**CNS Stimulants**

I**. OVERVIEW**

This chapter describes two groups of drugs that act primarily to stimu- late the central nervous system (CNS). The first group, the psychomotor stimulants, cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The second group, the hallucinogens, or psychotomimetic drugs, produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord. Figure 10.1 summarizes the CNS stimulants. As a group, the CNS stimulants have diverse clinical uses and are important as drugs of abuse, as are the CNS depressants described in Chapter 9 and the narcotics described in Chapter 14 (Figure 10.2).

**II. PSYCHOMOTOR STIMULANTS**

1. **Methylxanthines**

The methylxanthines include theophylline [thee-OFF-i-lin], which is found in tea; theobromine [thee-o-BRO-min], found in cocoa; and caf- feine [kaf-EEN]. Caffeine, the most widely consumed stimulant in the world, is found in highest concentration in coffee, but it is also pres- ent in tea, cola drinks, chocolate candy, and cocoa.

1. **Mechanism of action**: Several mechanisms have been proposed for the actions of methylxanthines, including translocation of extra cellular calcium, increase in cyclic adenosine monophos- phate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors. The latter most likely accounts for the actions achieved by the usual consumption of caffeine-containing beverages.

**2. Actions:**

**a. CNS:** The caffeine contained in one to two cups of coffee (100– 200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of caffeine (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimu- lated only by very high doses (2–5 g) of caffeine. Tolerance can rapidly develop to the stimulating properties of caffeine, and withdrawal consists of feelings of fatigue and sedation.

b. **Cardiovascular system**: A high dose of caffeine has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions.]

c. **Diuretic action**: Caff eine has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.

d. **Gastric mucosa**: Because all methylxanthines stimulate secretion of hydrochloric acid from the gastric mucosa, individuals with peptic ulcers should avoid foods and beverages containing methyl xanthines.

3. **Therapeutic uses**: Caff eine and its derivatives relax the smooth muscles of the bronchioles. [Note: Previously the mainstay of asthma therapy, theophylline has been largely replaced by other agents, such as β2 agonists and corticosteroids.]

4. **Pharmacokinetics**: The methylxanthines are well absorbed orally. Caff eine distributes throughout the body, including the brain. These drugs cross the placenta to the fetus and are secreted into the moth- er’s milk. All the methylxanthines are metabolized in the liver, gener- ally by the CYP1A2 pathway, and the metabolites are then excreted in the urine.

5**. Adverse eff ects**: Moderate doses of caff eine cause insomnia, anxi- ety, and agitation. A high dosage is required for toxicity, which is manifested by emesis and convulsions. The lethal dose is 10 g of caf- feine (about 100 cups of coff ee), which induces cardiac arrhythmias. Death from caff eine is, therefore, highly unlikely. Lethargy, irritability, and headache occur in users who routinely consumed more than 600 mg of caff eine per day (roughly six cups of coff ee per day) and then suddenly stop.

B. **Nicotine**

Nicotine [NIK-o-teen] is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessa- tion therapy), nicotine remains important because it is second only to caff eine as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug. In combination with the tars and carbon monoxide found in cigarette smoke, nicotine represents a seri- ous risk factor for lung and cardiovascular disease, various cancers, and other illnesses. Dependency on the drug is not easily overcome.

1**. Mechanism of action**: In low doses, nicotine causes ganglionic stim- ulation by depolarization. At high doses, nicotine causes ganglionic blockade. Nicotine receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

2. **Actions:**

**a. CNS**: Nicotine is highly lipid soluble and readily crosses the blood- brain barrier. Cigarette smoking or administration of low doses of nicotine produces some degree of euphoria and arousal as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of nicotine result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 10.3). Nicotine is also an appetite suppressant.

b. **Peripheral effects**: The peripheral effects of nicotine are complex. Stimulation of sympathetic ganglia as well as the adrenal medulla increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral vascular disease experience an exac er bation of symptoms with smoking. For example, nicotine- induced vasoconstriction can decreased coronary blood flow, adversely affecting a patient with angina. Stimulation of parasympathetic ganglia also increases motor activity of the bowel. At higher doses, blood pressure falls, and activity ceases in both the gastrointestinal (GI) tract and bladder musculature as a result of a nicotine-induced block of parasympathetic ganglia.

3**. Pharmacokinetics:** Because nicotine is highly lipid soluble, absorp- tion readily occurs via the oral mucosa, lungs, GI mucosa, and skin. Nicotine crosses the placental membrane and is secreted in the milk of lactating women. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of nicotine per cigarette (most cigarettes contain 6 to 8 mg of nicotine). The acute lethal dose is 60 mg. More than 90 percent of the nicotine inhaled in smoke is absorbed. Clearance of nicotine involves metabolism in the lung and the liver and urinary excretion. Tolerance to the toxic effects of nicotine develops rapidly, often within days after beginning usage.

4. **Adverse effects:** The CNS effects of nicotine include irritability and tremors. Nicotine may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smok- ing increases the rate of metabolism for a number of drugs.

5. **Withdrawal syndrome**: As with the other drugs in this class, nico- tine is an addictive substance, and physical dependence develops rapidly and can be severe (Figure 10.4). Withdrawal is character- ized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI pain often occurs. [Note: Smoking cessation programs that combine pharma- cologic and behavioral therapy are the most successful in helping individuals to stop smoking.] The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine with- drawal symptoms and to help smokers stop smoking. For example, the blood concentration of nicotine obtained from nicotine chew- ing gum is typically about one-half the peak level observed with smoking (Figure 10.5). Bupropion, an antidepressant (see p. 155), can reduce the craving for cigarettes.

**C. Varenicline**

Varenicline [ver-EN-ih-kleen] is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS. Because varenicline is only a partial agonist at these receptors, it produces less euphoric effects than those produced by nicotine itself (nicotine is a full agonist at these receptors). Thus, it is useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptoms. Additionally, varenicline tends to attenuate the rewarding effects of nicotine if a person relapses and uses tobacco. Patients should be monitored for suicidal thoughts, vivid nightmares, and mood changes.

**D. Cocaine**

Cocaine [KOE-kane] is a widely available and highly addictive drug that is currently abused daily by more than 3 million people in the United States. Because of its abuse potential, cocaine is classified as a Schedule II drug by the U.S. Drug Enforcement Agency.

1. **Mechanism of action:** The primary mechanism of action underlying the central and peripheral effects of cocaine is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals from which these neurotransmitters are released (Figure 10.6). This blockade is caused by cocaine binding to the monoaminergic reuptake transporters, and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain’s pleasure system (limbic system) produces the intense euphoria that cocaine initially causes. Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine that temporarily relieves severe depression (Figure 10.7).

2**. Actions:**

a**. CNS:** The behavioral effects of cocaine result from powerful stimulation of the cortex and brainstem. Cocaine acutely increases mental awareness and produces a feeling of well- being and euphoria similar to that caused by amphetamine. Like amphetamine, cocaine can produce hallucinations and delusions of paranoia or grandiosity. Cocaine increases motor activity, and, at high doses, it causes tremors and convulsions, followed by respiratory and vasomotor depression.

b. **Sympathetic nervous system**: Peripherally, cocaine potentiates the action of norepinephrine, and it produces the “fight-or- flight” syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction. Recent evidence suggests that the ability of baroreceptor reflexes to buffer the hypertensive effect may be impaired.

**c. Hyperthermia**: Cocaine is unique among illicit drugs in that death can result not only as a function of dose, but also from the drug’s propensity to cause hyperthermia. [Note: Mortality rates for cocaine overdose rise in hot weather.] Even a small dose of intranasal cocaine impairs sweating and cutaneous vasodilation. Perception of thermal discomfort is also decreased.

**3. Therapeutic uses**: Cocaine has a local anesthetic action that repre- sents the only current rationale for the therapeutic use of cocaine. For example, cocaine is applied topically as a local anesthetic during eye, ear, nose, and throat surgery. Whereas the local anesthetic action of cocaine is due to a block of voltage-activated sodium channels, an interaction with potassium channels may contribute to the ability of cocaine to cause cardiac arrhythmias. [Note: Cocaine is the only local anesthetic that causes vasoconstriction. This effect is responsible for the necrosis and perforation of the nasal septum seen in association with chronic inhalation of cocaine powder.]

**4. Pharmacokinetics**: Cocaine is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection. The peak eff ect occurs 15 to 20 minutes after intranasal intake of cocaine pow- der, and the “high” disappears in 1 to 1.5 hours. Rapid but short-lived eff ects are achieved following IV injection of cocaine or by smoking the freebase form of the drug (“crack”). Because the onset of action is most rapid, the potential for overdosage and dependence is great- est with IV injection and crack smoking. Cocaine is rapidly de-esteri- fi ed and demethylated to benzoylecgonine, which is excreted in the urine. Detection of this substance in the urine identifi es a user.

**5. Adverse eff ects**:

a. **Anxiety:** The toxic response to acute cocaine ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. [Note: Little tolerance to the toxic CNS eff ects of cocaine (for example, convulsions) occurs with prolonged use.] Because of the irritability, many users take cocaine with alcohol. A product of cocaine metabolites and ethanol is cocaethylene, which is also psycho active and believed to contribute to cardiotoxicity.

**b. Depression**: As with all stimulant drugs, cocaine stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing from cocaine exhibit physical and emotional depression as well as agitation. The latter symptom can be treated with benzodiazepines or pheno thiazines.

**c. Toxic eff ects:** Cocaine can induce seizures as well as fatal cardiac arrhythmias (Figure 10.8). Use of IV diazepam may be required to control cocaine-induced seizures. The incidence of myocardial infarction in cocaine users is unrelated to dose, to duration of use, or to route of administration. There is no marker to identify those individuals who may have life-threatening cardiac eff ects after taking cocaine.

E**. Amphetamine**

Amphetamine [am-FET-a-meen] is a sympathetic amine that shows neurologic and clinical eff ects quite similar to those of cocaine. Dextroamphetamine [dex-troe-am-FET-a-meen] is the major member of this class of compounds. Methamphetamine [meth-am-FET-a-mine] (also known as “speed”) is a derivative of amphetamine available for prescription use. It can also be smoked and is preferred by many abus- ers. 3,4-Methylenedioxymethamphetamine (also known as MDMA, or Ecstasy), a synthetic derivative of methamphetamine with both stimu- lant and hallucinogenic properties, is discussed on p. 537

**1. Mechanism of action:** As with cocaine, the eff ects of ampheta mine on the CNS and peripheral nervous system are indirect. That is, both depend upon an elevation of the level of catecholamine neu- rotransmitters in synaptic spaces. Amphetamine, however, achieves this eff ect by releasing intracellular stores of catecholamines (Figure 10.9). Because amphetamine also inhibits monoamine oxidase (MAO), high levels of catecholamines are readily released into syn- aptic spaces. Despite diff erent mechanisms of action, the behavioral effects of amphetamine and its derivatives are similar to those of cocaine.

2. **Actions:**

**a. CNS**: The major behavioral effects of amphet amine result from a combination of its dopamine and norepinephrine release- enhancing properties. Amphetamine stimulates the entire cerebro spinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. These CNS stimulant effects of amphetamine and its derivatives have led to their use in therapy for hyperactivity in children, for narcolepsy, and for appetite control. At high doses, psychosis and convulsions can ensue.

**b. Sympathetic nervous system**: In addition to its marked action on the CNS, amphetamine acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release.

3. **Therapeutic uses**: Factors that limit the therapeutic usefulness of amphetamine include psychological and physiological dependence similar to those with cocaine and, with chronic use, the development of tolerance to the euphoric and anorectic effects.

a. **Attention deficit hyperactivity disorder (ADHD):** Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes. Dextroam- phetamine and the amphetamine derivative methylphenidate [meth-ill-FEN-ih-date] can help improve attention spans and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing the hyperkinesia that such children demonstrate. Lisdexamfetamine [lis-dex-am-FET-a- meen] is a prodrug that is converted to the active component dextroamphetamine after GI absorption and metabolism. Lisdexamfetamine prolongs the patient’s span of attention, allowing better function in a school atmosphere. Atomoxetine [AT-oh-MOX-ih-teen] is a nonstimulant drug approved for ADHD in children and adults. [Note: This drug should not be taken by individuals on MAO inhibitors and by patients with narrow-angle glaucoma.] Unlike methylphenidate, which blocks dopamine reuptake, atomoxetine is a norepinephrine-reuptake inhibitor. Therefore, it is not habit forming and is not a controlled substance.

b. **Narcolepsy:** Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. It is sometimes accompanied by catalepsy, a loss in muscle control, and even paralysis brought on by strong emotions such as laughter. However, it is the sleepiness for which the patient is usually treated with drugs, such as amphetamine or meth- ylphenidate. Recently, a newer drug, modafinil [moe-DA-fi-nil], and its R-enantiomer derivative, armodafinil [ahr-moe-DA-fi-nil], have become available to treat narcolepsy. Modafinil produces fewer psychoactive and euphoric effects as well as fewer altera- tions in mood, perception, thinking, and feelings typical of other CNS stimulants. It does promote wakefulness. The mechanism of action remains unclear, but may involve the adrenergic and dopaminergic systems, although it has been shown to diff er from that of amphetamine. Modafi nil is eff ective orally. It is well dis- tributed throughout the body and undergoes extensive hepatic metabolism. The metabolites are excreted in urine. Headaches, nausea, and rhinitis are the primary adverse eff ects. There is some evidence to indicate the potential for abuse and physical dependence with modafi nil.

4**. Pharmacokinetics**: Amphetamine is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. [Note: Administration of urinary alkalinizing agents will increase the non- ionized species of the drug and decrease its excretion.] Amphetamine abusers often administer the drugs by IV injection and/or by smok- ing. The euphoria caused by amphetamine lasts 4 to 6 hours, or four- to eightfold longer than the eff ects of cocaine.

**5. Adverse eff ects:** The amphetamines may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable eff ects.

**a. CNS eff ects:** Undesirable side eff ects of amphetamine usage in- clude insomnia, irritability, weakness, dizziness, tremor, and hy- peractive refl exes (Figure 10.10). Amphetamine can also cause confusion, delirium, panic states, and suicidal tendencies, espe- cially in mentally ill patients. Chronic amphetamine use produces a state of “amphetamine psychosis” that resembles the psychotic episodes associated with schizophrenia. Whereas long-term amphetamine use is associated with psychic and physical de- pendence, tolerance to its eff ects may occur within a few weeks. Overdoses of amphetamine are treated with chlorpromazine or haloperidol, which relieve the CNS symptoms as well as the hy- pertension because of their α-blocking eff ects. The anorectic ef- fect of amphetamine is due to its action in the lateral hypotha- lamic feeding center.

b. **Cardiovascular eff ects**: In addition to its CNS eff ects, amphet- amine causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur. Because of its cardiovascular eff ects, amphetamine should not be given to patients with cardiovascular disease and those receiving MAO inhibitors.

c. **GI system eff ects**: Amphetamine acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Administration of sodium bicarbonate will increase the reabsorption of dextroamphetamine from the renal tubules into the bloodstream.

**d. Contraindications**: Neither patients with hypertension, cardiovascular disease, hyperthyroidism, or glaucoma should be treated with this drug, nor should patients with a history of drug abuse, nor anyone taking MAO inhibitors.

**F. Methylphenidate**

Methylphenidate has CNS-stimulant properties similar to those of amphetamine and may also lead to abuse, although its addictive poten- tial is controversial. It is a Schedule II drug. It is presently one of the most prescribed medications in children. It is estimated that 4 to 6 million children in the United State take methyl phenidate daily for ADHD. The pharmacologically active isomer, dexmethylphenidate, has also been approved in the United States for the treatment of ADHD.

1. **Mechanism of action**: Children with ADHD may produce weak dopamine signals, which suggests that once-interesting activities provide fewer rewards to these children. Methylphenidate is a dop- amine transport inhibitor and may act by increasing dopamine in the synaptic space. [Note: Methylphenidate may have less poten- tial for abuse than cocaine, because it enters the brain much more slowly than cocaine and, thus, does not increase dopamine levels as rapidly.]

**2. Therapeutic uses:** Methylphenidate has been used for several decades in the treatment of ADHD in children ages 6 to 16 years. It is also effective in the treatment of narcolepsy. Unlike methylphenidate, dexmethylphenidate is not indicated in the treatment of narcolepsy.

3**. Pharmacokinetics:** Both methylphenidate and dexmethyl phenidate are readily absorbed upon oral administration. Methylphenidate is available in extended release capsules and as a transdermal patch. The de-esterified product, ritalinic acid, is excreted in urine.

4**. Adverse reactions:** GI effects are the most common and include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. In seizure patients, methylpheni- date seems to increase the seizure frequency, especially if the patient is taking antidepressants. Methylphenidate is contraindicated in patients with glaucoma.

5. **Drug interactions**: Studies have shown that methylphenidate can interfere in the metabolism of warfarin, phenytoin, phenobarbital, primidone, and the tricyclic antidepressants.