35 Contemporary Drug Abuse

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The phrases *substance abuse* and *drug abuse* are often applied to the use of an illegal or *illicit* chemical substance (e.g., LSD, heroin). However, these terms may be applied when a legally obtainable medication is used excessively and for unintended purposes or is diverted to someone else's use. Also, some legal substances (e.g., nicotine, alcohol) are used to the detriment of the individual. Inappropriate use, or abuse, is the excessive *self-administration* of any substance for nonmedical purposes. An additional aspect of drug abuse is the production of hazardous or harmful effects to the individual and/or to society. The etiology of substance abuse is a complicated phenomenon that is sometimes a function of genetics, socioeconomic status, education, peer pressure, thrill seeking, or experimenting behavior and sometimes an inappropriate at-

tempt at *self-medication* to treat a real or perceived disease state. It is also clear that drug abuse is a function of the pharmacology of each drug. Almost all abused substances produce an effect on the brain that is perceived as desirable and will initiate *drug-seeking behavior.*

The professionals in the drug abuse field have such diverse backgrounds that adopting a common terminology for terms such as *addiction* and *dependence* has been difficult. These terms are best defined in the context of the pattern and consequences of drug use. Regardless of the characteristics of the drug-induced *intoxication,* the properties of the drug that are responsible for drug-seeking behavior are often referred to as the *reinforcing properties.* These drugs produce effects that are so desirable that the user is compelled to obtain more of the drug.

Recurrent abuse of a drug may properly be termed an *addiction* when the individual becomes so obsessed with constantly obtaining and using a drug that it becomes a primary goal and disrupts the ability to function in family, social, or career settings. Typically, especially during the initial stages of drug addiction, the primary reinforcing property is the production of *euphoria,* a term indicating anything from happiness or pleasantness to an excitement resembling sexual orgasm. Euphoria is considered to be a *positive reinforcing property,* one that the individual would desire or seek. The evaluation of drugs for their reinforcing properties is an assessment of their *abuse potential.* The craving or desire to obtain additional drug, especially when it is not available, was at one time termed *psychological addiction* or *psychological dependence,* though today these terms are not necessarily descriptive or specific. The term *addiction* should be used to describe recurrent drug abuse, while the term *dependence* (discussed later) refers to another state, a function of drug use, not drug craving per se. *Addiction* has also been used to describe recurrent substance abuse by individuals who realize it is harmful to their health but cannot fulfill their desire to stop, such as with tobacco.

Chronic use of a drug over a long period sometimes produces a state of tolerance that may be classified as pharmacokinetic, pharmacodynamic, or behavioral. The degree of tolerance is generally proportional to the drug dose and the duration of use. In some cases, partial or complete tolerance to the euphoric effect of the drug develops. However, tolerance to many of the other acute effects also generally develops. Termination of drug abuse may create a condition of *drug abstinence,* which coincides with the emergence of a measurable physical syndrome. This *abstinence syndrome* is an indication of *dependence,* is often referred to as drug *withdrawal,* and was once termed *physical dependence* to distinguish it from psychological dependence. It is assumed that adaptation, or tolerance, to repeated administration of drug is responsible for physical dependence. Generally, the severity of the abstinence syndrome or level of dependence is proportional to the degree of tolerance attained. However, the relationship between tolerance and dependence has not been fully resolved; tolerance and dependence can occur separately.

Epidemiological studies indicate that most individuals who abuse any one drug often also abuse, or coabuse, other drugs during the same period. *Polydrug abuse* complicates conclusions drawn from epidemiological and clinical studies. One reason for coabuse of drugs relates to similarities in pharmacological effects. In these cases, once tolerance to the primary drug develops, the individual also has *cross-tolerance* to related classes of drugs. For example, the development of tolerance to one CNS depressant, such as barbiturates, anxiolytic agents, or alcohol, simultaneously produces some degree of tolerance to the other depressants. Users may attempt to ameliorate selected drug effects by coabuse of drugs with opposite pharmacological profiles.

Drugs of abuse are derived from numerous chemical classes, and therefore, it is not surprising that they produce distinctive pharmacological effects. Also, the consequences of acute and chronic use vary considerably among different classes of compounds, as summarized in Table 35.1.

TABLE 35.1 Consequences of Drug Abuse

Substance or Drug Class	Drug	Abuse Potential[a]	Acute Intoxication[b]	Withdrawal Symptoms[c]	Additional Consequences of Use[d]
Sympathomimetic stimulants	Cocaine	++++	Euphoria	+	+++
	Amphetamine	+++			
	Methamphetamine		Increased alertness	Drug craving	Depression
	Phenmetrazine		Increased motor activity	Dysphoria	Toxic psychosis
	Methylphenidate			Sleepiness	Sexual dysfunction
	MDMA			Fatigue	
	MDA			Bradycardia	Cerebrovascular accidents

TABLE 35.1 Consequences of Drug Abuse—cont'd

Substance or Drug Class	Drug	Abuse Potential[a]	Acute Intoxication[b]	Withdrawal Symptoms[c]	Additional Consequences of Use[d]
Tobacco	Nicotine	++	Subtle effects Anxiolytic Mild stimulant Increased alertness	+ Anxiety Restlessness Bradycardia Weight gain	Cardiovascular accidents +++ Cancer Cardiovascular disease Bronchitis
Opioid agonists	Heroin Morphine Methadone LAAM Oxycodone Meperidine Fentanyl Sufentanil Alfentanil Oxymorphone Hydrocodone Hydromorphone Levorphanol	+++	Euphoria Relaxation Anxiolytic Rush Sedation	+++ Opioid craving Irritability Hyperalgesia Cramps Nausea, vomiting Muscle aches Mydriasis Sweating Piloerection Tachycardia Hypertension Fever Is rarely life-threatening	+++ Life expectancy decreased by 50% Increased risk of HIV transmission in IV users
Opioid mixed agonist–antagonists	Pentazocine Nalbuphine Butorphanol Buprenorphine	++	Same as opioid agonists but less intense	Same as opioid agonists but less intense	
Opioids (miscellaneous)	Codeine Propoxyphene	++	Same as opioid agonists but less intense	Same as opioid agonists but less intense	
Alcohol	Ethanol	++	Stimulant at low doses including euphoria and increased talkativeness Depressant at high doses producing ataxia, slurred speech, decreased motor skills	+++ Tremor Nausea Sweating Hypertension Seizure Delirium tremens Life-threatening	+++ Liver disease Fetal alcohol syndrome Life-expectancy decreased by 10 yrs Contributes to highway fatalities
Barbiturates	Secobarbital Pentobarbital Amobarbital	+++	Intoxication similar to alcohol	+++ See alcohol Life-threatening	+++ Death from drug overdose Suicide
Benzodiazepines and other mild tranquilizers	Diazepam Chlordiazepoxide Midazolam Lorazepam Flurazepam Meprobamate Methaqualone	+	Intoxication similar to alcohol	++ Cramps Myoclonic jerks Agitation, anxiety Seizure (rarely)	+
Inhalants	Gasoline Paint thinner Lighter fluid Solvents	++	Intoxication Dizziness Flushing	Some indication of alcohol-like withdrawal	+ Cardiac arrhythmias Liver and kidney damage Provide adolescents easy entry into drug abuse

TABLE 35.1 Consequences of Drug Abuse

Substance or Drug Class	Drug	Abuse Potential[a]	Acute Intoxication[b]	Withdrawal Symptoms[c]	Additional Consequences of Use[d]
Marijuana	Δ-THC	+	Euphoria Heightened sensory perception Hallucinations and motor impairment at high doses	+ Restlessness Irritability Agitation Sleep disturbances Nausea	+ Bronchitis Disruption of short-term memory Impaired motor skills
Hallucinogens	LSD (lysergide) Psilocybin, psilocin DMT, mescaline DOM, STP	+	Distortion of perception, mood, and thought	−	+++ Neurotoxicity Flashbacks Toxic psychosis
	PCP (phencyclidine)	+	Severe CNS depression	−	PCP can be lethal
Anabolic steroids	Testosterone Nandrolone	+/−	No acute behavioral effects	−/+	+ Liver damage Altered sex drive

Severity ratings: −, none; +, low; ++, intermediate; +++, high; ++++, very high.
[a]Abuse potential: abuse liability, reinforcing property, drug-seeking, craving, psychological effect.
[b]Intoxication: acute pharmacological effects.
[c]Withdrawal: withdrawal signs, abstinence syndrome, physiological effect.
[d]Consequence: detrimental personal effect (health), negative societal effects (economic, social).

OPIOIDS

For centuries opium was used for both medicinal and recreational purposes. Derived from the poppy *Papaver somniferum,* it contains numerous opiates, the primary one of which is morphine. The term *opiate* has largely been replaced by *opioid,* which represents all compounds with morphinelike activity and includes morphine, morphine derivatives, and peptides. *Opiate* is used to refer to morphinelike drugs derived from the plant and structurally similar analogues. These drugs are frequently referred to as narcotics, a Greek term for stupor, which is scientifically obsolete. Even in its early history, opium presented a problem when it was smoked or taken orally. The introduction of the hypodermic needle and syringe, however, drastically enhanced the euphoric properties of opioids and thereby altered their abuse liability. In addition, the synthesis of heroin resulted in an opioid that was more potent than morphine and ideally suited for intravenous administration.

Extent and Pattern of Abuse

The abuse of opioids falls into two distinct categories of users, those who initiate use solely for recreational purposes and those who become physically dependent as a result of being treated medically with opioids. As discussed in Chapter 26, the primary use of opioids is for the control of moderate to severe pain. However, few patients receiving opioids for pain management become dependent. Furthermore, dependence is less likely if opioids are used judiciously. Acute pain can be controlled with opioids such as hydromorphone or oxycodone, which have a rapid onset and short duration of action. In contrast, chronic pain is better treated with opioids such as methadone or morphine (e.g., *Duramorph, MS Contin*), which are less likely to produce euphoria because of their slow onset of action. Dependence in patients is most likely to occur in those with pain of unexplained or poorly defined etiology. Avoiding long-term use of opioids in this population reduces the risk of developing dependence. *Development of dependence should not be a consideration in the management of terminal cancer pain.*

The primary illicit opioid is heroin (diacetylmorphine), which was once used almost exclusively by the intravenous route. In recent years, the purity of street heroin has risen to levels that allow it to be smoked or snorted.

Pharmacological Aspects

First-time users frequently experience unpleasant, or dysphoric, effects that may include nausea and vomiting. The frequent user experiences a rush, or warm flushing feeling, in the skin and lower extremities that is often equated with sexual orgasm. This intense euphoria lasts

for one to several minutes and is followed by sedation, relaxation, and tranquility lasting up to an hour. This latter period is sometimes called being on the nod. All effects have largely dissipated within 3 to 5 hours, which requires the user to inject at frequent intervals.

Pharmacokinetics plays a very important role in the manner in which opioids are abused. Morphine and many of its derivatives are slowly and erratically absorbed after oral administration, which makes this route suitable for long-term management of pain but not for producing euphoria. In addition, opioids undergo considerable first-pass metabolism, which accounts for their low potency after oral administration. Heroin is more potent than morphine, although its effects arise primarily from metabolism to morphine. The potency difference is attributed to heroin's greater membrane permeability and resultant increased absorption into the brain.

Tolerance and Dependence

Tolerance to the unpleasant effects experienced by some individuals at the initiation of opioid use develops readily. Significant tolerance also occurs to the analgesic, respiratory depressant, emetic, and euphoric effects, although it develops somewhat more slowly to respiratory depression. Little tolerance to the GI effects and miosis develops. Cross-tolerance occurs with all known opioid analgesics. Opioid tolerance develops more quickly and to a greater extent than it does for most other drugs of abuse. The lethal opioid dose can be 20-fold higher in a tolerant individual than in a neophyte. Tolerance develops within a few days if potent opioids are given at frequent intervals, such as every 4 to 6 hours. Development of tolerance requires several weeks if the opioid is given only twice a day.

The continued use of opioids results in the development of physical dependence, as demonstrated by the appearance of a characteristic abstinence syndrome upon interruption or cessation of use. The symptoms of withdrawal include hyperactivity, anxiety, restlessness, yawning, diarrhea, vomiting, chills, fever, lacrimation, and runny nose. Piloerection (gooseflesh or cold turkey), mydriasis, increased blood pressure and heart rate, and hyperpyrexia may be observed. Tremors, abdominal cramps, and muscle and joint pain may be present. Drug craving is an important feature of opioid withdrawal. In contrast to some other drugs of abuse, withdrawal is not life threatening.

Treatment of Opioid Dependence

Although the ultimate goal of treatment programs is to achieve drug-free status as quickly as possible, it is rarely achieved without pharmacotherapy. The most commonly used strategy is to switch the patient from a short-acting opioid, such as heroin, to a long-acting agonist, such as methadone. It is easier to withdraw patients from methadone because it produces a protracted withdrawal syndrome that is less intense than that produced by heroin.

Opioid antagonists, such as naltrexone, provide another treatment option in that addicts who are completely withdrawn from an opioid can be maintained on antagonists that will block the pleasurable effects of subsequent injections of heroin. Mixed opioid agonist–antagonists show promise in that they have sufficient agonist effects to reduce craving while at the same time exhibiting antagonist properties.

STIMULANTS

A variety of drugs in distinct pharmacological and chemical classes can be considered under the broad classification as stimulants. Xanthines and methylxanthines constitute a weak class of stimulants that includes caffeine, theophylline (aminophylline), and theobromine. Caffeine is freely available in coffee, colas, and certain over-the-counter pills. A low degree of tolerance develops to some of their effects and a mild withdrawal syndrome is observed following immediate cessation of their repeated use.

The primary class of stimulants for which there is a tremendous addiction problem is the sympathomimetic stimulants, which include cocaine, amphetamine, methamphetamine (*Desoxyn*), methylphenidate (*Ritalin*), and phenmetrazine.

Extent and Pattern of Abuse

Sympathomimetic stimulant drugs have very high abuse potential. They are typically used repeatedly for a short period during which time the user escalates the dose to greater and greater levels to attain the desired degree of euphoria. Extended uninterrupted use of stimulants for 24 to 72 hours is often referred to as a *run* and usually ends in a *crash* (24–36 hours of sleep) once the individual is exhausted physically. Besides illicit sources of stimulants, approximately 5 billion doses of these drugs are prescribed per year, and there appears to be a significant degree of abuse via prescription diversion.

While some stimulants, such as amphetamine and methylphenidate, are taken orally, others are either volatilized for inhalation or snorted as the solid (nasal insufflation). *It is necessary to convert cocaine and methamphetamine to their free base so that they can be volatilized.* Methamphetamine and cocaine are also abused via the intravenous route.

Pharmacological Aspects

Most of the sympathomimetic stimulants exhibit similar pharmacological properties, differing primarily in the

magnitude of their effects. Acute drug administration produces feelings of euphoria, elation, and alertness. Intravenous injections of cocaine and amphetamine can produce a very intense *rush* of sensations that resemble sexual orgasm. At small doses cognition increases and mood is elevated. As the dose of drug escalates during a run, the overall activity of the individual changes from task performance to one generally characterized by stereotypical movements. The person starts performing certain behaviors repeatedly. Some grind or gnash their teeth. Many continuously touch or pick at their face or extremities. At this stage the individual becomes suspicious and may develop anxiety or paranoia. Acute toxic paranoid psychosis can develop, but it usually requires a longer period of abuse than a single acute session.

Besides stimulating the CNS, these drugs activate the autonomic nervous system. Individuals have tachycardia, hypertension, and possibly arrhythmias. Autonomic hyperactivity is also expressed as hyperthermia and mydriasis. More serious effects include the possibility of myocardial infarction, cerebrovascular hemorrhage, seizure, and death.

Mechanism of Action

The sympathomimetic drugs are discussed in Chapter 10. In brief, the most commonly abused of these drugs, such as cocaine, work primarily as indirect agonists of the catecholamine neurotransmitter systems via inhibitory actions upon the transmitter reuptake system. Considerable evidence supports a role for dopamine in mediating the rewarding effects of cocaine. There is also evidence that blockade of serotonin uptake may contribute to cocaine's actions.

Tolerance and Dependence

Tolerance to stimulants develops fairly rapidly, even in the therapeutic dose range. It is the rapid development of tolerance that leads to the escalation of dose during drug abuse runs.

Other Adverse Effects of Chronic Abuse

Chronic stimulant abuse alters the personality of the abuser. These and related changes are the result of neurotoxicity and are not characterized as either acute drug effects or withdrawal signs. Individuals have delusions of being pursued or persecuted and therefore become suspicious and paranoid. They become self-occupied and hostile toward others. Long-term abuse can produce toxic psychosis that closely resembles schizophrenia and must be treated with neuroleptic drugs (haloperidol, chlorpromazine). This psychosis can develop even within 1 to 2 weeks if the person is on a run of very high doses of stimulants.

NICOTINE

Pharmacological Actions

The behavioral effects of nicotine have been defined as both stimulant and depressant, effects that are influenced by the present mental status and expectations of the smoker. Smokers may feel alert and relaxed. Nicotine produces myriad effects on the central nervous system (CNS), almost all of which appear to be mediated through nicotinic receptors. Additionally, nicotine influences multiple neuronal systems. One of its most prominent effects is stimulated release of dopamine, particularly in the nucleus accumbens, which is a major component of the reward system. Nicotine also stimulates the release of endogenous opioids and glucocorticoids.

Tolerance and Dependence

Tolerance to nicotine's effects develops rapidly and most likely involves multiple processes, although the pattern and extent of tolerance development is not identical for all of nicotine's effects. It has been proposed that rapid tolerance or desensitization occurs to the behavioral or reinforcing effects of nicotine. These effects are of such a short duration that a smoker continually cycles between a sensitized and desensitized state. This notion is consistent with the fact that drugs with high abuse liability have a rapid onset and short duration of action.

Regardless of the mechanism of tolerance, nicotine is a highly addicting drug. Even though most individuals are unaware of nicotine's reinforcing properties when smoking, many individuals feel intense, long-lasting craving when attempting to stop. Although most smokers wish to quit, only about one-third attempt to do so each year.

SEDATIVE–HYPNOTICS

The CNS depressants include barbiturates, nonbarbiturate sedatives, and the benzodiazepines. As the medical use of barbiturates decreased, primarily because of their high addiction liability and the danger of acute lethality, the use of the benzodiazepine anxiolytics increased. The most commonly abused barbiturates are secobarbital, pentobarbital, and amobarbital. Phenobarbital is not generally abused, because of its slow onset of action. The most commonly abused anxiolytics include diazepam, chlordiazepoxide, midazolam, lorazepam, and flurazepam. These drugs are readily attainable from illicit sources.

Abused nonbarbiturate sedatives include glutethimide and meprobamate.

Pharmacological Aspects

CNS depressants, including barbiturate, benzodiazepine, and ethanol, produce a similar intoxication. These drugs are abused for their euphoric effects and as a means to reduce anxiety and limit insomnia. As the dose of depressant increases, along with the degree of intoxication, the effects progress from anxiety reduction and muscle relaxation to motor impairment and unconsciousness. The difference between the classes of drugs is primarily dose responsiveness. Intoxication progresses from mild to severe over a relatively narrow dose range in the case of the barbiturates. The benzodiazepine dose–response curve is such that great increases in dose are necessary to make such a transition. Thus, the benzodiazepines are a safer class of depressant drugs.

The acute effects of depressants can include euphoria, anxiety reduction, anticonvulsant activity, sedation, ataxia, motor incoordination, impaired judgment, anesthesia, coma, and respiratory depression resulting in death. *The benzodiazepines are rarely involved in lethality, but all CNS depressants enhance the effects of other depressant drugs.* The physiological effects of high-dose depressants include miosis, shallow respiration, and reduction in reflex responses.

Tolerance and Dependence

Tolerance to many of the effects of the depressants develops. Unlike opioids, barbiturate and benzodiazepine tolerance develops slowly. Also, tolerance is incomplete in some instances or does not influence some pharmacological effects. One such exception is the lack of tolerance to barbiturate lethality. The lethal dose in a tolerant individual is not much different from that of the general population. Cross-tolerance develops to some degree between the depressant classes of drugs.

Dependence on benzodiazepines, as evidenced by a withdrawal syndrome, can develop to large doses of drugs. Mild dependence is produced at therapeutic doses.

Individuals report some craving for drug during withdrawal from benzodiazepines, but the level is not as great as among those who abuse alcohol. Once the withdrawal syndrome has dissipated, the abusers of benzodiazepines are not as likely to resume drug consumption as are alcoholics. Withdrawal signs appear to be more likely following chronic exposure to short-acting benzodiazepines, such as alprazolam (half-life of less than 15 hours) or lorazepam than long-acting drugs. Despite gradual dose reduction, individuals may have anxiety attacks, confusion, agitation, restlessness, sweating, clouded sensorium, heightened sensory perception, perceptual disturbances, sleep disruption, muscle cramps, muscle twitches, and tremors; 2% of addicts may have a seizure during withdrawal. Withdrawal signs peak the second day after abrupt withdrawal and last for at least 5 to 7 days. Withdrawal symptoms following long-acting benzodiazepines (diazepam, clorazepate) peak during the second week of abstinence. In contrast to alcohol and the barbiturate sedatives, withdrawal from benzodiazepines is not life threatening.

ETHANOL

Ethanol is the most widely abused drug in the world. There are more than 10 million alcoholics in the United States alone. Excessive consumption of alcoholic beverages has been linked to as many as half of all traffic accidents, two-thirds of homicides, and three-fourths of suicides, and it is a significant factor in other crimes, in family problems, and in personal and industrial accidents. The annual cost to the American economy has been estimated to exceed $100 billion in lost productivity, medical care, and property damage.

Alcoholism has been difficult to define because of its complex nature. A person is generally considered an alcoholic, however, when his or her lifestyle is dominated by the procurement and consumption of alcoholic beverages and when this behavior interferes with personal, professional, social, or family relations.

A *light drinker* generally is defined as one who consumes an average of one drink or less per day, usually with the evening meal; a *moderate drinker* is one who has approximately three drinks per day; and a *heavy drinker* is one who has five or more drinks per day (or in the case of binge drinkers, at least once per week with five or more drinks on each occasion).

Chemistry

Ethanol (ethyl alcohol, alcohol) is a simple organic molecule composed of a single hydroxyl group and a short two-carbon aliphatic chain, CH_3CH_2OH. The hydroxyl and ethyl moieties confer both hydrophilic and lipophilic properties on the molecule. Therefore, ethanol is an *amphophile,* a property important to its pharmacological activity.

Absorption, Distribution, Metabolism, and Excretion

After oral administration, ethanol is almost completely absorbed throughout the gastrointestinal tract. The rate of absorption is largely determined by the quantity consumed, the concentration in the beverage, the rate of consumption, and the composition of the gastric contents. Eating food before or during drinking retards absorption, especially if the food has a high lipid content.

After absorption, ethanol is distributed throughout body water. In organs with high blood flow, such as the brain, liver, lungs, and kidney, equilibrium occurs rapidly. Conversely, in organs with low blood flow, such as

muscle, equilibrium occurs more slowly. *Ethanol readily passes through the blood–placenta barrier into the fetal circulation.* Although the concentration of ethanol in the blood can be quite predictable, measurements of blood ethanol, especially when the concentrations are rising, may lead to erroneous conclusions, since the values obtained can underestimate the concentration of ethanol in the brain. This fact can confound legal proceedings in drunk-driving cases where blood ethanol concentrations are considered an accurate and legally acceptable determinant of the amount of ethanol consumed.

Ethanol is metabolized primarily in the liver by at least two enzyme systems. The best-studied and most important enzyme is zinc dependent: alcohol dehydrogenase. Salient features of the reaction can be seen in Fig. 35.1. The *rate* of metabolism catalyzed by alcohol dehydrogenase is generally linear with time except at low ethanol concentrations and is relatively independent of the ethanol concentration (i.e., zero-order kinetics). The rate of metabolism after ingestion of different amounts of ethanol is illustrated in Fig. 35.2.

In adults, ethanol is metabolized at about 10 to 15 mL/hour. Since metabolism of ethanol is slow, ingestion must be controlled to prevent accumulation and intoxication. *There is little evidence* that chronic ingestion of ethanol leads to a significant induction of alcohol dehydrogenase, even in heavy drinkers.

Some populations, most notably East Asians, exhibit an unusual response after drinking ethanol. The symptoms include facial flushing, vasodilation, and tachycardia. These individuals apparently have a genetic deficiency of the enzyme aldehyde dehydrogenase, which leads to an accumulation of acetaldehyde even after they drink relatively small amounts of ethanol. If drugs such as metronidazole, griseofulvin, quinacrine, the hypoglycemic sulfonylureas, phenothiazines, and phenylbutazone are coadministered with ethanol, a similar accumulation of acetaldehyde may occur.

In addition to alcohol dehydrogenase, *ethanol can be oxidized to acetaldehyde by the microsomal mixed-function oxidase system (cytochrome P450 2 EI),* as illustrated in Figure 35.1. Although this microsomal ethanol-oxidizing system probably has minor impor-

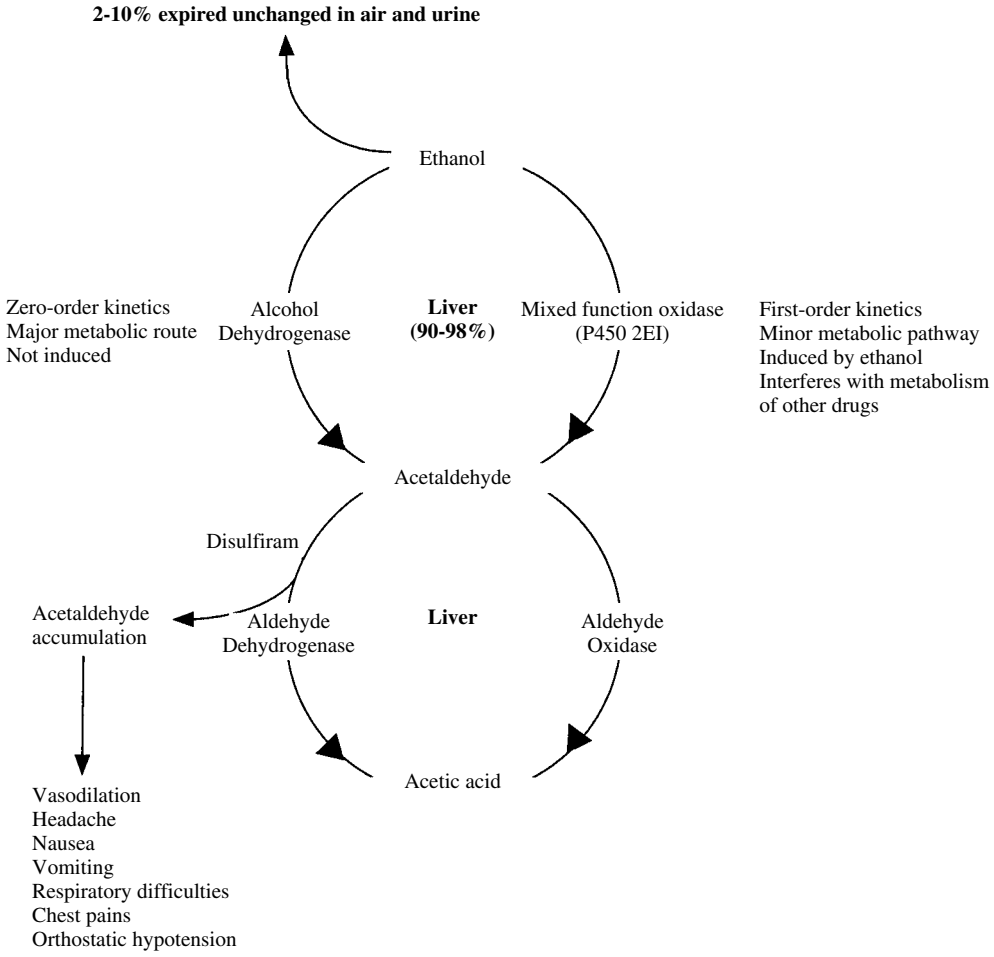

FIGURE 35.1
Metabolism and excretion of ethanol.

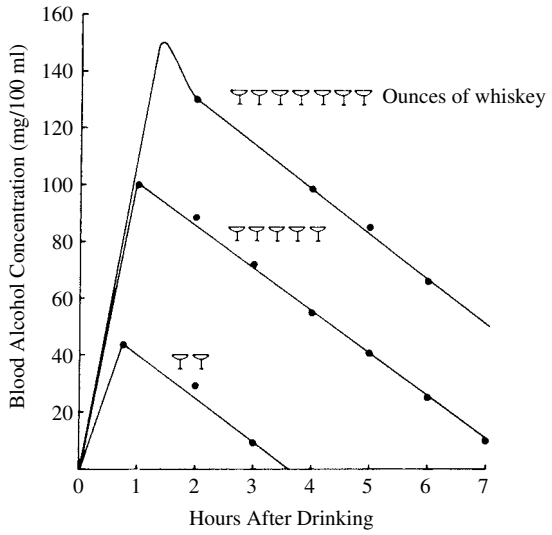

FIGURE 35.2
Blood alcohol concentration (mg/dL) after the consumption of various amounts of alcohol (for an adult of about 150 lb).

tance in the metabolism of ethanol in humans, it may be involved in some of the reported interactions between ethanol and other drugs that are also metabolized by this system. *Microsomal mixed-function oxidases may be induced by chronic ethanol ingestion.* Because ethanol is metabolized in the liver, it can interfere with the metabolism of other drugs by blocking microsomal hydroxylation and demethylation. Drug classes whose metabolism is most affected include the barbiturates, coumarins, and anticonvulsants, such as phenytoin. *Liver damage resulting from chronic abuse of ethanol can impair metabolism of a variety of drugs.*

Normally, 90 to 98% of an ingested dose of ethanol is metabolized by the liver. Most of the remaining 2 to 10% is excreted unchanged in the urine and expired air. The ethanol content in the urine is normally about 130% of the blood concentration and is quite constant; the expired air contains about 0.05% of the blood ethanol level, a concentration that also is remarkably consistent.

Mechanism of Action

A great deal of attention has been focused on a class of proteins termed the *ligand-gated ion channels* as being important to the mechanism of action of alcohol. These integral membrane proteins function as gates or pores that allow the passage of certain ions into and out of neurons upon binding of the appropriate neurotransmitter. This flux of ions largely determines the degree of neuronal activity. Two distinct types of ligand-gated ion channels are particularly sensitive to concentrations of alcohol that produce intoxication and sedation. These are the α-aminobutyric acid (GABA) chloride ionophore and the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor. The GABA–chloride ion channel reduces neuronal activity by hyperpolarizing the neurons, while activation of the NMDA receptor causes neuronal depolarization or excitation. Alcohol has been shown to increase chloride flux through the $GABA_A$ receptor and reduce calcium flux through the NMDA receptor. These actions result in powerful suppression of nerve cell activity, which is consistent with the depressant actions of alcohol in the brain.

Pharmacological Actions

Central Nervous System

Alcohol is primarily a CNS depressant, and the degree of depression is directly proportional to the quantity of ethanol consumed. However, behavioral *stimulation* can be found after ingestion of small amounts of ethanol. This stimulation is expressed as decreased social and psychological inhibition and is most likely the result of a depression of inhibitory pathways in the brain with release of cortical activity. The behavioral and physiological effects are associated with different blood ethanol concentrations. As the blood ethanol concentration begins to increase, behavioral activation, characterized by euphoria, talkativeness, aggressiveness, and loss of behavioral control, generally precedes the overt CNS depression induced by ethanol. At progressively higher blood ethanol concentrations, the stage of relaxation is transformed into decreased social inhibitions, slurred speech, ataxia, decreased mental acuity, decreased reflexive responses, coma, and, finally, death resulting from respiratory arrest. In moderation, however, there is no evidence that the judicious use of small amounts of alcoholic beverages (e.g., a glass of wine with meals) is permanently harmful.

Other Body Systems

In general, ethanol in low to moderate amounts, is relatively benign to most body systems. A moderate amount of ethanol causes peripheral vasodilation, especially of cutaneous vessels, and stimulates the secretion of salivary and gastric fluids; the latter action may aid digestion. On the other hand, ethanol consumption in high concentrations, as found in undiluted spirits, can induce hemorrhagic lesions in the duodenum, inhibit intestinal brush border enzymes, inhibit the uptake of amino acids, and limit the absorption of vitamins and minerals. In addition, ethanol can reduce blood testosterone levels, resulting in sexual dysfunction.

Ethanol is a diuretic. This effect may be caused by its ability to inhibit secretion of antidiuretic hormone from the posterior pituitary, which leads to a reduction in renal tubular water reabsorption. The large amount of fluid normally consumed with ethanol also contributes to increased urine production.

Adverse Effects

Acute Ethanol Intoxication and Hangover

Ethanol intoxication is probably the best-known form of drug toxicity. Intoxicated individuals are a threat to themselves and others, particularly if they attempt to drive or operate machinery. Although death can result from ethanol overdose, usually the patient lapses into a coma before ingesting lethal quantities. Ethanol intoxication is sometimes mistakenly diagnosed as diabetic coma, schizophrenia, overdosage of other CNS depressant drugs, or skull fracture. An additional feature commonly associated with excessive ethanol consumption is difficulty in regulating body temperature. *Hypothermia* frequently results, with body temperature falling toward that of the ambient environment. This problem can be particularly severe in the elderly, who normally have difficulty regulating their body temperature.

One of the consequences of ethanol intoxication is the hangover, a condition characterized by headache, nausea, sweating, and tremor. Although unpleasant, a hangover is not dangerous, even though the person having one may feel otherwise.

Treatment for Acute Intoxication

Generally, no treatment is required for acute ethanol intoxication. Allowing the individual to sleep off the effects of ethanol ingestion is the usual procedure. Hangovers are treated similarly; that is, no effective remedy exists for a hangover, except for controlling the amount of ethanol consumed. Sometimes ethanol overdose is a medical emergency. For example, prompt treatment is required if the patient is in danger of dying of respiratory arrest, is comatose, has dilated pupils, is hypothermic, or displays tachycardia.

Treatment for severe ethanol overdose is generally supportive. Increased intracranial pressure can be relieved by intravenous administration of hypertonic mannitol. Hemodialysis can accelerate the removal of ethanol from the body. Stimulants of ethanol metabolism, such as fructose, are not sufficiently effective, and *use of analeptics is not recommended because of the possibility of precipitating convulsions.*

Alcoholism

Alcoholism is among the major health problems in most countries. *Dependence on ethanol, as with other addictive drugs, is expressed as drug-seeking behavior and is associated with a withdrawal syndrome that occurs after abrupt cessation of drinking.* The ethanol withdrawal syndrome is characterized by tremors, seizures, hyperthermia, hallucinations, and autonomic hyperactivity.

A number of organs are affected adversely by chronic ethanol use, the result of a *direct cytotoxic action.* Hepatic fatty infiltration and cirrhosis are common in alcoholics; cancer may develop in advanced stages of hepatic disease.

Ethanol produces a number of depressant effects on the myocardium. Atrial arrhythmias and ventricular tachycardia may arise from chronic ethanol use. A serious clinical entity, *alcoholic cardiomyopathy,* has also been described.

A high rate of ethanol consumption can lead to inhibition of gastric secretion and irritation of the gastric mucosa. Ethanol irritates the entire gastrointestinal tract, which may lead to constipation and diminished absorption of nutrients. Other pathological effects include pancreatitis and peripheral neuropathy. Severe gonadal failure is often found in both men and women, accompanied by low blood levels of sex hormones.

A variety of pathological problems involving the CNS have been described in chronic alcoholics, the main ones being *Wernicke's encephalopathy* and *Korsakoff's psychosis.* Brain damage from chronic ethanol consumption can be especially severe in the elderly and may accelerate aging.

Ethanol readily passes across the placenta and into the fetal circulation. *The fetal alcohol syndrome has three primary features: microcephaly, prenatal growth deficiency, and short palpebral fissures.* Other characteristics include postnatal growth deficiency, fine motor dysfunction, cardiac defects, and anomalies of the external genitalia and inner ear. A definite risk of producing fetal abnormalities occurs when ethanol consumption by the mother exceeds 3 oz daily, the equivalent of about six drinks.

Treatment for Alcoholism

The immediate concern in the treatment of alcoholics is detoxification and management of the ethanol withdrawal syndrome. Once the patient is detoxified, long-term treatment requires complete abstinence, psychiatric treatment, family involvement, and frequently support from lay organizations such as Alcoholics Anonymous.

One pharmacological approach is aversion therapy using drugs such as disulfiram to associate drinking ethanol with unpleasant consequences. If ethanol is taken after disulfiram administration, blood acetaldehyde concentrations increase 5 to 10 times, resulting in vasodilation, pulsating headache, nausea, vomiting, severe thirst, respiratory difficulties, chest pains, orthostatic hypotension, syncope, and blurred vision. In certain cases, marked respiratory depression, cardiac arrhythmias, cardiovascular collapse, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and sudden death have been reported. Despite these potentially severe consequences, disulfiram is prescribed for some alcoholic patients.

Another pharmacological approach is the use of anticraving drugs, for example serotonin uptake inhibitors,

dopaminergic agonists, and opioid antagonists. The only treatment that has shown considerable promise is one that uses the opioid antagonist naltrexone.

MARIJUANA

The hemp plant, or cannabis (*Cannabis sativa*), continues to be the most frequently abused illicit substance in America. The dried leaves and flowering tops of the plant are referred to as marijuana, and it is typically smoked in pipes or rolled as cigarettes. It also may be consumed in baked goods. *Hashish* is a solid black resinous material obtained from the leaves of the plant and is usually smoked in a pipe.

Chemistry

The major psychoactive constituent in marijuana use is Δ^9-tetrahydrocannabinol (THC), the prototypical cannabinoid. Although marijuana contains a large number of cannabinoids, they lack behavioral activity with the exception of cannabinol, which is approximately one-tenth as potent as THC. The THC content in hashish is more than double that in marijuana.

Pharmacokinetic Aspects

Δ^9-THC is readily absorbed when marijuana is smoked. Pharmacological effects are produced rapidly and generally peak within 30 minutes of the onset of smoking. The dynamics of smoking (number of puffs, spacing, hold time, and lung capacity) substantially influence how much drug is absorbed. Although oral ingestion of marijuana produces similar pharmacological effects, Δ^9-THC is absorbed more slowly than by smoking. Impairment on various performance measures related to driving skills has been demonstrated immediately following marijuana smoking and up to 24 hours thereafter. Generally, behavioral and physiological effects return to baseline levels 4 to 6 hours after usage. Blood concentrations of Δ^9-THC peak prior to drug-induced effects. This time discordance between blood concentrations of Δ^9-THC and effects has made it difficult to establish a meaningful relationship between blood concentrations and effects.

Δ^9-THC is rapidly distributed to all tissues despite being tightly bound by plasma proteins. Δ^9-THC is a highly lipophilic substance and so accumulates in tissue high in lipid content. Traces of Δ^9-THC have been found in adipose tissue more than 30 days after the subject smoked a single joint. The terminal half-life of Δ^9-THC in plasma ranges from 18 hours to 4 days.

Mechanism of Action

A cannabinoid receptor identified in the brain of several species, including humans, is termed *CB1*. It is one of the most abundant receptors in the CNS, and its distribution within the brain reflects the pharmacological effects produced by Δ^9-THC. High receptor densities in the extrapyramidal motor system and the cerebellum are consistent with the actions of cannabinoids on many forms of movement. The effects of cannabinoids on cognition and memory may be due to the relatively dense receptor populations in the hippocampus and cortex. The presence of cannabinoid receptors in the ventromedial striatum and nucleus accumbens suggests an association with dopamine neurons hypothesized to mediate brain reward.

Pharmacological Actions

Central Nervous System

Marijuana produces a distinctive behavioral syndrome that is easily distinguished from that of most other drugs. The most prominent feature is the initial period of euphoria, or high, which has been described as a sense of well-being and happiness. Euphoria is frequently followed by a period of drowsiness or sedation. Perception of time is altered, along with distortions in both hearing and vision. However, illusions and hallucinations occur infrequently. The subjective effects also include dissociation of ideas.

The subjective effects of marijuana vary from individual to individual as a function of dose, route of administration, the experience and expectation of the subjects, and individual vulnerability to certain psychoactive substances. Motor coordination also may decrease, especially in situations requiring highly complex motor skills, such as flying an airplane and driving an automobile.

Increased appetite is frequently attributed to smoking marijuana. Cannabinoids are effective antiemetics, particularly in treating emesis arising during chemotherapy. Δ^9-THC has been reported to be as effective as codeine as an analgesic, although pronounced behavioral effects occur with analgesic doses.

Other Organ Systems

The most consistent pharmacological effect produced by marijuana is tachycardia, which is closely associated with the blood levels of Δ^9-THC. There is relatively little effect on blood pressure unless large quantities of marijuana are smoked, in which case there can be marked orthostatic hypotension. Cannabinoids are also vasodilatory, which results in the characteristic conjunctival reddening following marijuana smoking. They also reduce intraocular pressure and are capable of producing bronchodilation.

Adverse Effects

Marijuana is unique among drugs of abuse in that there have been no credible reports of fatal overdose. The

most prominent effect of acute marijuana use is intoxication, which can impair the cognitive and motor skills needed to complete complex tasks. Anxiety and panic reactions are occasionally reported in inexperienced users or following use of large quantities of marijuana. Δ^9-THC causes its greatest effects on short-term memory, as measured in free-recall tasks. Marijuana does not affect the retrieval of previously learned facts. In contrast to alcohol, there is no residual hangover from a single use of high quantities of marijuana.

Heavy marijuana smoking produces bronchitis, and some individuals have evidence of precancerous lung conditions. However, definitive evidence of the relationship between marijuana smoking and the incidence of lung cancer is lacking.

Tolerance develops to many of Δ^9-THC's effects in heavy marijuana users. Although chronic cannabis use does not result in severe withdrawal symptoms, numerous case reports attest to development of dependence in subjects taking high doses of THC for several weeks. The most prominent symptoms were irritability and restlessness; others included insomnia, anorexia, increased sweating, and mild nausea. Cessation of mild or moderate use of marijuana, however, does not produce a withdrawal syndrome.

HALLUCINOGENS

The term *hallucinogen* is often used to describe a drug that produces a change in sensory perception, usually either visual or auditory. Drugs commonly assigned to this class include lysergic acid diethylamide (LSD), mescaline (derived from the peyote cactus), and psilocybin (derived from a mushroom). However, this rather limited definition fails to include the other prominent property of this class of drugs, which is a change in thought and mood. For this reason the term is sometimes used interchangeably with *psychedelic* or *psychotomimetic,* the latter term representing the CNS effects beyond the hallucination itself. Most literal definitions of the term *hallucinogen* are inadequate, but it should be used to signify substances that consistently produce changes in sensory perception, thought, and mood. An hallucinogen is a drug that *reliably* produces alterations in perceptions as a primary effect. Drugs that should not be included are those that produce alterations in sensory perception only at toxic doses (e.g., antimuscarinic agents, antimalarials, and opioids) and fail to produce these effects in all individuals. This does not preclude a drug's being classified as an hallucinogen if it has other properties as well. Several drugs that reliably alter mood at low doses and produce altered sensory perceptions at slightly higher doses are close chemical analogues to the CNS stimulant class of drugs. These drugs that also reliably produce differing degrees of CNS stimulation in a dose-responsive fashion include phencyclidine (PCP), methylenedioxymethamphetamine (MDMA), and methylenedioxyamphetamine (MDA).

The hallucinogens generally fall into two chemical classes. The indole alkylamines include LSD, psilocybin, psilocin, dimethyltryptamine (DMT), and diethyltryptamine (DET), all of which are structurally similar to serotonin. The other chemical subclass of hallucinogens contains phenylethylamine derivatives such as mescaline, MDMA, MDA, and DOM (dimethoxymethyl amphetamine). A related stimulatory hallucinogen, PCP, is a piperidine analogue that produces unique effects.

Extent and Pattern of Abuse

LSD is very potent and produces both CNS and peripheral effects. Because of the rapid tolerance produced with these drugs, the typical abuser does not use the drug on a daily basis. Generally, an hallucinogen is abused approximately once per month.

Illicit PCP abuse began in the 1960s, primarily by oral ingestion. However, its use was limited because PCP frequently produced dysphoria, which was unpredictable.

Pharmacological Aspects

The effects of LSD may be observed for 8 hours. The specific acute effects of a drug like LSD include euphoria, depersonalization, enhanced awareness of sensory input, alterations in the perception of time or space or body image, and to some extent, minor stimulant effects. Sometimes the dreamlike quality of the experience produces relaxation, good humor, and a sense of wonder or euphoria.

Often the effect is a function of expectation and environmental conditions. Someone who is anxious about the use of the hallucinogen may have drug-induced anxiety, panic, or even paranoid ideation. The loss of individuality can be perceived as a disintegration of the person and can lead to a panic attack. Even if the drug experience initially is euphoric, tremendous mood swings can occur and suddenly plunge the abuser into emotions of great anxiety or terror. These negative phenomena are not always precipitated by an unexpected or sudden frightful event but can be a function of the labile mood induced by the drug.

The visual hallucinations are often composed of extremely vivid colors of geometric patterns, such as cones, spirals, or cobweb-like structures. Other types of hallucinations are possible. A true hallucination involves the belief by the individual that the (altered) sensations and perceptions actually represent reality. However, generally the person abusing LSD and related drugs retains the ability to test reality versus illusion and knows that the experience is not real. Thus, the

typical drug-induced hallucinatory state would be more appropriately termed a *pseudohallucination,* though real hallucinations are possible. The subjective or psychotomimetic changes are those considered to be changes in mood. These effects are somewhat more variable than the hallucinatory effects or changes in sensory perception. Though these effects can occur with LSD, they seem to be more common with other specific hallucinogens, such as MDMA and MDA.

MDMA (XTC, or *ecstasy*) possesses hallucinogenic activity similar to that of mescaline but also produces stimulant activity similar to that of amphetamine. Initially MDMA produces euphoria, increases the ability to communicate with others, increases the degree of intimacy one feels toward others in the surroundings, increases self-esteem and mood, and generally appears reduce perceived intensity of psychological problems. Hallucinatory activity occurs at higher doses. One residual effect of abuse is the MDMA hangover, which is the occurrence on the second day after abuse of drowsiness and sore jaw muscles along with other possible side effects due to the stimulant properties of the drug.

MDA, which is similar to MDMA, has been termed the *love drug* because it produces a feeling of closeness to others. Typically, a dose of 75 mg produces the primary psychotomimetic effects, while a dose of 150 mg produces LSD-like effects, and a dose of 300 mg produces amphetaminelike CNS stimulation. The amphetaminelike stimulation of the CNS and periphery is prominent with both MDA and MDMA. To a lesser degree this stimulation also occurs with LSD. The effects that can be produced by stimulatory doses of hallucinogens include tachycardia, hypertension, and arrhythmias.

PCP is unique in terms of its hallucinogenic properties and its other pharmacological effects. It possesses CNS stimulatory actions, but it is also a dissociative anesthetic. It induces a wide variety of psychotomimetic and hallucinatory effects during emergence from anesthesia. Because it possesses CNS stimulant properties comparable with those of amphetamine, it does not produce depression of the cardiovascular system like other anesthetics, though it does depress the respiratory system. At a low dose, individuals believe they are thinking and acting rapidly and efficiently. The general mood is happiness, though (especially at higher doses) the individual can vacillate between euphoria and depression. It primarily produces auditory hallucinations. At higher doses the stimulatory effects are more pronounced and the likelihood of tremendous mood swings more likely. At near anesthetic doses, it produces more typical depressant effects, including motor incoordination, catalepsy, vacant stare, or even amnesia. Coma is produced subsequent to respiratory depression.

Tolerance and Dependence

Tolerance to the effects of hallucinogens develops rapidly. In fact, a high degree of tolerance can be produced after as few as three to four daily doses of drug. Generally, the abuser self-imposes the requirement for a 2- to 3-day drug-free period before another drug session. Additionally, there is a tremendous degree of cross-tolerance between the hallucinogens, so other LSD-like hallucinogens cannot be abused during the drug-free period either. One danger with the stimulant subclass of hallucinogens is rapid development of tolerance to some of their effects while the stimulatory properties remain and produce various side effects. Despite the apparent overlap of effects with stimulant drugs, however, there is no cross-tolerance with the CNS stimulants such as amphetamine.

There are no observable physical withdrawal signs during drug abstinence, nor is there a tremendous craving for drug during the drug-free period. Therefore, clearly no dependence is attributed to the hallucinogens. Though there is an abuse potential with this class of drug, and individuals express drug-seeking behavior, there does not seem to be the magnitude of craving found with other drug classes, such as the CNS stimulants.

Treatment Strategies

The difference between the abused and the lethal dose of LSD is very large, so little pharmacological intervention is necessary. Treatment involves limiting external stimuli and placing the individual in a safe environment.

Treatment of PCP intoxication also involves limiting external stimuli, minimizing lighting, noise, and unnecessary physical contact. The life-threatening nature of PCP overdose, however, may require symptomatic treatment of respiratory depression by artificial respiration or use of neuroleptics to control violent rage or panic anxiety.

Mechanism of Action

Hallucinogens disorganize neural function in the CNS. The structural similarities between the indole hallucinogens and the endogenous neurotransmitter serotonin led to the hypothesis that a primary mechanism of action for the hallucinogens is the activation of the 5-HT_2-receptor. LSD acts directly on this receptor as an agonist. Other drugs, such as MDMA, induce the release of endogenous serotonin, which activates the serotonin receptor.

INHALANTS

Volatile chemicals and gases that produce behavioral effects are subject to abuse. These agents represent a broad range of chemical classes but in general can be

classified as gases, volatile organic solvents, and aliphatic nitrites. Inhalant abuse differs from that of many other drugs in that it is confined primarily to juveniles and young adults. The use of gases is primarily confined to nitrous oxide by young medical professionals who have ready access to this agent. It produces short-lived mild intoxication that typifies the early stages of anesthesia. Deaths occur occasionally by individuals inhaling nitrous oxide alone. Volatile organic solvents are usually aliphatic and aromatic hydrocarbons. They include substances such as gasoline, paint and lacquer thinners, lighter fluid, degreasers (methyl chloride and methylene chloride), and the solvents in airplane glue, typewriter correction fluid, and bathroom deodorizers. These agents produce a sense of exhilaration and light-headedness. Judgment and perception of reality are impaired, and hallucinations may be produced. The mechanism by which inhalants produce their behavioral effects are poorly understood, but there are some indications that their actions are similar to those of other centrally acting depressants, including alcohol. Toxicity depends on the properties of the individual solvents. The consequences of inhaling these substances can be severe, for they have been implicated in producing cancer, cardiotoxicity, neuropathies, and hepatotoxicity.

DESIGNER DRUGS

In an effort to avoid federal regulations, chemists in clandestine laboratories adopted the strategy of synthesizing analogues of controlled substances. Although these drugs are technically not illegal until scheduled, the consequences of their abuse are unpredictable and in some instances lethal. Efforts to make synthetic heroin led to the synthesis of at least six chemicals that are structurally similar to fentanyl. These agents gained considerable attention because their increased potency over fentanyl and heroin led to a rash of overdoses and numerous deaths. The two derivatives are referred to as China White and are 900 and 1,100 times as potent as morphine. Meperidine has also been used as a template for preparing synthetic heroin, the end product being 1-methyl-4-propionoxy-4-phenylpi-peridine (MPPP). However, MPPP is sometimes contaminated with the side reaction product 1-methyl,4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which produces a parkinsonian syndrome through nigrostriatal lesions. Several substituted derivatives of amphetamine have also been called designer drugs. The most widely known of this group is the hallucinogen MDMA (*ecstasy*).

ANABOLIC STEROIDS

Historically, drugs used to increase the ability of an athlete to perform in a given sport included the use of stimulants to diminish the onset of fatigue or opiates to diminish the pain of exertion. Recently, abuse of *anabolic–androgenic steroids* (derivatives of testosterone) has increased. They are used to increase muscle size and definition (in the case of body-building competitors) and are sometimes coabused with other growth enhancers, such as human growth hormone. In sports in which mass, physical size, or even total strength (a function of total muscle mass) is important, the abuse of anabolic steroids provides a shortcut to attainment of the physical stature that might otherwise require much more extensive training and exercise. However, it is a misconception to believe that anabolic steroid abuse is limited to professional athletes and body builders. There is clear evidence that these drugs are abused by adult men and women who are not athletes, who are blue-collar and white-collar workers, and by male and female athletes at the college, high school, and junior high school levels. For more details see Chapter 63.

Study Questions

1. A 28-year-old man, a long-term opioid user, is brought to the emergency department with typical abstinence symptoms and asks for your help in breaking his heroin habit. What do you do?
(A) You prescribe a 3-day regimen of meperidine.
(B) You prescribe methadone and indicate it may be for an extended period.
(C) You prescribe a one-time dose of naltrexone.

2. A patient is brought into the emergency department on Saturday night exhibiting paranoia and hostility and tells you that he is being pursued by strangers. He is emaciated, hungry, and filthy. What is the best solution for this case?
(A) He has schizophrenia and should be admitted to the psychiatric ward.
(B) He abuses alcohol and should undergo detoxification.
(C) He has acutely abused a stimulant and should be treated with a neuroleptic drug.
(D) He abuses heroin and should be prescribed methadone maintenance.

3. Barbiturate abuse is much less common now than it was 25 years ago. What is the main reason?
   (A) Barbiturate use is much less now than it was 25 years ago.
   (B) Barbiturates available today are much safer than those of 25 years ago.
   (C) People who abuse drugs today choose heroin and cocaine over barbiturates.
   (D) The antidotes to barbiturates prevent the abuse.
4. The most widely abused drug in the world is
   (A) Marijuana
   (B) Cocaine
   (C) Heroin
   (D) Alcohol
   (E) Amphetamine
5. A patient has piloerection, mydriasis, increased blood pressure, and abdominal cramps. Your diagnosis is
   (A) Alcohol abstinence
   (B) Barbiturate abstinence
   (C) Benzodiazepine abstinence
   (D) Opioid abstinence
   (E) Amphetamine abstinence

ANSWERS

1. **B.** The most commonly used treatment and the most effective is to stabilize the patient with methadone and gradually reduce the maintenance dose until the patient is drug free. The administration of meperidine would reverse the abstinence syndrome but it is unlikely to help the patient terminate his opioid habit. The use of naltrexone would likely further precipitate the abstinence syndrome and without additional counseling, would not likely offer long-term benefit.
2. **C.** Abuse of stimulants can produce toxic psychosis that closely resembles schizophrenia. An agent such as haloperidol or a phenothiazine will provide immediate relief of the symptoms. The fact that he is emaciated and hungry is evidence that he has been on a prolonged run with stimulants. The symptoms are very different from those seen with alcohol or with opioids.
3. **A.** Barbiturates are seldom prescribed. The lack of availability is a major reason these compounds are only rarely abused.
4. **D.** There are more than 10 million alcoholics in the United States alone. The numbers of individuals who abuse the other drugs listed are much lower.
5. **D.** These are classic features of opioid abstinence syndrome. The abstinence syndrome in chronic alcohol or barbiturate users consists of hallucinations, tremors, hyperthermia, and autonomic hyperactivity. The abstinence syndrome for users of cocaine and amphetamine is not as stereotyped as for opioids or CNS depressants, such as alcohol and barbiturates.

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CASE Study Alcohol Toxicity

A 24-year-old medical student is brought into the emergency department complaining of vomiting, light-headedness, chest pains, and difficulty breathing. You discover that he fell ill at a party following the block examinations midway during the first semester. Initially he and his friends deny any drugs other than a couple of beers at the party. You are at a loss to explain the symptoms until his girlfriend states that the only drug she is aware he is taking is something for his athlete's foot. You continue checking and discover that he has been taking metronidazole for about the past 10 days to alleviate the symptoms of athlete's foot. What might be the cause of his symptoms?

ANSWER: Metronidazole shares the ability of disulfiram to block the metabolism of alcohol and cause an accumulation of acetaldehyde. The student's symptoms are consistent with an accumulation of this agent.