

Section	Psychiatric Disorders
Subject	Drug Use and Dependence

## Introduction

Among people who use drugs, some do so in large enough amounts often enough and long enough to become dependent. A single definition for drug dependence is elusive. Concepts that aid in defining drug dependence are tolerance and psychologic and physical dependence.

**Tolerance** describes the need to progressively increase the drug dose to produce the effect originally achieved with smaller doses.

**Psychologic dependence** includes feelings of satisfaction and a desire to repeat the drug experience or to avoid the discontent of not having it. This anticipation of effect is a powerful factor in the chronic use of psychoactive drugs and, with some drugs, may be the only obvious factor associated with intense craving and apparent compulsive use. Craving and compulsion to use a drug leads to its use in larger amounts or over a longer period than was intended when use began. Psychologic dependence involves giving up social, occupational, or recreational activities because of drug use and persistent use despite knowledge of having a physical or mental problem that is likely caused or exacerbated by using the drug. Drugs that cause psychologic dependence often have one or more of the following effects: reduced anxiety and tension; elation, euphoria, or other mood changes pleasurable to the user; feelings of increased mental and physical ability; altered sensory perception; and changes in behavior. Drugs that cause chiefly psychologic dependence include marijuana, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and hallucinogens, such as lysergic acid diethylamide (LSD), mescaline, and psilocybin.

**Physical dependence** is manifested by a withdrawal (abstinence) syndrome, in which untoward physical changes occur when the drug is stopped or when its effect is counteracted by a specific antagonist that displaces the agonist from its binding site on cell receptors. Drugs that cause strong physical dependence include heroin, alcohol, and cocaine.

**Addiction**, a concept without a consistent, universally accepted definition, is used in this chapter to refer to compulsive use and overwhelming involvement with a drug, including spending an increasing amount of time obtaining the drug, using the drug, or recovering from its effects; it may occur without physical dependence. Addiction implies the risk of harm and the need to stop drug use, regardless of whether the addict understands and agrees.

**Drug abuse** is definable only in terms of societal disapproval. It may involve experimental and recreational use of drugs, which is usually illegal; unsanctioned or illegal use of psychoactive drugs to relieve problems or symptoms; or use of drugs first for the previous 2 reasons but later because of dependence and the need to continue at least partially to prevent withdrawal. Illicit drug use, although considered abuse simply because it involves illegality, does not always involve dependence. Conversely, use of legal substances, such as alcohol, may involve dependence and abuse. Abuse of prescription and illegal drugs cuts across socioeconomic groups and includes people with advanced education and professional status.

**Recreational drug use** has increasingly become a part of Western culture, although in general, it is not sanctioned by society. Some users apparently are unharmed; they tend to use drugs episodically in relatively small doses, precluding clinical toxicity and development of tolerance and physical dependence. Many recreational drugs (eg, crude opium, alcohol, marijuana, caffeine, hallucinogenic mushrooms, coca leaf) are "natural," ie, close to plant origin; they contain a mixture of relatively low concentrations of psychoactive compounds and are not isolated psychoactive chemicals. Recreational drugs are most often taken orally or inhaled. Taking these drugs by injection makes it harder to predict and control desired and unwanted effects. Recreational use is often accompanied by ritualization, with a set of observed rules, and is seldom practiced alone. Most drugs used this way are psychostimulants or hallucinogens designed to induce a "high" or altered consciousness rather than to relieve mental distress; depressant drugs are difficult to use in this controlled way.

**Intoxication** refers to development of a reversible substance-specific syndrome of mental and behavioral changes that may involve cognitive impairment, impaired judgment, impaired physical and social functioning, mood lability, and belligerence.

In the US, the Comprehensive Drug Abuse Prevention and Control Act of 1970 and subsequent modifications require the pharmaceutical industry to maintain physical security and strict record keeping for certain of these classes.

Controlled substances are divided into 5 schedules (or classes) on the basis of their potential for abuse, accepted medical use, and accepted safety under medical supervision. Schedule I substances have a high potential for abuse, no accredited medical use, and a lack of accepted safety. Schedule V substances are least likely to be abused. The schedule classification determines how a substance must be controlled. Schedule I drugs can be used only under government-approved research conditions. Prescriptions for Schedule II to IV drugs must bear the physician's federal Drug Enforcement Administration (DEA) license number. Some drugs in Schedule V do not require a prescription. State schedules may vary from federal schedules.

### Etiology of Drug Dependence

Commonly used psychoactive drugs vary in their potential for creating dependence. Drug dependence develops in a manner both complex and unclear. The process is influenced by the properties of the psychoactive drugs; the user's predisposing physical characteristics (probably including genetic predisposition), personality, and socioeconomic class; and the cultural and social setting. The psychology of the user and the availability of the drug determine the choice of psychoactive drug and, at least initially, the pattern and frequency of use.

Progression from experimentation to occasional use and then to dependence is only partially understood. Factors leading to increased use and dependence or addiction may include peer or group pressure, emotional distress that is symptomatically relieved by specific drug effects, sadness, social alienation, and environmental stress (particularly if accompanied by feelings of impotence to effect change or to accomplish goals). Physicians may inadvertently contribute to harmful use of psychoactive drugs by overzealously prescribing them to patients under stress and may fall victim to manipulative patients. Many social factors and the mass media may contribute to the expectation that drugs can safely relieve distress or gratify needs. Stated simply, the outcome of drug use depends on interaction between the drug, the user, and the setting.

Few differences exist between the biochemical, drug dispositional, and physical responsiveness of people who become addicted or dependent and those who do not, although such differences have been vigorously sought. Exceptions exist, however; nonalcoholic relatives of alcoholics have a diminished physical response to alcohol. Because of their higher tolerance, they need to drink more to get the desired effect.

A neural substrate for reinforcement (the tendency to seek more drugs and other stimuli) has been identified in animal models. In these studies, self-administration of such drugs as opioids, cocaine, amphetamine, nicotine, and benzodiazepines (anxiolytics) is associated with enhanced dopaminergic transmission in specific midbrain and cortical circuits. This finding suggests the existence of a brain reward pathway involving dopamine in the mammalian brain. However, evidence that hallucinogens and cannabinoids activate this system is insufficient, and not everyone who experiences these "rewards" becomes dependent or addicted.

An addictive personality has been described variously by behavioral scientists, but little scientific evidence backs this claim. Some experts describe addicts as escapist, ie, people who cannot face reality and who run away. Others describe addicts as people with schizoid traits, such as fearfulness, withdrawal from others, feelings of depression, and a history of frequent suicide attempts and numerous self-inflicted injuries. Addicts have also been described as dependent and grasping in their relationships, frequently exhibiting overt, unconscious rage and immature sexuality. However, before people develop drug dependence, they generally do not exhibit the deviant, pleasure-oriented, irresponsible behavior usually attributed to addicts. Clinicians, patients, and the culture often perceive drug abuse within the context of a dysfunctional life or life episode yet blame the drug exclusively rather than place any blame on the addict's psychologic characteristics. Sometimes addicts justify drug use as a way to alleviate temporary anxiety or depression resulting from a crisis, job pressure, or a family catastrophe. Most addicts abuse alcohol along with other drugs, and they may have repeated hospital admissions for overdose, adverse reactions, or withdrawal problems.

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Alcohol

Excessive alcohol use can result in serious physical and mental problems. Chronic excessive use that involves a compulsion to drink, increased tolerance, and withdrawal symptoms is called alcohol dependence or, alternatively, alcoholism.

Alcohol abuse generally refers to a maladaptive pattern of episodic drinking resulting in failure to fulfill obligations, exposure to physically hazardous situations, legal problems, or social and interpersonal problems without evidence of dependence.

Alcohol dependence refers to frequent consumption of large amounts of alcohol over time, resulting in tolerance, psychologic dependence, and physical dependence and a dangerous withdrawal syndrome. Alcoholism is often used as an equivalent term for alcohol dependence, especially when drinking results in significant clinical toxicity and tissue damage.

About 2/3 of American adults drink alcohol. The male:female ratio is about 4:1. Lifetime prevalence of alcohol abuse and dependence combined is about 15%. (See also the US Preventive Services Task Force's recommendations on Screening for Alcohol Misuse.)

People who abuse or who are dependent on alcohol usually experience serious social consequences from their drinking. Frequent intoxication is obvious and destructive; it interferes with the ability to socialize and work. Eventually, drunkenness may lead to failed relationships as well as job loss due to absenteeism. People may be arrested for drunkenness or be apprehended for driving while intoxicated, adding to the social consequences they incur from their drinking. In the US, the legal blood alcohol concentration (BAC) while driving is  $\leq 80$  mg/dL (0.08%) in most states.

Female alcoholics are, in general, more likely to drink alone and are less likely to experience some of the social stigma. Alcoholics may seek medical treatment for their drinking. Eventually, they may be hospitalized for delirium tremens (DT) or cirrhosis. Injuries are common. The earlier in life these behaviors are evident, the more crippling the disorder.

**Etiology of Disorders**

Drinking to the point of becoming intoxicated or forming a maladaptive pattern of drinking that constitutes alcohol abuse begins with a desire to reach a state of feeling high. Some drinkers who find the feeling rewarding then focus on repeatedly reaching that state.

Certain personality traits are more common in those who abuse alcohol chronically or become dependent on alcohol: isolation, loneliness, shyness, depression, dependency, hostile and self-destructive impulsivity, and sexual immaturity. Alcoholics frequently come from a broken home and have a disturbed relationship with their parents. Societal factors—attitudes transmitted through the culture or child rearing—affect patterns of drinking and consequent behavior.

The incidence of alcoholism is higher in biologic children of alcoholics than in adoptive children, and the percentage of children of alcoholics who are problem drinkers is greater than that of the general population. Thus, in some populations and countries, prevalence is high. There is evidence of genetic or biochemical predisposition, including data that suggests some people who become alcoholics are less easily intoxicated, ie, they have a higher threshold for CNS effects.

**Symptoms and Signs**

**Acute use**

Alcohol is absorbed into the blood, principally from the small bowel. It accumulates in blood because absorption is more rapid than oxidation and elimination. About 5 to 10% of ingested alcohol is excreted unchanged in urine, sweat, and expired air; the remainder is oxidized to CO<sub>2</sub> and water at a rate of 5 to 10 mL/h (of absolute alcohol); each milliliter furnishes about 7 kcal. Alcohol chiefly depresses the CNS.

A BAC of 50 mg/dL produces sedation or tranquility; 50 to 150 mg/dL, lack of coordination; 150 to 200 mg/dL, delirium; and 300 to 400 mg/dL, unconsciousness. BAC > 400 mg/dL may be fatal. Sudden death from either respiratory depression or arrhythmias may occur when large quantities are drunk rapidly. This problem is emerging in US colleges but has been known in other countries in which the syndrome is more common.

**Chronic use**

People who drink large amounts of alcohol repetitively over time become tolerant to its effects, such that eventually, similar amounts have less of an intoxicating effect. Tolerance is caused by adaptational changes of CNS cells (cellular, or pharmacodynamic, tolerance). People who develop tolerance may reach an incredibly high BAC. However, ethanol tolerance is incomplete, and some degree of intoxication and impairment occurs with a high-enough dose. Even tolerant drinkers may die of respiratory depression secondary to alcohol overdose. Alcohol-

tolerant people are susceptible to alcoholic ketoacidosis (see [Diabetes Mellitus and Disorders of Carbohydrate Metabolism: Alcoholic Ketoacidosis](#)), especially during binge drinking. Alcohol-tolerant people are cross-tolerant to many other CNS depressants (eg, barbiturates, nonbarbiturate sedatives, benzodiazepines).

The physical dependence accompanying tolerance is profound, and withdrawal produces potentially fatal adverse effects. Alcoholism eventually leads to organ damage, most commonly hepatitis and cirrhosis (see [Alcoholic Liver Disease](#)); gastritis; pancreatitis; cardiomyopathy, often accompanied by arrhythmias; peripheral neuropathy (see [Peripheral Nervous System Disorders: Peripheral Neuropathy](#)); and brain damage (including Wernicke's encephalopathy [see [Drug Use and Dependence: Wernicke's Encephalopathy](#)], Korsakoff's psychosis [see [Drug Use and Dependence: Korsakoff's Psychosis](#)], Marchiafava-Bignami disease [see [Drug Use and Dependence: Marchiafava-Bignami Disease](#)] and alcoholic dementia).

A continuum of symptoms and signs accompanies alcohol withdrawal, usually beginning 12 to 48 h after cessation of intake. The mild withdrawal syndrome includes tremor, weakness, sweating, hyperreflexia, and GI symptoms. Some patients have generalized tonic-clonic seizures, but usually not more than 2 in short succession (alcoholic epilepsy, or rum fits).

Alcoholic hallucinosis follows abrupt abstinence from prolonged, excessive alcohol use. Symptoms include auditory illusions and hallucinations that frequently are accusatory and threatening; the patient is usually apprehensive and may be terrified by the hallucinations and by vivid, frightening dreams. The syndrome may resemble schizophrenia, although thought usually is not disordered and the history is not typical of schizophrenia. Symptoms do not resemble the delirious state of an acute organic brain syndrome as much as does DT or other pathologic reactions associated with withdrawal. Consciousness remains clear, and the signs of autonomic lability seen in DT are usually absent. When hallucinosis occurs, it generally precedes DT and is transient. Recovery usually occurs in 1 to 3 wk; recurrence is likely if the patient resumes drinking.

DT usually begins 48 to 72 h after alcohol withdrawal along with anxiety attacks, increasing confusion, poor sleep (accompanied by frightening dreams or nocturnal illusions), marked sweating, and profound depression. Fleeting hallucinations that arouse restlessness, fear, and even terror are common. Typical of the initial delirious, confused, and disoriented state is a return to a habitual activity; eg, the patient frequently imagines that he is back at work and attempts to perform some related activity. Autonomic lability, evidenced by diaphoresis and increased pulse rate and temperature, accompanies the delirium and progresses with it. Mild delirium is usually accompanied by marked diaphoresis, a pulse rate of 100 to 120 beats/min, and a temperature of 37.2 to 37.8° C. Marked delirium, with gross disorientation and cognitive disruption, is associated with significant restlessness, a pulse of > 120 beats/min, and a temperature of > 37.8° C.

During DT, the patient is suggestible to many sensory stimuli, particularly to objects seen in dim light. Vestibular disturbances may cause the patient to believe that the floor is moving, the walls are falling, or the room is rotating. As the delirium progresses, resting tremor of the hand develops, sometimes extending to the head and trunk. Ataxia is marked; care must be taken to prevent self-injury. Symptoms vary among patients but are usually the same for a particular patient with each recurrence.

#### **Treatment**

##### **Acute use**

When people drink to the point of intoxication, the 1st priority of treatment is to stop them from drinking any additional alcohol, which could lead to unconsciousness and death. The 2nd priority is to ensure their safety and the safety of others by preventing drinkers from operating a motor vehicle or any other mode of transportation or from engaging in any other activity that would create a high risk of death or injury while impaired by alcohol. Somnolent patients may become alert and combative as their BAC decreases.

##### **Chronic use**

Medical evaluation is needed initially to detect intercurrent illness that might complicate withdrawal and to rule out CNS injury that might mimic or be masked by the withdrawal syndrome. Withdrawal symptoms must be identified and treated. Steps must be taken to prevent Wernicke-Korsakoff syndrome (see [Drug Use and Dependence: Diagnosis, Prognosis, and Treatment](#)).

Some drugs commonly used to treat withdrawal resemble alcohol in their pharmacologic effects. All patients entering withdrawal are candidates for CNS depressants, but not all need them. Many patients can be detoxified without drugs if proper attention is paid to psychologic support and reassurance and if the approach and environment are nonthreatening. However, these methods may not be possible in general hospitals or emergency departments.

Benzodiazepines are the mainstay of therapy. Dosage depends on vital signs and mental status. In most situations, chlordiazepoxide, initially 50 to 100 mg po, is recommended; doses may need to be repeated q 2 to 4 h. Diazepam, given 5 to 10 mg IV or po hourly until sedation occurs, is a useful alternative. Compared with short-acting benzodiazepines (lorazepam, oxazepam), long-acting benzodiazepines (eg, chlordiazepoxide, diazepam) provide less frequent dosing and, when the dose is tapered, a smoother decrease in serum levels. For significant liver disease, a short-acting benzodiazepine (lorazepam) or one metabolized by glucuronidation (oxazepam) is preferred. (Note: Benzodiazepines may cause intoxication, physical dependence, and withdrawal in alcoholics and therefore should not be continued after the detoxification period. Carbamazepine 200 mg po qid may be used as an alternative and then tapered.)

Isolated seizures need no specific therapy; repeated seizures respond to diazepam 1 to 3 mg IV. Routine administration of phenytoin is unnecessary. Outpatient therapy with phenytoin is almost always a waste of time and drug, because seizures occur only under the stress of alcohol withdrawal, and patients who are withdrawing or heavily drinking do not take their anticonvulsants.

Although DT may begin to resolve within 24 h, it may be fatal and thus must be treated promptly. Patients with DT are extremely suggestible and respond well to reassurance. They generally should not be restrained. Fluid balance must be maintained, and large doses of B and C vitamins, particularly thiamin, must be given promptly. Appreciably

elevated temperature with DT is a poor prognostic sign. If improvement is not marked within 24 h, other disorders, such as subdural hematoma, a hepatic or renal disorder, or other mental disturbances, should be suspected.

### **Maintenance**

Maintaining sobriety is difficult. The patient should be warned that after a few weeks, when he has recovered from his last bout, he is likely to find an excuse to drink. He should also be told that he may be able to practice controlled drinking for a few days or, rarely, a few weeks, but he will most likely lose control eventually.

A rehabilitation program is often the best approach. Most inpatient rehabilitation programs last 3 to 4 wk and are conducted in a center that does not permit leaving for the duration of the course of treatment. Rehabilitation programs combine medical supervision and psychotherapy, including one-on-one and group therapy. Psychotherapy involves techniques that enhance motivation and teach patients to avoid circumstances that precipitate drinking. Social support of abstinence is important, including the support of family and friends.

Alcoholics Anonymous (AA) has benefited alcoholics more than any other approach. The patient must find an AA group in which he is comfortable. AA provides the patient with nondrinking friends who are always available and a nondrinking environment in which to socialize. The patient also hears others confess before the group every rationalization he has ever used for his own drinking. The help he gives other alcoholics may give him the self-regard and confidence formerly found only in alcohol. In the US, unlike in other countries, AA groups include a high proportion of nonvoluntary enrollees whose attendance is mandated by court or probation officer order. Many alcoholics are reluctant to go to AA and find individual counseling or group or family treatment more acceptable. Alternative organizations, such as LifeRing Recovery (Secular Organizations for Sobriety), exist for those seeking a more secular approach.

Drug therapy should be used in combination with psychotherapy. Disulfiram interferes with the metabolism of acetaldehyde (an intermediary product in the oxidation of alcohol) so that acetaldehyde accumulates. Drinking alcohol within 12 h of taking disulfiram produces facial flushing in 5 to 15 min, then intense vasodilation of the face and neck with suffusion of the conjunctivae, throbbing headache, tachycardia, hyperpnea, and sweating. With high doses of alcohol, nausea and vomiting may follow in 30 to 60 min and may lead to hypotension, dizziness, and sometimes fainting and collapse. The reaction can last up to 3 h. Few patients risk ingesting alcohol while taking disulfiram because of the intense discomfort. Drugs that contain alcohol (eg, tinctures; elixirs; some OTC liquid cough/cold preparations, which contain as much as 40% alcohol) must also be avoided. Disulfiram is contraindicated during pregnancy and in patients with cardiac decompensation. It may be given on an outpatient basis after 4 or 5 days of abstinence. The initial dosage is 0.5 g po once/day for 1 to 3 wk, followed by a maintenance dosage of 0.25 g once/day. Effects may persist for 3 to 7 days after the last dose. Periodic physician visits are needed to encourage continuation of disulfiram as part of an abstinence program. Disulfiram's general usefulness has not been established, and many patients are noncompliant. Compliance usually requires adequate social support, such as observation of ingestion.

Naltrexone, an opioid antagonist (see [Drug Use and Dependence: Maintenance](#)), decreases the relapse rate in most patients who take it consistently. Naltrexone is given as 50 mg po once/day. It is unlikely to be useful without supportive counseling. Acamprostate, a synthetic analogue of gamma-aminobutyric acid, is given as 2 g po once/day. Acamprostate decreases the relapse rate and drinking days in patients who relapse; like naltrexone, it works best when combined with counseling. Nalmefene and topiramate are under investigation for their ability to decrease alcohol craving.

### **Wernicke's Encephalopathy**

Wernicke's encephalopathy is a disorder characterized by acute onset of confusion, nystagmus, partial ophthalmoplegia, and ataxia due to thiamin deficiency. Diagnosis is primarily clinical. The disorder may remit with treatment, persist, or degenerate into Korsakoff's psychosis. Treatment consists of thiamin and supportive measures. Wernicke's encephalopathy results from inadequate intake or absorption of thiamin plus continued carbohydrate ingestion. Severe alcoholism is a common underlying condition. Excessive alcohol intake interferes with thiamin absorption from the GI tract and hepatic storage of thiamin; the poor nutrition associated with alcoholism often precludes adequate thiamin intake. Wernicke's encephalopathy may also result from other conditions that cause prolonged undernutrition or vitamin deficiency (eg, recurrent dialysis, hyperemesis, starvation, gastric plication, cancer, AIDS). Loading carbohydrates in patients with thiamin deficiency (ie, refeeding after starvation or giving IV dextrose-containing solutions to high-risk patients) can trigger Wernicke's encephalopathy.

Not all thiamin-deficient alcohol abusers develop Wernicke's encephalopathy, suggesting that other factors may be involved. Genetic abnormalities that result in a defective form of transketolase, an enzyme that processes thiamin, may be involved.

Characteristically, lesions are symmetrically distributed around the 3rd ventricle, aqueduct, and 4th ventricle. Changes in the mamillary bodies, dorsomedial thalamus, locus ceruleus, periaqueductal gray matter, ocular motor nuclei, and vestibular nuclei are common.

### **Symptoms and Signs**

Clinical changes occur acutely. Oculomotor abnormalities, including horizontal and vertical nystagmus and partial ophthalmoplegias (eg, lateral rectus palsy, conjugate gaze palsies), are common. Pupils may be abnormal; they are usually sluggish or unequal.

Vestibular dysfunction without hearing loss is common, and the oculovestibular reflex may be impaired. Gait ataxia may result from vestibular disturbances and cerebellar dysfunction, gait is wide-based and slow, with short-spaced steps.

Global confusion is often present, characterized by profound disorientation, indifference, inattention, drowsiness, or stupor. Peripheral nerve pain thresholds are often elevated, and many patients develop severe autonomic dysfunction characterized by sympathetic hyperactivity (eg, tremor, agitation) or hypoactivity (eg, hypothermia, postural hypotension, syncope). In untreated patients, stupor may progress to coma, then to death.

### **Diagnosis, Prognosis, and Treatment**

Diagnosis is clinical and depends on recognition of underlying undernutrition or vitamin deficiency. There are no characteristic abnormalities in CSF, evoked potentials, brain imaging, or EEG. However, these tests, as well as laboratory tests (eg, blood tests, glucose, CBC, liver function tests, arterial blood gas measurements, toxicology screening), should be done to rule out other etiologies.

Prognosis depends on timely diagnosis. If begun in time, treatment may correct all abnormalities. Ocular symptoms usually begin to abate within 24 h after early thiamin administration. Ataxia and confusion may persist days to months. Untreated, the disorder progresses; mortality is 10 to 20%. Of surviving patients, 80% develop Korsakoff psychosis (the combination is called Wernicke-Korsakoff syndrome).

Treatment consists of immediate administration of thiamin 100 mg IV or IM, continued daily for at least 3 to 5 days. Mg is a necessary cofactor in thiamin-dependent metabolism, and hypomagnesemia should be corrected using Mg sulfate 1 to 2 g IM or IV q 6 to 8 h or Mg oxide 400 to 800 mg po once/day. Supportive treatment includes rehydration, correction of electrolyte abnormalities, and general nutritional therapy, including multivitamins. Patients with advanced disease require hospitalization. Alcoholism cessation is mandatory.

Because Wernicke's encephalopathy is preventable, all malnourished patients should be treated with parenteral thiamin (typically 100 mg IM followed by 50 mg po daily) plus vitamin B<sub>12</sub> and folate (both 1 mg/day po), particularly if IV dextrose is necessary. Thiamin is also prudent before any treatment is begun in patients who present with a reduced level of consciousness. Patients who are malnourished should continue to receive thiamin as outpatients.

#### **Korsakoff's Psychosis**

Korsakoff's psychosis is a late complication of persistent Wernicke's encephalopathy that results in memory deficits, confusion, and behavioral changes.

Korsakoff's psychosis (Korsakoff's amnesic syndrome) occurs in 80% of untreated patients with Wernicke's encephalopathy. A severe or repeated attack of postalcoholic delirium tremens can trigger Korsakoff's psychosis whether or not a typical attack of Wernicke's encephalopathy has occurred first. Other triggers include subarachnoid hemorrhage, thalamic hemorrhage, thalamic ischemic stroke, and, infrequently, tumors affecting the paramedian posterior thalamic region. Why Korsakoff's psychosis develops in only some patients with Wernicke's encephalopathy is unclear.

#### **Symptoms and Signs**

Immediate memory is severely affected; retrograde and anterograde amnesia occurs in varying degrees. Patients tend to draw on memory of remote events, which appears to be less affected than memory of recent events. Disorientation to time is common. Emotional changes are common; they include apathy, blandness, or mild euphoria with little or no response to events, even frightening ones. Spontaneity and initiative may be decreased. Confabulation is often a striking early feature; bewildered patients unconsciously fabricate imaginary or confused accounts of events they cannot recall; these fabrications may be so convincing that the underlying disorder is not detected.

#### **Prognosis and Treatment**

Prognosis is fairly good for patients with head injury, subarachnoid hemorrhage, or both; the amnesia is transient. Prognosis is poor when the cause is thiamin deficiency or infarct; prolonged institutional care is required for about 25% of patients, and only about 20% recover completely. However, they may improve up to 12 to 24 mo after onset, and patients should not be prematurely institutionalized. Treatment consists of thiamin and adequate hydration.

#### **Marchiafava-Bignami Disease**

Marchiafava-Bignami disease is a rare demyelination of the corpus callosum that occurs in chronic alcoholics, predominantly men.

The pathology and circumstances link this disorder to osmotic demyelination syndrome (previously called central pontine myelinolysis), of which it may be a variant (see [Fluid and Electrolyte Metabolism: Osmotic demyelination syndrome](#)). In Marchiafava-Bignami disease, agitation and confusion occur with progressive dementia and frontal release signs. Some patients recover over several months; others experience seizures and coma, which may precede death.

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## Amphetamines

Amphetamines can be taken as pills, injected, snorted, or smoked. Amphetamines can cause elevated mood; increased wakefulness, alertness, concentration, and intensified physical performance; and a feeling of well-being. Prolonged use can cause dependence.

Among the drugs classified as amphetamines are amphetamine and methamphetamine (commonly known as ice, crystal, crystal meth, speed, crank, or glass).

Methamphetamine, sometimes used medically (for attention-deficit hyperactivity disorder, obesity, and narcolepsy), is easily manufactured illicitly, and its use has become widespread in Holland, Great Britain, and North America. Illicit use of methamphetamine is the chief type of amphetamine abuse in North America.

### Symptoms and Signs

#### **Acute use**

The psychologic effects of using amphetamines are similar to those produced by cocaine and include alertness, euphoria, and feelings of competence and power. Amphetamines typically cause erectile dysfunction in men but enhance sexual desire. Use is associated with unsafe sex practices, and users are at higher risk of sexually transmitted infections, including HIV infection.

#### **Chronic use**

Repeated use of amphetamines has been shown to cause death of large numbers of brain cells. Repeated use also induces dependence. Tolerance develops slowly, but amounts several hundred-fold greater than the amount originally used may eventually be ingested or injected. Tolerance to various effects develops unequally, so that tachycardia and enhanced alertness diminish, but hallucinations and delusions may occur. However, even massive doses are rarely fatal. Long-term users have reportedly injected as much as 15,000 mg of amphetamine in 24 h without observable acute illness.

Amphetamine abusers are prone to accidents, because the drug produces excitation and grandiosity followed by excess fatigue and sleeplessness. Taken IV, amphetamine may lead to serious antisocial behavior and can precipitate a schizophrenic episode.

A paranoid psychosis may result from long-term use of high IV or oral doses. Rarely, the psychosis is precipitated by a single high dose or by repeated moderate doses. Typical features include delusions of persecution, ideas of reference, and feelings of omnipotence. People who use high IV doses usually accept that they will eventually experience paranoia and often do not act on it. Nevertheless, with very intense drug use or near the end of weeks of use, awareness may fail and the user may respond to the delusions. Recovery from even prolonged amphetamine psychosis is usual. Thoroughly disorganized and paranoid users recover slowly but completely. The more florid symptoms fade within a few days or weeks, but some confusion, memory loss, and delusional ideas commonly persist for months.

An exhaustion syndrome occurs with repeated use of methamphetamine, involving intense fatigue and need for sleep after the stimulation phase. Methamphetamine can also produce a psychosis in which the person misinterprets others' actions, hallucinates, and becomes unrealistically suspicious. Some users experience a prolonged depression, during which suicide is possible. Methamphetamine use has also led to deaths attributed to severe dehydration, disseminated intravascular coagulation, and renal failure. Users have a high rate of severe tooth decay affecting multiple teeth; causes involve decreased salivation, acidic combustion products, and poor oral hygiene. Although no stereotypical withdrawal syndrome occurs upon stopping methamphetamine or other amphetamines, EEG changes occur, considered by some to fulfill the physical criteria for dependence. Abruptly stopping use may uncover underlying depression or precipitate a serious depressive reaction. Withdrawal is often followed by 2 or 3 days of intense fatigue or sleepiness and depression.

### Treatment

#### **Acute use**

People in the acute agitated psychotic state, with paranoid delusions and auditory and visual hallucinations, respond well to phenothiazines; chlorpromazine 25 to 50 mg IM rapidly reverses this state but may produce severe postural hypotension. Haloperidol 2.5 to 5 mg IM is effective; it rarely produces hypotension but may produce an alarming acute extrapyramidal motor reaction. Usually, reassurance and a quiet, nonthreatening environment are conducive to recovery and are often all that is needed. Ammonium chloride 1 g po q 2 to 4 h to acidify the urine hastens amphetamine excretion.

#### **Chronic use**

Cognitive-behavioral therapy (a form of psychotherapy) is effective in some patients. Depression sometimes occurs when amphetamines are stopped and may respond to antidepressants if depressive symptoms persist for weeks.



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Anabolic Steroids

Anabolic steroids are used to enhance physical performance and muscle growth. When used chronically at high doses and without medical supervision, they can cause erratic and irrational behavior and a wide range of physical adverse effects.

Anabolic steroids include testosterone and any drugs chemically and pharmacologically related to testosterone that promote muscle growth. Anabolic steroids have androgenic effects (eg, changes in hair or in libido, aggressiveness) and anabolic effects (eg, increased protein utilization, muscle mass changes). The androgenic effects cannot be separated from the anabolic, but some anabolic steroids have been synthesized to minimize the androgenic effects. Testosterone is rapidly degraded by the liver; oral testosterone is inactivated too rapidly to be effective, and injectable testosterone must be modified (eg, by esterification) to retard absorption or delay breakdown. Analogs modified by 17- $\alpha$ -alkylation are often effective orally but may have increased adverse effects. Transdermal preparations also are available.

Adverse effects vary significantly by dose and drug. There are few adverse effects at physiologic replacement doses (eg, methyltestosterone 10 to 50 mg/day or its equivalent). Athletes may use doses of 10 to 50 times this range. At high doses, some effects are clear, whereas others are equivocal (see [Table 1: Drug Use and Dependence: Adverse Effects of Anabolic Steroids](#)). Uncertainties exist because most studies involve abusers who may not report doses accurately and who also use black market drugs, many of which are counterfeit and contain (despite labeling) varying doses and substances.

Anabolic steroids are used clinically to treat low testosterone levels (see [Male Reproductive Endocrinology: Male Hypogonadism](#)). Additionally, because anabolic steroids are anticatabolic and improve protein utilization, they are sometimes given to burn, bedridden, or other debilitated patients to prevent muscle wasting. Some physicians prescribe them to patients with AIDS-related wasting and to those with cancer. There are few data, however, to recommend such therapy and little guidance on how supplemental androgens may affect underlying diseases. Testosterone has been reputed to benefit wound healing and muscle injury, although there are no data to support these claims.

Anabolic steroids are abused to increase lean muscle mass and strength; these effects are enhanced when combined with resistance training and proper diet. There is no direct evidence that anabolic steroids increase endurance or speed, but substantial anecdotal evidence suggests that athletes taking them can perform more frequent high-intensity workouts. Muscle hypertrophy is unequivocal.

Estimates of lifetime incidence of anabolic steroid abuse range from 0.5 to 5% of the population, but subpopulations vary significantly (eg, higher rates in bodybuilders and competitive athletes). In the US, the reported rate of use is 6 to 11% among high school-aged males, including an unexpected number of nonathletes, and about 2.5% among high school-aged females.

Athletes may take steroids for a certain period, stop, then start again (cycling) several times a year. Intermittent discontinuation of the drugs is believed to allow endogenous testosterone levels, sperm count, and the hypothalamic-pituitary-gonadal axis to return to normal. Anecdotal evidence suggests that cycling may decrease harmful effects and the need for increasing drug doses to attain the desired effect. Athletes frequently use many drugs simultaneously (a practice called stacking) and alternate routes of administration (oral,

**Table 1**

<b>Adverse Effects of Anabolic Steroids</b>
<b>Clearly demonstrated</b>
Erythrocytosis
Abnormal lipid profile (decreased HDL, increased LDL)
Liver abnormalities: * peliosis hepatitis, adenoma
Mood disorders (with high dose)
Androgenic effects: acne, baldness, virilization and hirsutism in females
Gonadal suppression (decreased sperm count, testicular atrophy)
Gynecomastia
Premature closure of epiphyses
<b>Equivocal</b>
Hypertension/LVH
Worsening of prostatic hypertrophy or preexisting carcinoma
Hepatic carcinoma
<b>Poorly shown</b>
Increased risk of sudden death in athletes
Significant mood disorder with low dose

IM, or transdermal). Increasing the dose through a cycle (pyramiding) may result in doses 5 to 100 times the physiologic dose. Stacking and pyramiding are intended to increase receptor binding and minimize adverse effects, but these benefits have not been proved.

#### **Symptoms and Signs**

The most characteristic sign is a rapid increase in muscle bulk. The rate and extent of increase is directly related to the doses taken. Patients taking physiologic doses will have slow and often unnoticeable growth; those taking mega-doses may increase lean body weight at several pounds/mo. Increases in energy level and libido (in men) occur but are more difficult to identify.

Psychologic effects (generally only with very high doses) are often noticed by the family: wide and erratic mood swings, irrational behavior, increased aggressiveness ("roid rage"), irritability, increased libido, and depression. Increased acne and gynecomastia are common complaints, as are virilizing effects in females. Some of these effects (eg, alopecia, enlarged clitoris, hirsutism, deepened voice) may be irreversible. Additionally, breast size may decrease; vaginal mucosa may atrophy; menstruation may change or stop; libido may increase or, less commonly, decrease; and aggressiveness and appetite may increase.

#### **Diagnosis, Prevention, and Treatment**

A urine screen usually detects users of anabolic steroids. Metabolites of anabolic steroids can be detected in urine up to 6 mo (even longer for some types of anabolic steroids) after the drugs are stopped.

Physicians caring for adolescents and young adults should be alert to the signs of steroid abuse and educate patients about its risks. Education about anabolic steroids should start by the beginning of middle school.

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HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVH = left ventricular hypertrophy.

\*Predominantly with 17 $\alpha$ -alkylated agents

Section	Psychiatric Disorders
Subject	Drug Use and Dependence

## Anxiolytics and Sedatives

Use of anxiolytics and sedatives (hypnotics) for medical purposes is common. Intoxication, with physical and mental impairment, can occur with acute use. Repetitive use can lead to abuse or dependence.

Tolerance and tachyphylaxis develop irregularly and incompletely, so considerable behavioral, mood, and cognitive disturbances persist, even in a regular user, depending on the dosage and the drug's pharmacodynamic effects. Some cross-tolerance exists between alcohol and barbiturates and nonbarbiturate anxiolytics and sedatives, including benzodiazepines. (Barbiturates and alcohol are strikingly similar in the dependence, withdrawal symptoms, and chronic intoxication they produce.) When intake of anxiolytics and sedatives is reduced below a critical level, a self-limited withdrawal syndrome ensues.

### Symptoms and Signs

#### Acute use

The signs of progressive anxiolytic and sedative intoxication are depression of superficial reflexes, fine lateral-gaze nystagmus, slightly decreased alertness with coarse or rapid nystagmus, ataxia, slurred speech, and postural unsteadiness. Further progression results in nystagmus on forward gaze, somnolence, marked ataxia with falling, confusion, deep sleep, constricted pupils, respiratory depression, and, ultimately, death. Patients taking large doses of sedatives frequently have difficulty thinking, slow speech and comprehension (with some dysarthria), poor memory, faulty judgment, narrowed attention span, and emotional lability.

#### Chronic use

In susceptible patients, psychologic dependence on the drug may develop rapidly, and after only a few weeks, attempts to stop using the drug exacerbate insomnia and result in restlessness, disturbing dreams, frequent awakening, and feelings of tension in the early morning. The extent of physical dependence is related to dose and duration of use; eg, pentobarbital 200 mg/day taken for many months may not induce significant tolerance, but 300 mg/day for > 3 mo or 500 to 600 mg/day for 1 mo may induce a withdrawal syndrome when the drug is stopped. Withdrawal from barbiturates taken in large doses produces an abrupt withdrawal syndrome in the form of a severe, frightening, and potentially life-threatening illness similar to delirium tremens. Occasionally, even after properly managed withdrawal over 1 to 2 wk, a seizure occurs. Within the first 12 to 20 h after withdrawal of a short-acting barbiturate, the untreated patient becomes increasingly restless, tremulous, and weak. By the 2nd day, the tremulousness becomes more prominent, deep tendon reflexes may be increased, and the patient becomes weaker. During the 2nd and 3rd days, seizures occur in 75% of patients who were taking  $\geq$  800 mg/day. Seizures may progress to status epilepticus and death. From the 2nd to the 5th day, the untreated withdrawal syndrome includes delirium, insomnia, confusion, and frightening visual and auditory hallucinations. Hyperpyrexia and dehydration often occur.

Withdrawal from benzodiazepines produces a similar withdrawal syndrome, although it is rarely as severe or life threatening. Onset may be slow because the drugs remain in the body a long time. A withdrawal syndrome of varying severity has been reported in people who have taken therapeutic doses, although the prevalence of this unusual phenomenon is unknown. Withdrawal may be most severe in those who used drugs with rapid absorption and quick decline in serum levels (eg, alprazolam, lorazepam, triazolam). Many people who misuse benzodiazepines have been or are heavy users of alcohol, and a delayed benzodiazepine withdrawal syndrome may complicate alcohol withdrawal.

#### Treatment

Acute intoxication generally requires nothing more than observation. On occasion, intoxication is severe enough to require respiratory support. The benzodiazepine receptor antagonist flumazenil can be used for treatment of severe sedation secondary to benzodiazepine overdose. Its clinical usefulness is not well defined, because most people who overdose on benzodiazepines recover without intervention. Occasionally, when used to reverse sedation, flumazenil precipitates seizures.

The procedure for managing dependence on sedatives, particularly barbiturates, is to withdraw the drug on a strict schedule, monitoring signs of withdrawal. Often it is best to switch to a long-acting compound, which is easier to taper. Before withdrawal is begun, sedative tolerance can be evaluated with a test dose of pentobarbital 200 mg po given to a nonintoxicated, fasting patient; if the patient is not tolerant, the dose produces drowsiness or shallow sleep 1 to 2 h later. A patient with intermediate levels of tolerance may show some sedation; a patient tolerant of  $\geq$  900 mg shows no signs of intoxication. If the 200-mg dose has no effect, the tolerance level can be determined by repeating the test q 3 to 4 h with a larger dose. Severe anxiety or agitation may increase the patient's tolerance. Once the 24-h dose still tempered by tolerance is determined, that dose is usually given qid for 2 or 3 days to stabilize the patient and is then decreased by 10%/day. Withdrawal should be undertaken in the hospital. Once the withdrawal syndrome has begun, reversing it is difficult, but with close monitoring, symptoms can be minimized. The reestablishment of

CNS stability requires about 30 days.

Alternatively, phenobarbital can be used. It does not produce the high of more rapidly acting drugs. Rapid-onset barbiturates, other sedatives, or minor anxiolytics can be replaced by a dose of phenobarbital equivalent to  $\frac{1}{3}$  the average daily dose of the drug on which the patient is dependent; eg, for secobarbital 1000 mg/day, the stabilizing dose of phenobarbital is 300 mg/day, typically given as 75 mg q 6 h. Phenobarbital is given orally qid, and the initial phenobarbital dose is reduced by 30 mg/day until the patient is drug-free. Because the initial daily dose must be estimated from the patient's history, a potential for error exists, and the patient must be observed closely for the first 72 h. If he remains agitated or anxious, the dose should be increased; if he is drowsy or dysarthric or has nystagmus, the dose should be decreased. While the patient is being detoxified, other sedatives and psychoactive drugs should be avoided. However, if the patient is also taking antidepressants, especially tricyclics, the antidepressant should not be abruptly stopped; the dose should be reduced over 3 to 4 days.

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Cocaine

High doses of cocaine can cause euphoric excitement or schizophrenic-like symptoms. Psychologic and physical dependence can lead to profound addiction.

Most cocaine users are episodic recreational users who voluntarily curtail their use. However, cocaine use and the development of addictive behavior in some users has increased in North America, although recent declines are recorded. Availability of highly biologically active forms, such as crack cocaine, has worsened the problem of cocaine dependence.

Although most cocaine in the US is snorted, smoking crack cocaine has become widely publicized. The hydrochloride salt is converted to a more volatile form, usually by adding NaHCO<sub>3</sub>, water, and heat. The converted material is combusted and the resultant smoke inhaled. Onset of effect is quicker, and intensity of the high is magnified. Crack use has not expanded to the suburbs or to the urban middle class: Low-income Americans continue to be the primary users.

Tolerance to cocaine occurs, and withdrawal from heavy use is characterized by somnolence, increased appetite, and depression. The tendency to continue taking the drug is strong after a period of withdrawal.

**Symptoms and Signs**

**Acute use**

Effects differ with different modes of use. When injected or smoked, cocaine produces hyperstimulation, alertness, euphoria, and feelings of competence and power. The excitation and high are similar to those produced by injecting amphetamine. These feelings are less intense and disruptive in users who snort cocaine powder.

An overdose may produce tremors, seizures, and delirium. Death may result from MI, arrhythmias, and heart failure. Patients with extreme clinical toxicity may, on a genetic basis, have decreased (atypical) serum cholinesterase, an enzyme needed for clearance of cocaine. The concurrent use of cocaine and alcohol produces a condensation product, cocaethylene, which has stimulant properties and may contribute to toxicity.

**Chronic use**

Because cocaine is a very short-acting drug, heavy users may inject it or smoke it q 10 to 15 min. This repetition produces toxic effects, such as tachycardia, hypertension, mydriasis, muscle twitching, sleeplessness, and extreme nervousness. Hallucinations, paranoid delusions, and aggressive behavior may develop, which can make the person dangerous. Pupils are maximally dilated, and the drug's sympathomimetic effect increases heart and respiration rates and BP.

Severe toxic effects occur in the compulsive heavy user. Rarely, repeated snorting causes nasal septal perforation due to local ischemia. Repeatedly smoking volatile crack cocaine in high doses can have serious toxic cardiovascular and behavioral consequences.

**Treatment**

Treatment of acute cocaine intoxication is generally unnecessary because the drug is extremely short-acting. If an overdose requires intervention, IV barbiturates or diazepam may be used, but close observation and supportive care is the appropriate approach. Anticonvulsants do not prevent seizures due to cocaine overdose. Hyperthermia or significantly elevated BP, which rarely results, must be treated.

Stopping sustained use requires considerable assistance, and the depression that may result requires close supervision and treatment. Many nonspecific therapies, including support and self-help groups and cocaine hotlines, exist. Extremely expensive inpatient therapy is available.

Treatment of infants born to cocaine-addicted mothers is discussed in [Metabolic, Electrolyte, and Toxic Disorders in Neonates: Prenatal Drug Exposure](#).

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Section	Psychiatric Disorders
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Gamma Hydroxybutyrate (GHB)

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Gamma hydroxybutyrate causes intoxication resembling alcohol or ketamine intoxication and can lead to respiratory depression and death, especially when combined with alcohol.

Gamma hydroxybutyrate (GHB, also called "G") is taken by mouth. It is similar to ketamine in its effects but lasts longer and is far more dangerous.

GHB produces feelings of relaxation and tranquility. It may also cause fatigue and disinhibition. At higher doses, GHB may produce dizziness and loss of coordination, nausea, and vomiting. Seizures and coma may also occur and can lead to respiratory failure and death. Combining GHB and any other sedative, especially alcohol, is extremely dangerous. Most deaths have occurred when GHB was taken with alcohol.

Withdrawal symptoms occur if GHB is not taken for several days after previous frequent use.

Treatment is needed only for overdose. Use of a ventilator may be needed if breathing is affected. Most people recover rapidly, although effects may not fade for 1 to 2 h.

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<b>Section</b>	Psychiatric Disorders
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Hallucinogens

Hallucinogens can cause intoxication, with altered perception and impaired judgment. Chronic use can further impair judgment and lead to depression, anxiety, or psychosis.

Hallucinogens include lysergic acid diethylamide (LSD), psilocybin, and mescaline. Some other drugs, including marijuana, also have hallucinogenic properties. The term hallucinogen persists, although use of these drugs may not produce hallucinations. Alternative terms, such as psychedelic and psychotomimetic, are even less appropriate.

**Symptoms and Signs**

**Acute use**

Hallucinogens induce intoxication in the form of CNS excitation and central autonomic hyperactivity manifested as changes in perception and mood (usually euphoric, sometimes depressive). True hallucinations are rare.

Responses to the hallucinogens depend on several factors, including the user's expectations, his ability to cope with perceptual distortions, and the setting. Untoward reactions (anxiety attacks, extreme apprehensiveness, or panic states) to LSD are rare. Most often, these reactions quickly subside with appropriate treatment in a secure setting. However, some people (especially after using LSD) remain disturbed and may show a persistent psychotic state. Whether drug use has precipitated or uncovered a preexisting psychotic potential or can produce this state in a previously stable person is unresolved.

**Chronic use**

The main features of chronic use are the psychologic effects and impaired judgment, which can lead to dangerous decision making or accidents. A high degree of tolerance for LSD develops and disappears rapidly. Users tolerant of any of these drugs are cross-tolerant of the others. Psychologic dependence varies greatly but usually is not intense, and no evidence of physical dependence is detected when the drugs are abruptly withdrawn.

Some people, especially those who are long-term or repeat users (particularly of LSD), experience apparent drug effects long after they have stopped drug use. These episodes (flashbacks) most commonly consist of visual illusions but can include distortions of virtually any sensation (including self-image or perceptions of time or space) and hallucinations. Flashbacks can be precipitated by use of marijuana, alcohol, or barbiturates or by stress or fatigue or can occur without apparent reason. The mechanisms of flashbacks are not known. Flashbacks tend to subside within 6 to 12 mo.

**Treatment**

**Acute use**

Reassurance that the bizarre thoughts, visions, and sounds are due to the drug and not to a nervous breakdown usually suffices. Phenothiazine antipsychotics must be used with extreme caution because of the danger of hypotension. Anxiolytics, such as chlordiazepoxide and diazepam, may help reduce frightening anxiety.

**Chronic use**

Withdrawal is usually easily accomplished; some people may need psychiatric treatment for associated problems. A helpful relationship with a physician, with frequent contact, can be beneficial.

Persistent psychotic states or other mental disorders require appropriate psychiatric care. Flashbacks that are transient or not unduly distressing to the patient require no special treatment. However, flashbacks associated with anxiety and depression may require therapy similar to that for acute adverse reactions.

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## Ketamine

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Ketamine (also called “K” or Special K) can cause intoxication, sometimes with confusion or a catatonic state. Overdose can cause collapse.

Ketamine is an anesthetic. When used illicitly, it is generally snorted.

A giddy euphoria occurs with lower doses, often followed by bursts of anxiety or mood lability. Higher doses produce a withdrawn state (disassociation); when doses are higher still, disassociation can become severe (known as a “K-hole”) with ataxia, dysarthria, muscular hypertonicity, and myoclonic jerks. Cardiovascular status is usually unaffected. With very high doses, coma and severe hypertension may occur; deaths are unusual. Acute effects generally fade after 30 min.

The patient should be kept in a nonstimulatory environment and closely observed. Further treatment is rarely needed.

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Marijuana (Cannabis)

Marijuana is the most commonly used illicit drug. Psychologic dependence can develop with chronic marijuana use, but there is very little clinically apparent physical dependence.

Any drug that causes euphoria and diminishes anxiety can cause dependence, and marijuana is no exception. However, heavy use and reports of inability to stop are unusual. Marijuana is most commonly used episodically without evidence of social or psychologic dysfunction. A mild withdrawal syndrome may occur similar to that of benzodiazepine withdrawal when the drug is stopped, but some heavy users report disrupted sleep and nervousness when they stop.

In the US, marijuana is commonly smoked in cigarettes made from the flowering tops and leaves of the dried plant or as hashish, the pressed resin of the plant. Dronabinol, a synthetic form of  $\Delta$ -9-tetrahydrocannabinol (the principal active constituent of marijuana), is used to treat nausea and vomiting associated with cancer chemotherapy and to enhance appetite in AIDS patients. This form is not sold on the street.

**Symptoms and Signs**

Smoked marijuana produces a dreamy state of consciousness in which ideas seem disconnected, unanticipated, and free-flowing. Time, color, and spatial perceptions may be altered. In general, a feeling of well-being and relaxation (a high) results. These effects last 2 to 3 h after inhalation. There is no persuasive evidence of a prolonged or hangover effect. Tachycardia, conjunctival injection, and dry mouth occur regularly. Many of the psychologic effects seem to be related to the setting in which the drug is taken. Panic reactions and paranoia have occurred, particularly in naive users, but have become unusual as the culture has become more familiar with the drug. Communicative and motor abilities are decreased, depth perception and tracking are impaired, and the sense of timing is altered—all hazardous in certain situations (eg, driving, operating heavy equipment). Appetite often increases. Psychotic symptoms may be exacerbated or even precipitated in schizophrenics by marijuana, even in patients being treated with antipsychotics. Critics of marijuana cite much scientific data regarding adverse effects, but most of the claims regarding severe biologic impact are unsubstantiated. Findings are sparse even among relatively heavy users and in areas intensively investigated, such as immunologic and reproductive function. However, high-dose smokers develop pulmonary symptoms (episodes of acute bronchitis, wheezing, coughing, and increased phlegm), and pulmonary function may be altered. Such alteration is manifested by large airway changes of unknown significance. Even daily smokers do not develop obstructive airway disease. Lung cancer has not been reported in people who smoke only marijuana, possibly because less smoke is inhaled than during cigarette smoking, and the smoke contains fewer carcinogenic substances. However, biopsies of bronchial tissue sometimes show precancerous changes, so cancer may occur. In a few case-control studies, diminished cognitive function was found in small samples of long-term high-dose users; this finding awaits confirmation.

The effect of prenatal marijuana use on newborns is not clearly known. Decreased fetal weight has been reported, but when all factors (eg, maternal alcohol and tobacco use) are accounted for, the effect on fetal weight decreases.  $\Delta$ -9-Tetrahydrocannabinol is secreted in breast milk. Although harm to breastfed babies has not been shown, breastfeeding mothers, as with pregnant women, should avoid using marijuana.

Because cannabinoid metabolites persist, urine tests after each use can remain positive for days or weeks after stopping use. Tests that identify an inactive metabolite identify use only, not dysfunction; the smoker may be free of drug effect by the time his urine is tested. The test can detect extremely small amounts and so is of little value in identifying the pattern of use.

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Section	Psychiatric Disorders
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Methylenedioxyamphetamine (MDMA)

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3,4-Methylenedioxyamphetamine (MDMA—commonly known as ecstasy or Adam or “E”) is an amphetamine analog. MDMA is usually taken as a pill. It has both stimulant and hallucinogenic effects. Prolonged use can cause dependence.

MDMA is often used at dance clubs, concerts, and “rave” parties. Ecstasy produces a state of excitement and disinhibition and accentuates physical sensation. Like amphetamines, ecstasy energizes but to a far lesser extent. Unlike amphetamines, its use has not been associated with unsafe sexual practices and the spread of sexually transmitted diseases. Although the toxic effects of this drug remain controversial, the brain death caused by typical amphetamines has not been shown. The effects of intermittent, occasional use are uncertain. Fulminant hepatic failure may occur rarely. Chronic, repeated use may produce problems similar to that of amphetamines. Some users develop paranoid psychosis. Cognitive decline may also occur with repeated, frequent use. Treatment for dependency is similar to that for amphetamines, although treatment for acute overdose is rarely needed.

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<b>Section</b>	Psychiatric Disorders
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Opioids

Use of opioids for medical purposes but without the supervision of health care practitioners and all use for nonmedical purposes can lead to consequences such as delirium and injury. Chronic use can lead to dependence. Dependence is marked by an overpowering compulsion to continue taking opioids, the development of tolerance so that the dosage must be increased to obtain the initial effect, and physical dependence that increases in intensity with increased dosage and duration of use.

Dependence on opioids is increasing. Heroin is the most commonly used recreational opioid, whereas opium use is uncommon. Dependence on prescription analgesic opioids, such as morphine and oxycodone, is increasing, with some of the increase accounted for by people who are taking them for legitimate medical purposes. Additionally, many people find that opioid use allows them to bear what they once considered the unbearable stresses of life. Physical dependence necessitates continued use of the same opioid or a related one to prevent withdrawal. Withdrawal of the drug or administration of an antagonist precipitates a characteristic, self-limited withdrawal syndrome.

Therapeutic doses taken regularly over 2 to 3 days can lead to some tolerance and dependence, and when the drug is stopped, the user may have mild withdrawal symptoms which are scarcely noticed or are flu-like.

Patients with chronic pain requiring long-term use should not be labeled addicts, although they may have some problems with tolerance and physical dependence. Opioids induce cross-tolerance so that abusers can substitute one for another. People who have developed tolerance may show few signs of drug use and may function normally in their usual activities, but obtaining the drug is an ever-present problem. Tolerance to the various effects of these drugs frequently develops unevenly. Heroin users, for example, may become largely tolerant to the drug's euphoric and lethal effects but continue to have constricted pupils and constipation.

**Symptoms and Signs**

Acute intoxication (overdose) is characterized by euphoria, flushing, itching (particularly with morphine), miosis, drowsiness, decreased respiratory rate and depth, hypotension, bradycardia, and decreased body temperature.

Physical dependence is suggested by a history of  $\geq 3$  opioid injections/day, fresh needle marks, withdrawal symptoms and signs, or morphine glucuronide in a urine specimen (heroin is biotransformed to morphine, conjugated with glucuronide, and excreted). Because heroin is often snorted, the nasal septum may be perforated.

The withdrawal syndrome generally includes symptoms and signs of CNS hyperactivity. Severity of the syndrome increases with the size of the opioid dose and the duration of dependence. Symptoms appear as early as 4 h after withdrawal and, for heroin, peak within 72 h. Anxiety and a craving for the drug are followed by increased resting respiratory rate ( $> 16$  breaths/min), usually with yawning, perspiration, lacrimation, and rhinorrhea. Other symptoms include mydriasis, piloerection (gooseflesh), tremors, muscle twitching, hot and cold flashes, aching muscles, and anorexia. The withdrawal syndrome in people who were taking methadone (which has a long half-life) develops more slowly and is overtly less severe than heroin withdrawal, although users may describe it as worse.

**Complications**

Complications of heroin addiction may be related to the unsanitary administration of the drug or to the drug's inherent properties, overdose, or intoxicated behavior accompanying drug use. Common complications are pulmonary, bone, and neurologic disorders; hepatitis; and immunologic changes.

Aspiration pneumonitis, pneumonia, lung abscess, septic pulmonary emboli, and atelectasis may occur. Pulmonary fibrosis from talc granulomatosis may develop when opioid analgesic tablets are injected. Chronic heroin addiction results in a decreased vital capacity and a mild to moderate decrease in diffusion capacity. These effects are distinct from the pulmonary edema that may occur acutely with heroin injection. Many opioid addicts smoke  $\geq 1$  pack of cigarettes/day, making them particularly susceptible to a variety of pulmonary infections.

Viral hepatitis types A, B, and C may develop. The combination of viral hepatitis and the frequently high alcohol intake may account for the high incidence of liver dysfunction.

Osteomyelitis (particularly lumbar vertebral) is the most common musculoskeletal complication, probably due to hematogenous spread of organisms from unsterile injections. Infectious spondylitis and sacroiliitis may occur. In myositis ossificans (drug abuser's elbow), the brachialis muscle is damaged by inept needle manipulation, followed by replacement of the muscle bundle with a calcific mass (extraosseous metaplasia).

Hypergammaglobulinemia of both IgG and IgM occurs in  $\leq 90\%$  of addicts. The reason is unknown but may reflect repeated antigenic stimulation from infections or from daily parenteral injection of foreign substances.

Hypergammaglobulinemia diminishes with methadone maintenance. Heroin addicts and other IV drug users are at extremely high risk of HIV infection and AIDS. In communities in which sharing of needles and syringes is common, the spread of AIDS is devastating.

Neurologic disorders in heroin addicts are usually noninfectious complications of coma and cerebral anoxia. Toxic

amblyopia (apparently due to adulteration of heroin by quinine), transverse myelitis, various mononeuropathies and polyneuropathies, and Guillain-Barré syndrome may occur. Cerebral complications include those secondary to bacterial endocarditis (bacterial meningitis, mycotic aneurysm, brain abscess, and subdural and epidural abscesses), those due to viral hepatitis or tetanus, and acute cerebral falciparum malaria. Some neurologic complications may be due to allergic responses to the heroin-adulterant mixture.

Superficial cutaneous abscesses, cellulitis, lymphangitis, lymphadenitis, and phlebitis from contaminated needles may occur. Many heroin addicts begin with subcutaneous injections (skin popping) and may return to this mode when extensive scarring makes their veins inaccessible. As addicts become more desperate, cutaneous ulcers in unlikely sites may be found. Contaminated needles and inoculum may lead to bacterial endocarditis, hepatitis, and HIV infection. These complications follow frequent injection. Because heroin potency has recently increased, more users are snorting and smoking, which may diminish problems with infectious contamination.

Some problems of the heroin-addicted mother are transferred to the fetus. Because heroin and methadone freely cross the placental barrier, the fetus readily becomes physically dependent. A mother infected with HIV or hepatitis B virus may transmit the virus to her newborn. Pregnant addicts seen early enough should be encouraged to enter a methadone maintenance program. Abstinence is better for the fetus, but abstinent mothers often revert to heroin use and withdraw from prenatal care. Withdrawal of heroin or methadone from pregnant women late in the 3rd trimester may precipitate early labor; thus, pregnant women seen at or near term may best be stabilized with methadone rather than disturbed by attempts to withdraw opioids. The methadone-maintained mother may nurse her newborn without causing any apparent clinical problems in the child, because concentration of the drug in breast milk is minimal. Infants of opioid-dependent mothers may present with tremors, a high-pitched cry, jitters, seizures (rarely), and tachypnea. Problems of the newborn, including drug withdrawal and fetal alcohol syndrome, are discussed in [Metabolic, Electrolyte, and Toxic Disorders in Neonates: Prenatal Drug Exposure](#).

#### **Treatment**

##### **Acute use**

Overdose is usually managed with the opioid antagonist naloxone (0.4 to 2 mg IV) because it has no respiratory depressant properties (see Table 8: [Poisoning: Symptoms and Treatment of Specific Poisons](#)). It rapidly reverses unconsciousness due to an opioid. Because some patients become agitated, delirious, and combative as they recover from a comatose state, physical restraints may be required and should be applied before the antagonist is given. All patients treated for overdose should be hospitalized and observed for at least 24 h because the action of naloxone is relatively short. Also, respiratory depression may recur within several hours, especially with methadone, at which time methadone should be re-administered at an appropriate dose. Severe pulmonary edema, which may cause death from hypoxia, is usually not responsive to naloxone and has an unclear relationship to overdose.

##### **Chronic use**

The clinical management of opioid addicts is extremely difficult. The AIDS epidemic has provoked a harm-reduction movement, seeking to offer services that reduce the harm of drug use without requiring cessation. For example, providing clean needles and syringes for injection users reduces the spread of HIV. Despite this evidence of harm reduction, US federal funding cannot be used to establish needle or syringe provision to IV users. Other harm-reduction approaches, including easy access to methadone or buprenorphine maintenance, alternative maintenance strategies, and eased restrictions on the prescribing of psychoactive drugs, are more prevalent in some European countries than in the US, where programs viewed as abetting drug consumption behavior are resisted. Physicians must be fully aware of federal, state, and local regulations. Treatment is complicated by the need to deal with the societal attitudes toward the treatment of addicts (including the attitudes of law enforcement officers and other physicians and health care practitioners). In most cases, the physician should refer addicts to specialized treatment centers rather than attempt to care for them alone.

To legally use an opioid drug in treating an addict, a physician must establish the existence of physical opioid dependence. However, many addicts who seek treatment use low-grade heroin, which may not cause physical dependence. Low-grade opioid dependence (as may occur in people who have used opioid analgesics for a long time) can be treated by reducing the opioid dose slowly, by substituting a weak opioid (eg, propoxyphene), or by using benzodiazepines (which are not cross-tolerant to opioids) in decreasing doses.

The withdrawal syndrome is self-limited and, although severely uncomfortable, is not life threatening. Minor metabolic and physical withdrawal effects may persist up to 6 mo. Whether this protracted withdrawal syndrome contributes to relapse is unclear. The patient's drug-seeking behavior usually begins with the first symptoms of withdrawal, and hospital personnel must be aware that he will try to obtain drugs. Visitors may have to be restricted. Many patients with withdrawal symptoms have other medical problems that must be diagnosed and treated.

Methadone substitution is the preferred method of opioid withdrawal for more seriously addicted patients because of its long half-life and less profound sedation and euphoria. Methadone is given orally in the smallest amount (generally, 15 to 40 mg once/day) that will prevent severe but not necessarily all symptoms of withdrawal. Higher doses should be given when evidence of withdrawal is observed. Doses of  $\geq 25$  mg can produce unconsciousness if the person has not developed tolerance. After the appropriate dose has been established, it should be reduced progressively by not more than 20%/day. Patients commonly become angry and request additional medication. The withdrawal syndrome induced by methadone resembles that of heroin, but onset is more gradual and delayed, beginning 36 to 72 h after stopping the drug. Acute manifestations of withdrawal usually subside within 10 days, but patients often report deep muscle aches. Weakness, insomnia, and severe pervasive anxiety are common for several months. Methadone withdrawal for addicts coming from a methadone maintenance program may be particularly difficult because their dose of methadone may be as high as 100 mg once/day. In general, detoxification should be started by reducing the dose to 60 mg once/day over several weeks before attempting complete detoxification. The central adrenergic drug clonidine can halt almost all signs of opioid withdrawal. It probably decreases central adrenergic outflow secondary to stimulation of central receptors (the same mechanism by which clonidine lowers BP). However, clonidine can cause hypotension and drowsiness, and its withdrawal may precipitate restlessness,

insomnia, irritability, tachycardia, and headache. Clonidine may help people withdraw from heroin or methadone before they begin oral naltrexone treatment. The mixed opioid agonist-antagonist buprenorphine also has been successfully used in withdrawal.

#### **Maintenance**

No consensus exists regarding long-term treatment of opioid-dependent users. In the US, thousands of opioid addicts are in methadone maintenance programs, which are intended to meet the supply problems of addicts by providing large doses of oral methadone, thus enabling addicts to be socially productive. Methadone blocks the effects of injected heroin and alleviates the user's drug hunger. For many, the program has worked. However, the widespread use of methadone has provoked societal and political anger, and many people distrust its usefulness as treatment.

Buprenorphine, an agonist-antagonist, is available as maintenance treatment for opioid addicts and is becoming preferred over methadone. It blocks receptors, thereby interfering with illicit use of heroin or of other opioid analgesics. Buprenorphine can be prescribed by specially trained physicians certified by the federal government. Typical dose is an 8- or 16-mg tablet once/day. For many opioid addicts, this option is preferable to methadone maintenance because it eliminates the need for attending a methadone maintenance clinic.

Levomethadyl acetate (LAAM) is a longer-acting opioid related to methadone. QT interval abnormalities have been found in some patients taking LAAM. Its use is therefore discouraged, and patients receiving it are best transferred to methadone therapy. LAAM is used 3 times/wk, thereby diminishing the expense and the problems of daily client visits or take-home drugs. A dose of 100 mg 3 times/wk is comparable to methadone 80 mg once/day.

Naltrexone, an orally bioavailable opioid antagonist, blocks the effects of heroin. It has little agonist effect, and many opioid addicts will not voluntarily consume it. The usual dose is 50 mg once/day or 350 mg/wk in 2 or 3 divided doses. The therapeutic community concept, pioneered by Daytop Village and Phoenix House, involves nondrug treatment in communal residential centers, where drug users receive training, education, and redirection to help them build new lives. Residency is usually 15 mo. These communities have helped, even transformed, some users. However, initial dropout rates are extremely high. How well these communities work, how many will be opened, and how much funding society will give remain unanswered.

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### Volatile Nitrites

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Nitrites (poppers, as amyl, butyl, or isobutyl, sold as Locker Room and Rush) may be inhaled to enhance sexual pleasure. Use is particularly prominent among urban male homosexuals. There is little evidence of significant hazard, although nitrites and nitrates produce vasodilation, with brief hypotension, dizziness, and flushing, followed by reflex tachycardia (see Table 8: [Poisoning: Symptoms and Treatment of Specific Poisons](#) ). They are, however, dangerous when combined with drugs used for erectile enhancement; the combination can lead to severe hypotension and death.

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Volatile Solvents

Inhalation of volatile industrial solvents and solvents from aerosol sprays can produce a state of intoxication. Chronic use can result in neuropathies and hepatotoxicity.

Use of volatile solvents continues to be an endemic problem among adolescents. About 10% of adolescents in the US have reportedly inhaled volatile solvents. Volatile solvents (eg, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, ketones, acetates, ether, chloroform, alcohol) produce temporary stimulation before depressing the CNS. Partial tolerance and psychologic dependence develop with frequent use, but a withdrawal syndrome does not occur.

Acute symptoms of dizziness, drowsiness, slurred speech, and unsteady gait occur early. Impulsiveness, excitement, and irritability may occur. As effects on the CNS increase, illusions, hallucinations, and delusions develop. The user experiences a euphoric, dreamy high, culminating in a short period of sleep. Delirium with confusion, psychomotor clumsiness, emotional lability, and impaired thinking develops. The intoxicated state may last from minutes to > 1 h. Complications of chronic use may result from the effect of the solvent or from other toxic ingredients, such as lead in gasoline. Carbon tetrachloride may cause a syndrome of hepatic and renal failure. Injuries to brain, liver, kidneys, and bone marrow may result from heavy exposure or hypersensitivity. Death most often results from respiratory arrest, arrhythmias, or asphyxia due to airway occlusion.

Treatment of solvent-dependent adolescents is difficult, and relapse is frequent. However, most users stop solvent use by the end of adolescence. Intensive attempts to broadly improve the patients' social skills and status in family, school, and society may help. For symptoms and treatment of poisoning with specific solvents, see Table 8:

[Poisoning: Symptoms and Treatment of Specific Poisons](#) .

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### Substance Use in Children and Adolescents

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Substance use disorders are common among children, especially in adolescents. Regardless of economic or ethnic background, alcohol, tobacco, and marijuana are consistently the most commonly used substances. Use of other substances, including amphetamines and methamphetamine, inhalants, hallucinogens, cocaine, anabolic steroids, opioids, and so-called date rape drugs and club drugs (eg, MDMA, ketamine, gamma hydroxybutyrate), is less common, and the prevalence of use of each is more variable over time. Of growing concern is a reported increase in random mixing of date rape and club drugs at parties.

Children and adolescents use drugs for a variety of reasons. Some may do so as a means of escaping from perceived pressures (eg, parental pressure, societal pressure), or of challenging authority. Influence of peers and portrayal of substances such as alcohol in the media are other commonly cited reasons. Parental attitudes and the examples that parents set in their own use of alcohol, tobacco, prescription drugs, and other substances are a powerful influence.

Primary care physicians should be prepared to provide their adolescent patients with adequate screening, counseling, and, when necessary, referral to other treatment services and resources.

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