promotion." Its mechanism of action is not well established; it does block dopamine transporters in the human brain in a manner similar to that exerted by cocaine (Volkow et al., 2009), but perhaps less potently (Loland et al., 2012). Modafinil shares common neurobiological mechanisms with psychostimulants. Recent studies have shown that modafinil can also be reinforcing to humans and that the reinforcing effects of modafinil may be related to the dopaminergic system, as in most drugs with abuse potential. It has been shown that modafinil increased dopamine levels in the nucleus accumbens shell and core of mice at levels similar to those induced by typical psychostimulants, and that this enhancement was due to blockade of DAT (Wuo-Silva et al., 2016). A potentially serious skin rash limits its use.

The FDA has approved modafinil for the treatment of three disorders: narcolepsy, shift-work sleep disorder, and obstructive sleep apnea with residual excessive sleepiness despite the use of a continuous positive airway pressure

device. Modafinil has also been used in the treatment of ADHD, although the FDA has not approved it for this use. One recent study did not find it effective for ADHD in adults (Arnold et al., 2014). Although it also had no significant cognitive effects in methamphetamine addicts except in a test of sustained attention (Dean et al., 2011), it has been used for enhancing cognition even in the absence of a therapeutic diagnosis.[3]

Laboratory investigations of putative cognitive enhancement from modafinil in healthy volunteers have shown consistent but relatively modest benefit. The drug, however, increased "motivation" in that participants described feeling more pleasure in performing the experimental tasks (Müller et al., 2013). This effect may have produced the cognitive improvement. Battleday and Brem (2015) provided the first review of modafinil's actions in non-sleep-deprived people since 2008. They argue that the cognitive effects of this drug may depend on the type of assessment used. Benefits are not consistent or very impressive when "basic" tests are used, but more "complex assessments" show enhancement of attention, executive function, and learning. They did not observe any substantial evidence for side effects or mood changes. However, according to Nicholson and coworkers (2015), this is not consistent with other reports of headache, dizziness, tachycardia, nervousness and insomnia, and GI complaints. Postmarketing surveys report Stephens-Johnson syndrome, a potentially fatal skin eruption. Nicholson and coworkers (2015) also discuss serious adverse events associated with modafinil and note that almost half occur when used for nonindicated reasons. Andrade (2016) provides the results of an extensive literature in humans, concluding that there is no serious risk of seizure with either modafinil or armodafinil (below), even in patients with ADHD, head injury, brain tumors, or seizure disorders. But he notes that either modafinil or armodafinil may affect the levels of some anticonvulsant drugs by pharmacokinetic interactions and that this possibility needs to be considered in individual situations.

Armodafinil (Nuvigil; Figure 7.6) is the active (R)-isomer of the racemic drug modafinil. As with citalopram/escitalopram, methylphenidate/dexmethylphenidate, and amphetamine/dextroamphetamine, when an older racemic medicine goes generic and becomes less expensive, a manufacturer can market the active "half" of the drug under a new patent (making it more expensive). That seems to be the situation with armodafinil, making it twice as "potent" as the racemic counterpart (therefore, one uses half of the milligram dosage). Nuvigil is protected by a U.S. patent that expires in 2023. Armodafinil has the same FDA indications as modafinil (Krystal et al., 2010) and at least one formulation has been generic since 2012, while

others were released in 2016. Armodafinil is also approved for the treatment of sleepiness due to jet lag, a lower dose of 50 to 150 milligrams being recommended.

Pharmacological Treatment of Stimulant Dependency

At the outset, it should be stated that there are no pharmacotherapies for stimulant addiction that have been proven or approved by the FDA (Haile et al., 2012a; Ling et al., 2014; Shorter and Kosten, 2011). Pharmacological strategies include blocking euphoria, reducing withdrawal and negative mood symptoms (such as depression), and ameliorating craving by enhancing the prefrontal glutaminergic cortical projections that seem to be impaired in drug dependency (discussed in more detail in Chapter 4) (Elkashef and Montoya, 2012; Elkashef and Vocci, 2011; Karila et al., 2011; Olive et al., 2012).

Dopaminergic/Adrenergic Treatment Approaches

The subjective effects and euphoria of cocaine are believed to be due to the blockade of the dopamine transporter and consequent buildup and release of dopamine in the reward pathways. But even a single cocaine dose may cause an upregulation of the transporter that can last as long as a month. This means that even after acute use, there is a decrease in dopamine molecules in the synapse, which may lead to drug craving and seeking (Zheng and Zhan, 2012a). There is also experimental evidence that low dopamine receptor function is correlated with a greater likelihood of relapse in methamphetamine abusers (Wang et al., 2012). Therefore, drugs that are either direct or indirect dopaminergic agonists might replace the drug-induced dopaminergic stimulation and reduce both craving and relapse. An extraordinary number of such drugs has been assessed, but results are not impressive. One review of clinical trials examined three direct dopamine agonists (amantadine, bromocriptine, and L-dopa/carbidopa) and concluded that none of them were effective for the treatment of cocaine abuse or dependence (Amato et al., 2011). Another study found little benefit for the dopamine agonist ropinirole or the antipsychotic partial dopamine agonist aripiprazole (Meini et al., 2011). Aripiprazole was also ineffective for the treatment of methamphetamine dependence (Coffin et al., 2013). The antidepressant drug *bupropion* (Wellbutrin,

[illegible] (Zyban, and other brand names) acts primarily to block the uptake of dopamine, although it also has some effect on norepinephrine. *Bupropion* is approved by the FDA for treatment of nicotine addiction. It has not shown substantial effectiveness, however, against either cocaine (Shoptaw et al., 2008) or methamphetamine addiction (Elkashef et al., 2008; Heinzerling et al., 2013). The serotonergic antidepressants are also not very effective in this regard (Shorter and Kosten, 2011). Similarly, the sustained release formulation of *methylphenidate* (Ritalin), which is a well-established stimulant treatment for ADHD, has been investigated in cocaine abusers with and without comorbid ADHD. Although it appears effective in regard to reducing ADHD symptoms, methylphenidate does not seem to be very useful against cocaine addiction (Grabowski et al., 1997; Haile et al., 2012a). In parallel with the success of "agonist replacement" treatment for nicotine and opioid addiction, amphetamine and methamphetamine have also been tested for treatment of cocaine abuse. Sustained-release amphetamine and methamphetamine agents are being studied as possible "replacement" options, but understandably only in certain patients who would not be considered at risk for abuse and diversion (Grabowski et al., 2001; Herin et al., 2010; Mariani and Levin, 2012; Rush and Stoops, 2012). Heroin-dependent persons also addicted to cocaine used less cocaine when given sustained-release dexamfetamine. The effect, however, was modest (44.9 days versus 60.6 days) (Nuijten et al., 2016).

The "wakefulness-promoting" drug *modafinil* (Provigil) has also generated interest, especially because it was shown not to be reinforcing on its own in cocaine abusers (Vosburg et al., 2010). Unfortunately, it was not effective in reducing either methamphetamine abuse (Anderson et al., 2012) or cocaine abuse (Dackis et al., 2012; Nuijten et al., 2015). Modafinil might be helpful in improving the sleep quality of people undergoing stimulant withdrawal (Shorter and Kosten, 2011). The fact that psychostimulants have noradrenergic effects as well as dopaminergic actions has prompted studies of adrenergic antagonists for cocaine abuse. The α-1 receptor antagonist doxazosin has a long half-life of 22 hours and has been found to decrease positive subjective effects of cocaine in cocaine-dependent persons who have not sought treatment (Newton et al., 2012), which suggests that it may have some therapeutic benefit. Finally, the drug *buspirone* (BuSpar), a nonbenzodiazepine anxiolytic that acts on both serotonin and dopamine, was shown to selectively reduce responding for cocaine (but not food) in rhesus monkeys (Mello et al., 2013), but was not effective in a clinical trial in cocaine-dependent persons (Winhusen et al., 2014).

(Somoza et al., 2013). Although in some cases the drugs may affect subjective reports of drug craving, none of these studies have found significant decreases in cocaine use. In regard to glutamate, the broad effects of this excitatory transmitter make it even more difficult to isolate a drug that would exert a specific antiaddictive action. But the substance N-acetylcysteine has received some attention because it appears to modulate the presynaptic control of cortical glutamate release (on the reward pathway) that is regulated by the metabotropic glutamate autoreceptor, mGluR2/3 (see Chapter 4). By improving the function of this autoreceptor, N-acetylcysteine may help to reduce glutamate release and thereby decrease drug craving (Amen et al., 2011). Other glutamatergic agents relevant to this approach are also being assessed (Xia et al., 2013).

Miscellaneous Agents

Disulfiram (Antabuse) is used to treat alcoholism because it blocks the enzyme aldehyde dehydrogenase, which metabolizes alcohol (see Chapter 5). This inhibition causes the metabolite acetaldehyde to build up, which is very unpleasant and produces several noxious symptoms. It has been discovered that disulfiram also blocks the enzyme dopamine-beta-hydroxylase (DBH; DβH), which converts dopamine (DA) to norepinephrine (NE), thereby decreasing the levels of norepinephrine relative to dopamine. In addition, this drug also inhibits enzymes that metabolize cocaine and has other biochemical actions that have produced conflicting outcomes in both laboratory and clinical experiments that complicate predictions about its antiaddictive actions (Gaval-Cruz and Weinshenker, 2009; Pani et al., 2010). Apparent conflicts in the data might be resolved by a recent clinical study that revealed a bimodal effect of this drug in cocaine users. These investigators found that the effect of disulfiram on cocaine use depended on the dose relative to body weight. Specifically, participants given 4 milligrams per kilogram of body weight self-administered the smallest amount of cocaine and those given 2 milligrams per kilogram self-administered the most (Haile et al., 2012b). Currently, a more selective inhibitor of DβH called nepicastat is being studied as a possible treatment for cocaine addiction.

Inhibition of the enzyme aldehyde dehydrogenase by another drug, ALDH2i, has also been found to reduce cocaine use and relapse in laboratory animals. Here, the mechanism seems to be due to a series of biochemical reactions initiated by

antagonism of the enzyme that leads to production of the substance tetrahydropapaveroline. This substance in turn blocks the enzyme tyrosine hydroxylase, which is the first step in dopamine synthesis. As a result, less dopamine is produced. It is hypothesized that the decrease in dopamine production and release is responsible for suppressing cocaine-seeking behavior in laboratory studies (Yao et al., 2010).

Another agent of current interest is *tetrahydropalmatine* (THP), an alkaloid found in several different plant species, including the *Corydalis* family and the plant *Stephania rotunda*. These plants have traditional uses in Chinese herbal medicine as treatment for anxious insomnia and chronic pain. The pharmaceutical industry has synthetically produced the more potent enantiomer levo-tetrahydropalmatine (*l*-THP), which has been marketed worldwide under different brand names as an alternative to anxiolytic and sedative drugs of the benzodiazepine group and analgesics such as opiates. It is also sold as a dietary supplement. *l*-THP has several neurobiological actions: it antagonizes DA_1 and DA_2 receptors and perhaps DA_3 receptors also. It may also block the alpha-1 type of adrenergic receptor and it may modulate $GABA_A$ receptors. In laboratory experiments, it reduces cocaine self-administration and relapse (Shorter and Kosten, 2011; Wang and Mantsch, 2012).

Several drug combinations have also been assessed in efforts to find effective treatments for stimulant abuse. One example is the medication Prometa, which is a combination of three drugs: the benzodiazepine antagonist flumazenil, for recovery from sedation; the drug *gabapentin* (Neurontin), believed to reduce glutamate and relieve cravings; and the antihistamine agent hydroxyzine, believed to help manage withdrawal symptoms. In a randomized, double-blind, placebo-controlled 108-day study trial, 120 methamphetamine-dependent patients were administered this cocktail. Although drug use declined in the Prometa and placebo groups, there was no difference between them in any measure (Ling et al., 2012).

Another combination that has blocked cocaine use in laboratory animals is that of the opiate antagonist naltrexone and the partial opiate agonist buprenorphine. The concept behind this approach is that chronic cocaine use produces a negative emotional state of stress and a dysphoric mood that is actually mediated by the endogenous opiate dynorphin (see Chapter 10). It remains to be seen if this indirect method of reducing stimulant-induced stress will be useful (Wee et al., 2012a). Some positive outcomes, however, were seen in a clinical trial that evaluated the effect of a naltrexone–bupropion combination to treat methamphetamine use disorder. Out

of 49 participants with methamphetamine addiction, 11 were considered responders with a majority of negative urine screens during the last four weeks (out of an eight-week trial) (Mooney et al., 2016). Sushchyk and colleagues (2016) have reported that naltrexone and *l*-THP reduced cocaine relapse in laboratory animals.

Because methamphetamine activates the hypothalamic-pituitary-adrenal (HPA) axis, which causes an increase in the release of stress hormones, it may promote a stress-related increase in anxiety and depression and subsequent relapse. Drugs that reduce HPA dysfunction might be useful in the treatment of methamphetamine addiction (Zuloaga et al., 2015). Along those lines, Kablinger and colleagues (2012) conducted a preliminary study in 45 cocaine-dependent patients of two drugs, *metyrapone*, a drug that blocks the synthesis of the stress hormone cortisol, and the drug *oxazepam*, a benzodiazepine. The combination was well tolerated and was found to reduce craving and cocaine use. An earlier study had shown that metyrapone did not alter the pleasurable effect of methamphetamine in humans and produced some serious adverse reactions (Harris et al., 2003), but perhaps the addition of the benzodiazepine mitigated those effects.

The more general approach of trying to heal the neural damage produced by stimulant abuse is also the rationale for an ongoing clinical investigation of the drug *ibudilast* for methamphetamine abuse, summarized below. When individuals first become abstinent from methamphetamine, an inflammatory process occurs in brain cells, especially glial cells. By dampening inflammation in glial cells, it was proposed that ibudilast may preserve glial and other nerve cells during early abstinence. Ibudilast has been used safely in humans for 18 years in Japan and South Korea as a treatment for asthma and pulmonary and cardiovascular diseases; therefore, it is safe to use as a potential treatment for methamphetamine dependence.

The 11 methamphetamine addicts in this trial, all paid volunteers, were housed in a hospital unit and not allowed to leave for three weeks. They were intravenously injected with methamphetamine while being treated with ibudilast. After the initial results found that the combination was safe, the second phase of the study, a 12-week trial of 140 treatment-seeking human methamphetamine addicts, was started. Half the volunteers took ibudilast twice a day and the other half took a placebo. They visited the trial unit three times a week for drug-craving monitoring, urine drug screens, and medication adherence monitoring. In March 2016, results were published from the first phase of the clinical trial. The authors reported that ibudilast significantly reduced the subjective effects of methamphetamine in

persons with methamphetamine dependence (Worley et al., 2016). A second phase of the study will determine if the drug can maintain abstinence during at least the final 2 weeks of a 12-week trial. (For a review of ibudilast, see Rolan et al., 2013.)

Interestingly, in nonhuman laboratory animals, modafinil also showed some protection from the toxic effect of methamphetamine on dopamine neurons (Raineri et al., 2012). On the other hand, another compound, citicoline, known as *cytidine diphosphate-choline* (CDP-choline) or cytidine 5-diphosphocholine, had no effect on cocaine use or craving (Brown et al., 2015; Licata et al., 2011). This agent is a substance found in the biochemical pathways involving choline (used for making acetylcholine). It was hypothesized to be helpful because it has some benefit for treating neuronal damage from stroke or brain injury. Finally, there is evidence that the hormone *oxytocin* modulates behavioral effects of psychostimulants in rodents and might be a possible candidate for addiction treatment (Carson et al., 2013).

Pharmacokinetic Approaches to Psychostimulant Abuse—Metabolizing Enzymes

One novel approach to addressing cocaine abuse that has recently undergone rapid development is to intercept the drug molecule before it reaches the brain. These pharmacokinetic (PK) methods do not involve direct effects on either transporters or receptors. Rather, this approach counteracts cocaine either by binding to it as an antibody that prevents it from crossing the blood–brain barrier or as a cocaine-metabolizing enzyme, that breaks down the drug to inactive metabolites in the plasma so that only a small amount of the drug reaches the CNS (Gorelick, 2012). With regard to the antibody method, antibodies can be obtained "actively" through a vaccine or "passively" with antibodies produced in another host and then administered to the addict-patient. The disadvantage is that "passive" vaccines have a shorter half-life.

With regard to enzymes, the cocaine-metabolizing enzyme can be administered as an exogenous drug therapy or it can be provided as a gene therapy, which means the persons receiving the modified gene can then make the modified enzyme for themselves. In the exogenous enzyme approach, two types have been developed: one is a mutation of the butyrylcholinesterase enzyme found in humans, while the other comes from bacteria associated with the soil in which coca plants are grown. The breakdown of cocaine occurs more rapidly with these substances and they reduce the adverse actions of the drug in nonhuman animal models. Because the

reduce the adverse actions of the drug in nonhuman animal models. Because the human-derived mutants of butyrylcholinesterase would presumably not elicit an immune response if given to humans, it might be the better candidate. The past decade has seen rapid progress with alteration of butyrylcholinesterase-producing enzymes that destroy cocaine so efficiently that even though the enzyme is restricted to the blood, they prevent or interrupt drug actions in the CNS. During the same time, gene-transfer technology has also been improved such that enzymes can be delivered by endogenous gene transduction at high levels for periods of a year or longer after a single treatment (Brimijoin and Gao, 2012; Narasimhan et al., 2012; Schindler and Goldberg, 2012; Zheng and Zhan, 2012b; Zlebnik et al., 2014).

Cocaine-metabolizing enzymes have one advantage over vaccines and antibodies. At sufficiently high concentrations of cocaine, the antibodies may be saturated, leaving enough of the drug left over to produce the desired effect. In contrast, even if the cocaine-metabolizing enzyme is saturated, it maintains its effectiveness. That is, because it degrades the drug, each enzyme molecule can metabolize many cocaine molecules. One molecule of a currently available enzyme can metabolize 5700 cocaine molecules a minute (Zheng and Zhan, 2012a).

The short half-life of cocaine might seem to make this approach impractical. But because the half-life of cocaine is proportional to the dose, the half-life increases and becomes much longer under cocaine overdose conditions and there is enough time for an enzyme injection to be effective. Furthermore, because the drug is distributed equally in plasma, brain, and heart tissue, metabolism of cocaine molecules in the blood will rapidly cause the molecules in the brain and heart to return to the plasma to maintain equilibrium. Clinical trials of cocaine-metabolizing enzymes for cocaine addiction treatment have shown that it is safe and that it reduces many of the positive subjective effects of the drug (Zheng and Zhan, 2012a). Furthermore, the combination of enzyme *and* antibody administration gave an even better blockade of cocaine-induced behavioral stimulation in rodents (Carroll et al., 2012). Research is continuing to develop drugs that remain active in the body for longer periods of time and are more efficient (Smethells et al., 2016; Zheng et al., 2015).

Pharmacokinetic Approaches to Psychostimulant Abuse—Vaccines

The cocaine vaccine (termed *TA-CD*) is a cocaine derivative (succinyl norcocaine) coupled to recombinant cholera toxin B. It is designed to generate drug-specific

coupled to recombinant cholera toxin B. It is designed to generate drug-specific antibodies that bind to cocaine and prevent it from traveling to the brain from the blood, thereby neutralizing its psychoactive effect. The molecules are then broken down by cholinesterases in the blood to inactive metabolites and excreted. The concept is intriguing and promising but, as with all vaccines, the problems are (1) getting the concentration of antibodies high enough to block any amount of drug that might be used; and (2) compliance—getting the patients to return for the necessary number of injections to produce the required amount of antibody. Patients need to receive five vaccinations over the course of two to three months, during which time they are vulnerable to relapse. Incentives such as counseling and an escalating payment for successive vaccinations can improve adherence (Stitzer et al., 2010; Whitten, 2010).

The amount of antibody produced predicts clinical effectiveness. Antibody levels of 43 micrograms per milliliter (μg/mL) or higher resulted in more cocaine-free urine samples than those with levels less than 43 μg/mL. Unfortunately, only 31 percent of the vaccinated cocaine users attained antibody levels greater than 43 μg/mL (Shen et al., 2012) and even those had only two months of adequate cocaine blockade. The most common adverse effect was local injection site irritation. Even if the vaccine is successful, a cocaine-dependent person who has these antibodies in the blood may move to another drug or use large amounts of cocaine. Nevertheless, the methodology is improving and a recent version produced a high amount of antibody, which lasted for about four months in laboratory rats (Wee et al., 2012b). This may be one of the first antiaddiction vaccines approved by the FDA for human use. Improvements in vaccine development are ongoing (Lockner et al., 2015).

Vaccines for use in methamphetamine addiction are also in development, with several laboratories working on specific parameters. One problem is that the methamphetamine molecule is simple, which makes it unnoticeable to the immune system. Furthermore, both methamphetamine and its metabolite amphetamine also have a long half-life, which makes it difficult for vaccine development. Passive administration of antibodies has already been found to reduce methamphetamine self-administration in rats and to decrease stimulant-induced motor activity. Behavioral assays that are better at measuring the effectiveness of the vaccine are also needed. At present, vaccines capable of producing enough antibody to bind a sufficient amount of drug for a sufficient amount of time are not yet available. One new agent, however, named MH6 is most likely just the beginning of a successful effort to find more effective treatment options for psychostimulant abuse (Miller et al., 2013). Kosten and colleagues (2013) provide a review of current developments in vaccines for cocaine and methamphetamine.