CHAPTER

32

Drugs of Abuse

Drug abuse is usually taken to mean the use of an illicit drug or excessive or nonmedical use of a licit drug. It also denotes the deliberate use of chemicals that generally are not considered drugs by the lay public but may be harmful to the user. The primary motivation for drug abuse appears to be the anticipated feeling of pleasure derived from the CNS effects of the drug. The older term "physical (physiologic) dependence" is now generally denoted as **dependence,** whereas "psychological dependence" is more simply called **addiction.**

THE DOPAMINE HYPOTHESIS OF ADDICTION

Dopamine in the mesolimbic system appears to play a primary role in the expression of "reward," but excessive dopaminergic stimulation may lead to pathologic reinforcement such that behavior may become compulsive and no longer under control—common features of addiction. Though not necessarily the only neurochemical characteristic of drugs of abuse, it appears that most addictive drugs have actions that include facilitation of the effects of dopamine in the CNS.

SEDATIVE-HYPNOTICS

The sedative-hypnotic drugs are responsible for many cases of drug abuse. The group includes **ethanol, barbiturates,** and **benzodiazepines.** Benzodiazepines are commonly prescribed drugs for anxiety and, as Schedule IV drugs, are judged by the US government to have low abuse liability (Table 32–1). Short-acting barbiturates (eg, secobarbital) have high addiction potential. Ethanol is not listed in schedules of controlled substances with abuse liability.

A. Effects

Sedative-hypnotics reduce inhibitions, suppress anxiety, and produce relaxation. All of these actions are thought to encourage repetitive use. Although the primary actions of sedative-hypnotics involve facilitation of the effects of GABA and/or antagonism at ACh-N receptors, these drugs also enhance brain dopaminergic pathways, the latter action possibly related to the development of addiction. The drugs are CNS depressants, and their depressant effects are enhanced by concomitant use of opioid analgesics, antipsychotic agents, marijuana, and any other drug with sedative properties. Acute overdoses commonly result in death through depression of the medullary respiratory and cardiovascular centers (Table 32–2). Management of overdose includes maintenance of a patent airway plus ventilatory support. Flumazenil can be used to reverse the CNS depressant effects of benzodiazepines, but there is no antidote for barbiturates or ethanol.

Flunitrazepam (Rohypnol), a potent rapid-onset benzodiazepine with marked amnestic properties, has been used in "date rape." Added to alcoholic beverages, **chloral hydrate** or **γ-hydroxybutyrate** (GHB; sodium oxybate) also render the victim incapable of resisting rape. The latter compound, a minor metabolite of GABA, binds to $GABA_B$ receptors in the CNS. When used as a "club drug," GHB causes euphoria, enhanced sensory perception, and amnesia.

B. Withdrawal

Physiologic dependence occurs with continued use of sedative-hypnotics; the signs and symptoms of the withdrawal (abstinence) syndrome are most pronounced with drugs that have a half-life of less than 24 h (eg, ethanol, secobarbital, methaqualone). However, physiologic dependence may occur with any sedative-hypnotic, including the longer acting benzodiazepines. The most important signs of withdrawal derive from excessive *CNS stimulation* and include anxiety, tremor, nausea and vomiting, delirium, and hallucinations (Table 32–2). **Seizures** are not uncommon and may be life-threatening.

Treatment of sedative-hypnotic withdrawal involves administration of a long acting sedative-hypnotic (eg, chlordiazepoxide or diazepam) to suppress the acute withdrawal syndrome, followed by gradual dose reduction. Clonidine or propranolol may also be of value to suppress sympathetic overactivity. The opioid receptor antagonist **naltrexone,** and **acamprosate,** an antagonist at *N*-methyl-D-aspartate (NMDA) glutamate receptors, are both used in the treatment of alcoholism (see Chapter 23).

A syndrome of **therapeutic withdrawal** has occurred on discontinuance of sedative-hypnotics after long-term therapeutic administration. In addition to the symptoms of classic withdrawal presented in Table 32–2, this syndrome includes weight loss, paresthesias, and headache. (See Chapters 22 and 23 for additional details.)

High-Yield Terms to Learn

Abstinence syndrome	A term used to describe the signs and symptoms that occur on withdrawal of a drug in a dependent person
Addiction	Compulsive drug-using behavior in which the person uses the drug for personal satisfaction, often in the face of known risks to health; formerly termed psychological dependence
Controlled substance	A drug deemed to have abuse liability that is listed on governmental Schedules of Controlled Substances.[a] Such schedules categorize illicit drugs, control prescribing practices, and mandate penalties for illegal possession, manufacture, and sale of listed drugs. Controlled substance schedules are presumed to reflect current attitudes toward substance abuse; therefore, which drugs are regulated depends on a social judgment
Dependence	A state characterized by signs and symptoms, frequently the opposite of those caused by a drug, when it is withdrawn from chronic use or when the dose is abruptly lowered; formerly termed physical or physiologic dependence
Designer drug	A synthetic derivative of a drug, with slightly modified structure but no major change in pharmacodynamic action. Circumvention of the Schedules of Controlled Drugs is a motivation for the illicit synthesis of designer drugs
Tolerance	A decreased response to a drug, necessitating larger doses to achieve the same effect. This can result from increased disposition of the drug (metabolic tolerance), an ability to compensate for the effects of a drug (behavioral tolerance), or changes in receptor or effector systems involved in drug actions (functional tolerance)

[a]An example of such a schedule promulgated by the US Drug Enforcement Agency is shown in Table 32–1. Note that the criteria given by the agency do not always reflect the actual pharmacologic properties of the drugs.

TABLE 32–1 Schedules of controlled drugs.[a]

Schedule	Criteria	Examples
I	No medical use; high addiction potential	Flunitrazepam, heroin, LSD, mescaline, PCP, MDA, MDMA, STP
II	Medical use; high addiction potential barbiturates; strong opioids	Amphetamines, cocaine, methylphenidate, short acting
III	Medical use; moderate abuse potential moderate opioid agonists	Anabolic steroids, barbiturates, dronabinol, ketamine,
IV	Medical use; low abuse potential	Benzodiazepines, chloral hydrate, mild stimulants (eg, phentermine, sibutramine), most hypnotics (eg, zaleplon, zolpidem), weak opioids

[a]Adapted, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 11th ed, McGraw-Hill, 2009.

LSD, lysergic acid diethylamide; MDA, methylene dioxyamphetamine; MDMA, methylene dioxymethamphetamine; PCP, phencyclidine; STP (DOM), 2,5-dimethoxy-4-methylamphetamine.

TABLE 32–2 Signs and symptoms of overdose and withdrawal from selected drugs of abuse.

Drug	Overdose Effects	Withdrawal Symptoms
Amphetamines, methylphenidate, cocaine[a]	Agitation, hypertension, tachycardia, delusions, hallucinations, hyperthermia, seizures, death	Apathy, irritability, increased sleep time, disorientation, depression
Barbiturates, benzodiazepines, ethanol[b]	Slurred speech, "drunken" behavior, dilated pupils, weak and rapid pulse, clammy skin, shallow respiration, coma, death	Anxiety, insomnia, delirium, tremors, seizures, death
Heroin, other strong opioids	Constricted pupils, clammy skin, nausea, drowsiness, respiratory depression, coma, death	Nausea, chills, cramps, lacrimation, rhinorrhea, yawning, hyperpnea, tremor

[a]Cardiac arrhythmias, myocardial infarction, and stroke occur more frequently in cocaine overdose.

[b]Ethanol withdrawal includes the excited hallucinatory state of delirium tremens.

...ID ANALGESICS

...effects

...ussed in Chapter 31, the primary targets underlying the ...ne of the opioid analgesics are the μ, κ, and δ receptors. ...ome the opioids have other actions including disinhibition ...rgic pathways in the CNS. The most commonly ...se drugs in this group are **heroin, morphine, codeine,** ...adone, and among health professionals, **meperidine** and ...ntanyl. The effects of intravenous heroin are described by abus... ...a "rush" or orgasmic feeling followed by euphoria and then ...ation. Intravenous administration of opioids is associated with ...development of tolerance and psychological and physiologic ...endence. Oral administration or smoking of opioids causes ...ilar effects, with a slower onset of tolerance and dependence. ...erdose of opioids leads to respiratory depression progressing to ...sis and death (Table 32–2). Overdose is managed with intrave... ...ous naloxone or nalmefene and ventilatory support.

...Withdrawal

...ithdrawal of opioids in physiologically dependent individuals ...ads to an abstinence syndrome that includes lacrimation, rhinor... ...ea, yawning, sweating, weakness, gooseflesh ("cold turkey"), ...sea and vomiting, tremor, muscle jerks ("kicking the habit"), ...or hyperpnea (Table 32–2). Although extremely unpleasant, ...ithdrawal from opioids is rarely fatal (unlike withdrawal from ...ative-hypnotics). Treatment involves replacement of the illicit ...g with a pharmacologically equivalent agent (eg, **methadone**), ...lowed by slow dose reduction. **Buprenorphine,** a partial agonist ...t opioid receptors and a longer acting opioid (half-life >40 h), ...s also used to suppress withdrawal symptoms and as substitution ...apy for opioid addicts. The administration of naloxone to a ...rson who is using strong opioids (but not overdosing) may cause ...re rapid and more intense symptoms of withdrawal (precipitated ...ithdrawal). Neonates born to mothers physiologically dependent ...n opioids require special management of withdrawal symptoms.

STIMULANTS

A. Caffeine and Nicotine

1. Effects—Caffeine (in beverages) and nicotine (in tobacco products) are legal in most Western cultures even though they have adverse medical effects. In the United States, cigarette smoking is a major preventable cause of death; tobacco use is associated with a high incidence of cardiovascular, respiratory, and neoplastic disease. Addiction (psychological dependence) to caffeine and nicotine has been recognized for some time. More recently, demonstration of abstinence signs and symptoms has provided evidence of dependence.

...ithdrawal—Withdrawal from caffeine is accompanied ...argy, irritability, and headache. The anxiety and mental ...ort experienced from discontinuing nicotine are major impediments to quitting the habit. **Varenicline,** a partial agonist at the ACh-N($\alpha_2\beta_2$) subtype nicotinic receptors, which occludes the rewarding effects of nicotine, is used for smoking cessation. **Rimonabant,** an agonist at cannabinoid receptors, approved for use in obesity, is also used off-label in smoking cessation.

3. Toxicity—Acute toxicity from overdosage of caffeine or nicotine includes excessive CNS stimulation with tremor, insomnia, and nervousness; cardiac stimulation and arrhythmias; and, in the case of nicotine, respiratory paralysis (Chapters 6 and 7). Severe toxicity has been reported in small children who ingest discarded nicotine gum or nicotine patches, which are used as substitutes for tobacco products.

B. Amphetamines

1. Effects—Amphetamines inhibit transporters of CNS amines including dopamine, norepinephrine, and serotonin, thus enhancing their actions. They cause a feeling of euphoria and self-confidence that contributes to the rapid development of addiction. Drugs in this class include **dextroamphetamine** and **methamphetamine** ("speed"), a crystal form of which ("ice") can be smoked. Chronic high-dose abuse leads to a psychotic state (with delusions and paranoia) that is difficult to differentiate from schizophrenia. Symptoms of overdose include agitation, restlessness, tachycardia, hyperthermia, hyperreflexia, and possibly seizures (Table 32–2). There is no specific antidote, and supportive measures are directed toward control of body temperature and protection against cardiac arrhythmias and seizures. Chronic abuse of amphetamines is associated with the development of necrotizing arteritis, leading to cerebral hemorrhage and renal failure.

2. Tolerance and withdrawal—Tolerance can be marked, and an abstinence syndrome, characterized by increased appetite, sleepiness, exhaustion, and mental depression, can occur on withdrawal. Antidepressant drugs may be indicated.

3. Congeners of amphetamines—Several chemical congeners of amphetamines have hallucinogenic properties. These include 2,5-dimethoxy-4-methylamphetamine (**DOM [STP]**), methylene dioxyamphetamine (**MDA**), and methylene dioxymethamphetamine (**MDMA; "ecstasy"**). MDMA has a more selective action than amphetamine on the serotonin transporter in the CNS. The drug is purported to facilitate interpersonal communication and act as a sexual enhancer. Positron emission tomography studies of the brains of regular users of MDMA show a depletion of neurons in serotonergic tracts. Overdose toxicity includes hyperthermia, symptoms of the serotonin syndrome (see Chapter 30), and seizures. A withdrawal syndrome with protracted depression has been described in chronic users of MDMA.

C. Cocaine

1. Effects—Cocaine, also an inhibitor of the CNS transporters of dopamine, norepinephrine, and serotonin, has marked amphetamine-like effects ("super-speed"). Its abuse continues to

be widespread in the United States partly because of the availability of a free-base form ("crack") that can be smoked. The euphoria, self-confidence, and mental alertness produced by cocaine are short-lasting and positively reinforce its continued use.

Overdoses with cocaine commonly result in fatalities from arrhythmias, seizures, or respiratory depression (see Table 32–2). Cardiac toxicity is partly due to blockade of norepinephrine reuptake by cocaine; its local anesthetic action contributes to the production of seizures. In addition, the powerful vasoconstrictive action of cocaine may lead to severe hypertensive episodes, resulting in myocardial infarcts and strokes. No specific antidote is available. Cocaine abuse during pregnancy is associated with increased fetal morbidity and mortality.

2. Withdrawal—The abstinence syndrome after withdrawal from cocaine is similar to that after amphetamine discontinuance. Severe depression of mood is common and strongly reinforces the compulsion to use the drug. Antidepressant drugs may be indicated. Infants born to mothers who abuse cocaine (or amphetamines) have possible teratogenic abnormalities (cystic cortical lesions) and increased morbidity and mortality and may be cocaine dependent. The signs and symptoms of CNS stimulant overdose and withdrawal are listed in Table 32–2.

HALLUCINOGENS

A. Phencyclidine

The arylcyclohexylamine drugs include **phencyclidine** (PCP; "angel dust") and ketamine ("special K"), which are antagonists at the glutamate NMDA receptor (Chapter 21). Unlike most drugs of abuse, they have no actions on dopaminergic neurons in the CNS. PCP is probably the most dangerous of the hallucinogenic agents. Psychotic reactions are common with PCP, and impaired judgment often leads to reckless behavior. This drug should be classified as a **psychotomimetic.** Effects of overdosage with PCP include both horizontal and vertical nystagmus, marked hypertension, and seizures, which may be fatal. Parenteral benzodiazepines (eg, diazepam, lorazepam) are used to curb excitation and protect against seizures.

B. Miscellaneous Hallucinogenic Agents

Several drugs with hallucinogenic effects have been classified as having abuse liability, including **lysergic acid diethylamide** (LSD), **mescaline,** and **psilocybin.** Hallucinogenic effects may also occur with scopolamine and other antimuscarinic agents. None of these drugs has actions on dopaminergic pathways in the CNS, and interestingly, they do not cause dependence. Terms that have been used to describe the CNS effects of such drugs include "psychedelic" and "mind revealing." The perceptual and psychological effects of such drugs are usually accompanied by marked somatic effects, particularly nausea, weakness, and paresthesias. Panic reactions ("bad trips") may also occur.

MARIJUANA

A. Classification

Marijuana ("grass") is a collective term for the preparations and extracts of the plant *Cannabis sativa* L. and its active principles of which include the cannabinoid compounds **tetrahydrocannabinol** (THC), cannabidiol (CBD), and cannabinol (CBN). **Hashish** is a partially purified material that is more potent.

B. Cannabinoids

Endogenous cannabinoids in the CNS, which include anandamide and 2-arachidonyl glycerol, are released postsynaptically and act as retrograde messengers to inhibit presynaptic release of neurotransmitters including dopamine. The receptors for these compounds are thought to be the "targets" for exogenous cannabinoids present in marijuana.

C. Effects

CNS effects of marijuana include a feeling of being "high," euphoria, disinhibition, uncontrollable laughter, change in perception, and achievement of a dream-like state. Mental concentration may be difficult. Vasodilation occurs, and the pulse rate is characteristically increased. Habitual users show a redness of conjunctiva. A mild withdrawal state has been noted in some long-term heavy users of marijuana. The dangers of marijuana use concern its impairment of judgment and reflexes; effects that are potentiated by concomitant use of sedative-hypnotics, including ethanol. Potential therapeutic effects of marijuana include its ability to decrease intraocular pressure and its antiemetic action. **Dronabinol** (a controlled-substance formulation of THC) is used to combat severe nausea. **Rimonabant,** an agonist at cannabinoid receptors, is approved for use in the treatment of obesity.

INHALANTS

Certain gases or volatile liquids are abused because they produce a feeling of euphoria or disinhibition.

A. Anesthetics

This group includes nitrous oxide, chloroform, and halothane. Such agents are hazardous because they affect judgment and induce loss of consciousness. Inhalation of nitrous oxide as a pure gas (with no oxygen) has caused asphyxia and death. Ether is highly flammable.

B. Industrial Solvents

Solvents and a wide range of volatile compounds are present in commercial products such as gasoline, paint thinners, aerosol propellants, glues, rubber cements, and shoe polish. Because of easy availability, these substances are most frequently abused by children in early adolescence. Active ingredients that have been identified under