CHAPTER 152
Substance Abuse and Withdrawal: Alcohol, Cocaine, Opioids, and Other Drugs
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INTRODUCTION

Ethanol, illicit drugs, and prescription drugs used for non-medical purposes are a significant medical as well as social problem. The 2013 National Survey on Drug Use and Health found that 22.9% of Americans, or 60.1 million individuals, were binge alcohol drinkers (1). Also, an estimated 2.8 million people used an illicit drug for the first time, with the majority using marijuana. Casual or habitual use of these drugs may contribute to acute and chronic illness. Substance abuse also underlies many forms of injury, including vehicular accidents, falls, near-drowning, thermal injuries, homicide, and suicide. Other critical illnesses may be impacted by either substance use or substance withdrawal. This chapter will cover acute toxicity and withdrawal syndromes related to ethanol, cocaine, opioids, and other selected drugs likely to be of importance to the critical care practitioner.

ETHANOL

Alcohol abuse and alcoholism (a dependence on alcohol) are major social, economic, and public health problems throughout the world. Alcoholism is the third leading cause of death in the United States, reducing life expectancy by 10 to 12 years. An average of six people die in the United States of alcohol poisoning each day and about 75% of them are men aged 35 to 64 years (2). Men who imbibe more than 14 drinks per week or 7 drinks per week are at risk for alcohol poisoning each day and about 75% of them are men aged 35 to 64 years (2). Men who imbibe more than 14 drinks per week or 7 drinks per week are at risk for alcohol abuse and dependence (a standard drink is one 12-ounce beer or wine cooler, one 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled spirits).

Ethanol is rapidly absorbed in unaltered form from the stomach and small intestine; the presence of food (especially milk and fatty foods) in the stomach delays absorption, whereas the presence of water enhances absorption. Ethanol diffuses freely into body tissues, is primarily metabolized in the liver, and less than 10% is excreted by the lungs or kidneys or through the skin. Several hepatic enzyme systems independently metabolize ethanol to acetaldehyde. The primary degradation pathway is in the hepatic cytosol by alcohol dehydrogenase, with nicotinamide adenine dinucleotide (NAD) as a cofactor. Acetaldehyde generated by this process is in turn metabolized through the Krebs cycle to carbon dioxide and water with 7 kcal/g liberated in this process. Most people can metabolize about 150 mg of ethanol per kilogram body weight per hour. This is equivalent to about 12 ounces of beer or 1 ounce of 90-proof whiskey.

Acute Toxicity

Common features of acute ethanol intoxication are shown in Table 152.1. Intoxication with ethanol depends on the rate of rise of the blood alcohol level and the length of time the level is maintained. Blood alcohol levels can be measured directly in blood and indirectly in exhaled gas by infrared spectroscopy, or estimated by different formulae (3). Blood alcohol levels of 20 to 30 mg/dL are often associated with a mild euphoria, delayed reaction time, decreased inhibition, and alterations in judgment. Most people exhibit gross intoxication at levels above 150 mg/dL. Obtundation often develops at levels above 300 mg/dL, and death may result from respiratory depression, aspiration, or cardiovascular collapse when levels exceed 400 to 500 mg/dL (4).

Ethanol is a sedative–hypnotic drug and exerts its primary effects on the central nervous system (CNS). Patients can present with altered consciousness, agitation, euphoria, slurred speech, ataxia, stupor, and coma. Awareness of the environment (e.g., heat or cold exposure) and perception of pain are diminished. Ethanol may depress the respiratory center and lead to hypoventilation and respiratory arrest. Although seizures are more common in alcohol withdrawal, they may also occur with acute intoxication.

Acute ethanol intoxication is often associated with an increased heart rate and cardiac output, whereas prolonged intoxication may be associated with depressed myocardial contractility (5). Acute intoxication can also be associated with a variety of cardiac dysrhythmias, especially atrial fibrillation (“holiday heart” syndrome). Cutaneous vessels dilate, whereas splanchnic vessels constrict. Increased sweating associated with cutaneous vasodilation may account for the decrease in core temperature often associated with acute ethanol intoxication.

Metabolic problems related to alcohol ingestion can be life threatening. Hyponatremia may be associated with hypovolemia due to rapid diuresis, beer potomania, and chronic liver disease. Rapid correction of hyponatremia should be avoided because alcoholics have an increased risk of central pontine myelinolysis. Alcohol also enhances the urinary excretion of phosphate and magnesium that can result in clinically significant hypophosphatemia and hypomagnesemia. The chronic alcoholic patient often has decreased glycogen stores, and because alcohol also inhibits hepatic gluconeogenesis, profound hypoglycemia may occur. A variety of acid–base disturbances are seen in acute alcoholic intoxication. Metabolic acidosis may be secondary to ketoacids or lactic acid, but a significant acidosis should prompt consideration of conditions other than alcohol intoxication. Depression of the respiratory center in the severely intoxicated person may result in respiratory acidosis.
Nausea and vomiting may cause hypokalemia and metabolic alkalosis.

Ethanol ingestion may cause acute gastritis and gastrointestinal (GI) bleeding. Alcoholics have an increased incidence of peptic ulcer disease and pancreatitis; acute alcohol intoxication may precipitate alcoholic hepatitis in the chronic user. All bone marrow cell lines are suppressed by alcohol ingestion, and suppression of anti-diuretic hormone by ethanol causes diuresis and may lead to profound hypovolemia, especially if there is associated nausea, vomiting, or diarrhea.

### Assessment and Treatment of Acute Intoxication

Treatment of acute ethanol intoxication is primarily supportive, but a careful examination is needed to detect complications or concomitant conditions. The first priority is assessment and stabilization of the airway and ventilation. The respiratory rate, depth of respirations, SpO₂, mental status, and gag reflex should be rapidly evaluated, as should evaluation for the presence of vomitus. Arterial blood gas analysis should be obtained if hyperventilation is a concern, but is not obvious on clinical examination. Endotracheal intubation is indicated in the obtunded or comatose patient unable to protect his/her airway, or when aspiration has occurred or is likely. Positive pressure ventilation should be instituted to correct alveolar hypoventilation and hypoxemia. If the patient presents with altered mental status, 50 to 100 mg of thiamine and 25 g of glucose should be administered intravenously. Thiamine should be administered before glucose to avoid precipitation of acute beriberi and Wernicke–Korsakoff syndrome. If the patient responds to the administration of glucose or if blood glucose levels are low, a continuous infusion of glucose should be given. Intravenous (IV) naloxone may be administered if concomitant opioid use is suspected. Hypotension should be treated initially with volume resuscitation. GI bleeding should be considered in the hypotensive patient and further assessment may include a rectal examination and insertion of a nasogastric tube. GI decontamination is of limited utility because the majority of alcohol is already absorbed; ethanol is not adsorbed by activated charcoal, but charcoal may be administered if ingestion of other toxic drugs is suspected. Hypothermia should be corrected, as should be fluid, electrolyte, and acid–base disturbances, depending on the clinical presentation. A creatine phosphokinase (CPK) level may be warranted in the patient with trauma or prolonged muscle compression to evaluate for rhabdomyolysis. An ethanol blood level may be helpful in documenting the severity of intoxication and estimating the duration of impairment. The serum osmolar gap may be evaluated with an adjustment for blood ethanol level if coingestion of other alcohols is suspected. A low ethanol level in the setting of a patient with a depressed level of consciousness should prompt an evaluation for other etiologies. A chest radiograph is often necessary to assess for evidence of aspiration or other complications, such as pneumonia. Consider obtaining CT of the head if there is any suspicion of subdural hematoma or other intracranial injury. Pancreatitis should be promptly treated with IV hydration and supportive care.

### Alcohol Withdrawal

Chronic excessive alcohol ingestion depresses central α- and β-receptors and potentiates the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The brain adapts with a functional increase in N-methyl-D-aspartate (NMDA) receptors, which are part of an excitatory system. When alcohol consumption stops, the excess excitatory receptors and removal of the inhibitory effects mediated by GABA contribute to the hyperadrenergic state that causes the symptoms seen in alcohol withdrawal.

Alcohol withdrawal syndromes occur in dependent patients during the initial period of abstinence. The incidence of alcohol withdrawal syndromes in hospitalized and critically ill patients is difficult to assess due to varying definitions, patient populations, and type of ICU (6). Prevention of alcohol withdrawal syndromes has been shown to improve morbidity and mortality and to shorten hospital and ICU length of stay (7). Four stages of alcohol withdrawal have been described (8), but symptoms are a continuum of neuropsychiatric and hemodynamic manifestations. Patients may manifest one or more of these syndromes on presentation or develop additional manifestations and progress from less severe to more severe stages while hospitalized (Table 152.2). A key distinction is to determine if the patient has an intact or altered sensorium.

Assessment of the severity of withdrawal is needed to determine appropriate treatment. Although the revised

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**TABLE 152.1 Clinical Manifestations of Alcohol Intoxication**

<table>
<thead>
<tr>
<th>Central Nervous System</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Metabolic</th>
<th>Gastrointestinal</th>
<th>Hematologic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased inhibition</td>
<td>Hypoventilation</td>
<td>Vasodilation</td>
<td>Hypoglycemia</td>
<td>Gastritis</td>
<td>Suppression of all bone marrow cell lines</td>
<td>Suppression of antidiluretic hormone (diuresis)</td>
</tr>
<tr>
<td>Slowed reaction time</td>
<td>Hypoxemia</td>
<td>Cardiac arrhythmias</td>
<td>Electrolyte abnormalities</td>
<td>Increased incidence of peptic ulcer</td>
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<td>Increased sweating</td>
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<td>Visual disturbance</td>
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<td>Pancreatitis</td>
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<tr>
<td>Incoordination</td>
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<td>Alcohol hepatitis</td>
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<tr>
<td>Slurred speech</td>
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<td>Diplopia</td>
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<td>Nystagmus</td>
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<tr>
<td>Lethargy, stupor, coma</td>
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</table>

**Cardiovascular**

- Vasodilation
- Cardiac arrhythmias
- Myocardial depression

**Respiratory**

- Hypoventilation
- Aspiration

**Metabolic**

- Hypoglycemia
- Electrolyte abnormalities
  - Hypophosphatemia
  - Hypomagnesemia
- Acid-base disturbance:
  - Respiratory acidosis
  - Metabolic acidosis (vomiting)
  - Metabolic acidosis (alcoholic ketoacidosis, lactic acidosis)

**Gastrointestinal**

- Gastritis
- Increased incidence of peptic ulcer
- Pancreatitis
- Alcoholic hepatitis

**Hematologic**

- Suppression of all bone marrow cell lines

**Other**

- Suppression of anti-diuretic hormone (diuresis)
- Increased sweating
- Altered temperature regulation
Clinical Institute Withdrawal Assessment-Alcohol Scale (CIWA-Ar) is often used for assessment, it has limited applicability in critically ill patients and has not been validated in this patient population (9). Appropriate use of the CIWA-Ar requires recent alcohol use and the ability to communicate and these requirements result in misuse in many hospitalized patients (10).

Patients with minor withdrawal symptoms—tremulousness and hallucinosis—can usually be treated with IV or oral benzodiazepines. Benzodiazepines act as an alcohol substitute to dampen the excitatory neuronal activity, and additional benefits include prevention of seizures and delirium tremens (DTs). The choice of benzodiazepine in hospitalized patients may depend on severity of hepatic dysfunction, desired duration of action, and available routes of administration. While all benzodiazepines are effective when appropriate doses are used, high doses may cause respiratory depression. Fixed dosing and symptom-triggered regimens have been used effectively. Fixed dosing may be more appropriate in critically ill patients until other conditions have stabilized; treatment duration beyond 7 days is seldom required. Frequent reassessment and intervention is essential in the first 24 to 48 hours of withdrawal symptoms to prevent progression to DTs.

Benzodiazepines are clearly superior to placebo in treating alcohol withdrawal and also superior for seizure control when compared to baclofen, γ-hydroxybutyrate, anticonvulsants, and the psychotropic analgesic nitrous oxide (11). Many trials have been conducted in outpatients and have limited applicability to hospitalized and critically ill patients. IV ethanol may also be an option for alcohol withdrawal treatment or prophylaxis (12). However, it is not recommended for routine use due to dosing variability and lack of established efficacy (13). Other agents such as clonidine and β-blockers have been reported to be effective for minor withdrawal symptoms, but their use is less common; they do not prevent the development of delirium. All patients with alcohol withdrawal should receive supportive measures in addition to pharmacologic intervention. Thiamine (vitamin B₁) should be given intravenously or orally to prevent Wernicke encephalopathy. Magnesium sulfate may be needed to correct hypomagnesemia but there is no evidence that it prevents or treats alcohol withdrawal (14).

### Seizures
Approximately 5% to 10% of patients with untreated mild alcohol withdrawal symptoms progress to seizures, but seizures frequently occur in the absence of other withdrawal symptoms. Patients who have been drinking heavily for only a few years, but have several detoxification admissions are at higher risk of seizures than patients with long drinking histories but fewer detoxification admissions. Previous nonalcohol-related admissions also increase the risk of alcohol withdrawal seizures. This association has been termed the “kindling effect.” According to the kindling hypothesis, each withdrawal episode is an irritative phenomenon to the brain. The accumulation of multiple episodes lowers the seizure threshold (15). Most alcohol withdrawal seizures are brief and self-limited in duration. Alcohol withdrawal seizures are usually generalized tonic-clonic, but focal seizures may also occur. Multiple seizures—two to six episodes—occur in approximately 60% of patients and within a 12-hour period. It may be difficult to distinguish withdrawal seizures from a pre-existing seizure disorder or new onset of a nonalcohol-related seizure. Other causes of seizures such as hypoglycemia, metabolic abnormalities, trauma, infection, and other drug intoxication must be considered. A computed tomography (CT) scan of the head should be obtained for new-onset seizure, persistent...
neurologic deficits, or evidence or suspicion of trauma. Treatment is aimed at terminating active seizures and preventing subsequent seizures. Benzodiazepines have been shown to prevent withdrawal seizures compared to placebo and are used to terminate seizures (16). IV lorazepam or midazolam is commonly used; as the risk of a recurrent seizure is 13% to 24%, additional prophylactic treatment is indicated (17). Lorazepam (2 mg) significantly reduces the risk of recurrent seizure, whereas phenytoin has no effect (18). Less than 3% of patients develop status epilepticus and they should be treated with benzodiazepines or propofol. Phenytoin is not as effective.

**Delirium Tremens**

DTs is the most severe manifestation of alcohol withdrawal and these patients should be cared for in an ICU setting. Untreated DTs carries a mortality of 15%, declining to 1% if treated. The accumulation of multiple prior withdrawal episodes leads to more severe DTs with each episode (15). Patients with DTs have more severe autonomic hyperactivity than milder stages of withdrawal and manifest delirium that may fluctuate. Some patients with severe withdrawal symptoms may need intubation during treatment. Fluid requirements may be increased due to increased insensible losses (fever, diaphoresis) and lack of oral intake. High-dose IV benzodiazepines (diazepam, lorazepam, midazolam) administered at frequent intervals or as a continuous infusion are needed to control the hyper-adrenergic symptoms. Dosing should be individualized to achieve light somnolence (19,20). Benzodiazepines bind at the GABA–benzodiazepine receptor, and once these receptors are saturated, additional drug cannot bind. Thus, patients may tolerate high doses of benzodiazepines but do not necessarily benefit from them (21). Caution is advised when administering high doses of IV lorazepam or diazepam over long periods of time as the propylene glycol diluent may result in a lactic acidosis (22). Daily dose reductions of 25% can be initiated after the second or third day of treatment.

Dexmedetomidine, a central α₂-adrenergic agonist, and propofol have been used as adjunctive therapy with benzodiazepines in severe withdrawal in critically ill patients (23–26). One prospective study evaluating dexmedetomidine found decreased use of benzodiazepines in the short term but not long term, no difference in intubation or seizures, and a higher incidence of bradycardia (27). Propofol infusions may be useful for patients who are refractory to benzodiazepines as the former has a dual activity similar to alcohol (GABA agonist and NMDA antagonist properties) that may explain its efficacy. Propofol has a rapid onset of action, sedation, and anticonvulsive properties, but its use requires intubation and mechanical ventilation (28). Other adverse effects of propofol include hypotension, bradycardia, and propofol infusion syndrome. Other sedative–hypnotic drugs such as paralleldehyde and barbiturates are effective in treating DTs but are not commonly used. Neuroleptic agents are inferior to benzodiazepines and should not be used as single agents for treatment of DTs (20). Neuromuscular blockers may be considered to control agitation when high-dose sedatives are not effective. Cardiac monitoring is necessary to detect dysrhythmias early and institute therapy. **Torsade de pointes** may develop due to hypomagnesemia and/or prolongation of the QTc interval and should be treated aggressively with IV magnesium sulfate. β-Blockers may be needed to treat hypertension or tachycardia but they should not be administered to treat delirium; propranolol may worsen delirium. Thiamine supplementation (100 mg/d) is recommended for 3 days.

DTs usually lasts 2 to 5 days, but in 5% to 10% of cases, DTs lasts greater than a week. Elderly alcoholics have a longer withdrawal period with more symptoms than do younger ones (29). A small percentage of patients remain delirious for several weeks and require continuing treatment. Be aware, however, that after head trauma, a subdural hematoma can evolve subacutely in the alcoholic patient; repeat imaging of the brain may be warranted 7 to 10 days into a course of protracted delirium to rule out a slowly accumulating subdural hematoma (21).

**COCAINe**

Cocaine is the third most commonly used illicit drug after marijuana and prescription-type drugs (psychotherapeutics) (1). Cocaine (benzoylmethylecgonine) is an alkaloid derived from leaves of *Erythroxylon coca* and it is available in two forms. Cocaine hydrochloride is prepared by dissolving alkaloidal cocaine in hydrochloric acid resulting in a white water-soluble powder, crystals, or granules. This form of cocaine is used intranasally (snorting), orally, or intravenously. The other available form of cocaine is free base or crack cocaine. Heating cocaine hydrochloride in sodium bicarbonate or ammonia makes the hard crystallized cocaine base called crack because of the popping sound it makes when heated. Smoking crack cocaine has become a widespread practice due to the rapid absorption across the alveolar surface. Both forms of cocaine are readily absorbed from all body mucosal surfaces. The peak effects of cocaine range from 1 to 90 minutes depending on the route of administration. Inhalational and IV use result in the most rapid peak effects and the shortest duration of action. Cocaine is rapidly metabolized by hepatic and plasma cholinesterases and nonenzymatic hydrolysis to ecgonine methylether and benzoylecgonine, which are excreted in urine; the urinary excretion of unchanged cocaine ranges from 1% to 15%. The route of administration does not affect metabolic excretion patterns appreciably and half-lives of most metabolites range from 45 to 90 minutes (30). Subjective rating of euphoria declines within minutes after constant concentrations are achieved, demonstrating rapid desensitization and acute tolerance (31). Duration of positive urinary metabolites is somewhat dependent on the assay technique, the activity of plasma cholinesterases, and the duration and dosing of cocaine use.

Cocaine’s lipophilic nature, compounded with rapid distribution into and out of the CNS, suggests a highly abusive profile (rush and crash) and increased incidence of kindling. The major neurochemical actions of cocaine are CNS stimulation with release of dopamine; inhibition of neuronal norepinephrine and dopamine uptake, resulting in generalized sympathetic nervous system stimulation; release of serotonin or blockade of serotonin reuptake; and inhibition of sodium current in neuronal tissue, resulting in a local anesthetic effect.

**Toxicity**

Numerous morbidities have been associated with acute and chronic cocaine use (Table 152.3). Complications of particular interest to intensivists are discussed below (32).
Cardiovascular

Cocaine increases the heart rate, blood pressure, and left ventricular contractility, leading to an increase in myocardial oxygen demand (33). The increased demand may combine with underlying coronary artery disease, vasoconstriction, platelet aggregation, or in situ thrombus formation to produce ischemia and infarction. Chronic cocaine use also accelerates atherosclerosis (34). Apart from structural changes in epicardial vessels, wall thickening is described in the intramyocardial small coronary arteries in people with cocaine-induced chest pain (35).

Chest pain is the most common cocaine-associated complication in patients who present for medical care. All patients presenting with chest pain should be questioned regarding cocaine use. Myocardial ischemia can occur with all routes of abuse with no relation to the dose or chronicity of use. The onset of chest pain often occurs temporally related to the use of cocaine. However, chest pain may occur hours to days after the last use of cocaine. Electrocardiograms (ECGs) are often abnormal in patients presenting with cocaine-associated chest pain (36,37). Myocardial infarction may be present with a normal or abnormal ECG. Conversely, ECGs may suggest acute ischemia in the absence of infarction due to J-point elevation or repolarization changes (37). Cardiac troponins are more specific for assessing myocardial injury than creatine kinase-MB, which may be elevated due to skeletal muscle injury (38). Myocardial infarction is reported to occur in approximately 6% to 7% of patients and occurs with normal coronary arteries and in the presence of significant atherosclerotic disease (37,39,40). Periods of silent ischemia are common in chronic users of cocaine, as shown by ambulatory monitoring and during periods of withdrawal (41). Dilated cardiomyopathy, myocarditis, and congestive heart failure can occur secondary to chronic cocaine use (42).

Cocaine is dysrhythmogenic when taken in large quantities because of catecholamine effects. The dysrhythmias are usually transient and resolve when cocaine is metabolized. Sinus tachycardia, supraventricular tachycardia, atrial fibrillation, premature ventricular beats, ventricular tachycardia, ventricular fibrillation, bundle branch block, asystole, and torsade de pointes may occur.

Elevation of blood pressure occurs due to the acute effects of cocaine, but it is usually self-limited. Sustained elevations of blood pressure suggest the presence of chronic hypertension or another complication (e.g., intracranial process). The elevations of blood pressure may contribute to other catastrophic complications such as stroke and intracranial hemorrhage. Rupture of the ascending aorta in previously healthy individuals has been reported as well as aortic dissection (43).

Central Nervous System

In large doses, cocaine may cause a generalized impairment of neuronal impulse transmission leading to CNS depression, coma, respiratory depression, and respiratory arrest. At low doses, stimulation is the common feature of cocaine use. The euphoria produced by cocaine is the principal reason for its abuse. Excessive CNS stimulation can occur and is manifested by tremulousness, agitation, sleeplessness, paranoia, and frank psychosis; aggressive and assaultive behavior can occur in cocaine overdose.
Seizures can be induced, even on the first exposure, because cocaine lowers the threshold for seizures. Cocaine-related seizures are usually brief and self-limited, occurring soon after taking cocaine, although the interval between the last use of cocaine and the onset of seizures can be several hours (44). Sustained or repeated seizure activity suggests an additional complication such as hyperthermia, intracranial hemorrhage, metabolic abnormality, or massive intake of cocaine.

Cocaine use is associated with ischemic cerebrovascular accidents as well as transient ischemic attacks (44–46). Radiologic studies have demonstrated cerebral vasoconstriction as well as vessel thrombosis with cocaine (46,47). Although most symptoms occur during or immediately after cocaine use, neurologic symptoms may occur within hours to several days after the last use. Subarachnoid, parenchymal, and intraventricular hemorrhage may occur within moments of drug use, possibly related to blood pressure elevation. Some patients have anatomic abnormalities such as vascular malformation or aneurysm that may be amenable to specific therapy (44,48,49). Cerebral atrophy, predominantly in the temporofrontal regions, has been noted in patients with chronic cocaine abuse (50).

**Pulmonary**

Pulmonary complications associated with cocaine are much less common than cardiovascular and cerebrovascular events but include a variety of conditions (51,52). Inhalation of cocaine, in contrast to IV use, has been demonstrated to cause bronchoconstriction (53). This response may be due to an irritant effect and may contribute to wheezing and exacerbations of asthma in cocaine users (54,55). Barotrauma (pneumothorax and pneumomediastinum) is reported secondary to snorting cocaine and crack inhalation (56). Noncardiogenic pulmonary edema may occur and is described more commonly with the IV use of cocaine. Massive hemoptysis with diffuse alveolar hemorrhage is a rare complication of unknown etiology and has been reported with smoking free-base cocaine and other routes of abuse. Other rare pulmonary toxicities, more commonly reported after inhalation of cocaine, include interstitial pneumonitis, pulmonary infiltrates with peripheral and/or lung eosinophil prominence, and bronchiolitis obliterans (57). Septic pulmonary emboli and pulmonary vascular obstruction resulting from foreign body granulomas or angiothrombosis may develop as a consequence of IV cocaine use similar to IV heroin use (58).

**Hyperthermia/Rhabdomyolysis**

Hyperthermia may result from muscle hyperactivity or as a direct effect of cocaine on the hypothalamic temperature regulatory center. High ambient temperatures are associated with increased mortality from cocaine and hyperthermia is probably one of several factors that play a role (59). Cocaine impairs sweating and cutaneous vasodilation as well as heat perception under conditions of heat stress (60).

Cocaine-induced rhabdomyolysis is common and can lead to acute renal failure. Multiple factors such as hyperthermia, seizures, vasoconstriction with ischemia, excessive motor activity, concomitant use of other drugs, and even a direct toxic effect of cocaine may contribute to muscle injury; myalgias and muscle tenderness are infrequently present. Seizures, hypotension or hypertension, dysrhythmia, coma, and cardiac arrest identify a subgroup of patients who are prone to severe rhabdomyolysis (61,62).

**Other Toxicities**

Intestinal ischemia, infarction, and perforation have been reported following ingested, IV, and inhaled cocaine (63,64). Patients may present with complaints of acute or chronic abdominal pain. Acute renal failure may be precipitated by rhabdomyolysis, but other etiologies may include accelerated hypertension and glomerulonephritis (65). Rare cases of renal infarction have also been reported.

**Coingestions and Adulterants**

Cocaine may be abused with other drugs such as marijuana, opioids, amphetamines, ethanol, and benzodiazepines, and the toxicities of these drugs may also be evident. Cocaine and ethanol when consumed together form a more toxic compound, cocaethylene, in the liver; it produces more euphoria and has a longer duration of action (66).

There are several substances such as talc, benzoic acid, phenacetin, and thallium that may be used as adulterants of cocaine. Levamisole is a more recent adulterant found in the cocaine supply (67). Levamisole is an immunomodulatory agent and commonly used as an anti-helminth drug. It can cause agranulocytosis, arthralgias, vasculitis, retiform purpura, and skin necrosis (especially on ear lobes and the nasal tip). Levamisole can be detected using gas chromatography/mass spectrometry.

**Diagnosis of Acute Intoxication**

Patients with cocaine intoxication may present with a variety of primary complaints such as altered mental status, chest pain, syncope, palpitations, seizures, or attempted suicide. Characteristic findings of CNS stimulation such as agitation, mydriasis, sweating, hypertension, and tachycardia are often present. However, the effects of other drugs, the presence of complications, and delays in presentation may obscure the typical sympathomimetic manifestations. Other medical conditions such as meningitis, encephalopathy, epilepsy with status, and thyrotoxicosis may mimic cocaine intoxication (68). Confirmation of acute or recent cocaine exposure is made by urine toxicology testing.

**Treatment for Acute Intoxication**

Benzodiazepines are the pharmacologic agents of choice for control of cocaine-induced agitation. The agitation and psychosis of cocaine overdose usually can be managed with titrated doses of IV diazepam, 5 to 20 mg; lorazepam, 2 to 4 mg; or midazolam, 5 to 10 mg slowly. Haloperidol is not recommended as a first-line agent because of the lack of experimental support (69) and its potential to lower the seizure threshold. Although low-dose dexmedetomidine may decrease some sympathetic findings in an experimental setting of inhaled cocaine use, it has not been evaluated in acute intoxications (70,71). Adequate hydration and correction of electrolyte abnormalities are important.
No large clinical trials have evaluated treatment strategies for cocaine-associated ischemia. Treatment of cardiac toxicity due to cocaine is directed at reversing physiologic effects that cause ischemia or dysrhythmias. Aspirin should be administered as an antiplatelet agent for suspected myocardial ischemia unless there is evidence of cerebral hemorrhage. Oxygen may also help to limit myocardial ischemia. Benzodiazepines and nitroglycerin are considered first-line agents for relief of chest pain, but small clinical studies have yielded conflicting results on the benefit of combining the agents (72,73). Benzodiazepines decrease the blood pressure and heart rate, thus decreasing myocardial oxygen demand, and nitroglycerin may dilate coronary arteries or relieve vasoconstriction. β-Blockers such as propranolol have been recommended as a second-line treatment for unrelied pain, but are rarely needed (74). The use of β-blockers in the management of myocardial ischemia is debated. There is a potential concern of worsening vasoconstriction. Aspirin, nitroglycerin, and β-blockers are not administered by this route or as soon after cocaine use in most patients (75). However, β-blockers have been used, particularly in the setting of myocardial infarction, without complications. Administration of β-blockers might be avoided in patients manifesting acute sympathomimetic findings, but the benefits of these agents should be considered in other patients with ongoing myocardial ischemia.

Most patients with cocaine-associated chest pain will not have infarction. Patients can be managed in chest pain or observation units similar to other chest pain patients (76). Low-risk patients with normal cardiac markers can be risk stratified safely with stress testing.

Early therapy for cocaine-induced myocardial infarction should consist of oxygen, aspirin, and nitroglycerin as required for pain relief (77). The role of calcium channel blockers remains uncertain but they should not be used as first-line therapy. β-Blockers should be avoided in the presence of acute sympathomimetic symptoms. If pain persists, patients with cocaine-induced myocardial infarction are candidates for reperfusion therapy. Percutaneous coronary intervention (PCI) is preferred in patients with evidence of ST-elevation myocardial infarction, especially when the diagnosis may be in doubt (77). Thrombolytic therapy has been safely used in cocaine-associated myocardial infarction but should be reserved for patients who cannot receive PCI due to the risk of intracranial hemorrhage (78).

Dysrhythmias associated with cocaine use are usually transient. Standard therapy should be considered for sustained dysrhythmias unresponsive to control of pain and agitation. Although lidocaine is seldom used for ventricular dysrhythmias, theoretical concerns of enhancing cocaine toxicity do not appear to be clinically significant (79).

Sustained hypertension in acute cocaine intoxication is not common due to the short physiologic effects of the drug. Control of agitation with benzodiazepines often results in resolution of hypertension. IV labetalol is a reasonable option if the blood pressure needs to be lowered due to its combined α- and β-blocking effects; nicardipine and nitroglycerin are also reasonable options for lowering blood pressure. Cocaine-intoxicated patients should be considered to have acute elevations in blood pressure, and unless there is documentation or clinical evidence of long-standing hypertension, there should be little concern about cerebral hypoperfusion with immediate lowering of blood pressure to normal levels (80).

Seizures induced by cocaine are best controlled with IV benzodiazepines. Other standard antiepileptics can be added for refractory cases. If neuromuscular blockers are used, seizure activity may persist yet be unrecognized; hence, the use of this drug class warrants continuous electroencephalographic monitoring.

Interventions for ischemic strokes associated with cocaine use should be carefully considered. Since the etiology may involve vasoconstriction as well as thrombosis, the decision to use thrombolytic agents in patients presenting within 3 hours of symptom onset may be more difficult. Vascular imaging, if readily available, may be helpful. Blood pressure is not usually severely elevated, but if sustained hypertension is present, current guidelines should be followed for lowering blood pressure. Neurosurgical consultation should be sought for intracranial hemorrhages to evaluate for possible interventions. Patients with subarachnoid hemorrhage should be evaluated for vascular malformations that may be amenable to treatment.

Most pulmonary toxicities associated with cocaine are managed with usual care or supportive care (51,52). Bronchoscopy and asthma should be treated with inhaled β-agonists and corticosteroids, if indicated. Pneumomediastinum can be followed without hospital admission for most patients. Small pneumothoraces may also resolve without intervention, whereas large pneumothoraces will require tube thoracostomy. Noncardiogenic pulmonary edema may require supplemental oxygen and mechanical ventilation, but resolves within a few days unless other complications occur.

Hyperthermia associated with cocaine use should be treated aggressively by rapid cooling (see Chapter 68, Temperature Related Injuries). Control of coexisting agitation, psychosis, or seizures is essential to achieve and maintain cooling while avoiding brain, hepatic, and muscle cell destruction. There is no evidence that pharmacologic agents such as dantrolene are of benefit in cooling patients with life-threatening hyperthermia.

Patients with hyperthermia, severe agitation or motor activity, seizures, and obtundation should be evaluated for rhabdomyolysis. Aggressive fluid resuscitation to replete the intravascular volume and enhance urine output should often be initiated prior to definitive diagnosis. Serial tests of electrolytes, renal function, and CPK are needed to monitor the severity and response of rhabdomyolysis.

Individuals may ingest packets of cocaine or any illicit drug for the purpose of transport or concealment. Body stuffers swallow small amounts of drug (wrapped or unwrapped) in
order to avoid arrest. In this circumstance, drugs are not prepared for passage through the GI tract and drug is frequently absorbed. Due to the smaller quantities of drug, toxicity is usually mild (81). In contrast, body packers swallow larger quantities of drug in multiple packets that are specially prepared for smuggling to withstand transit through the GI tract. Abdominal radiographs often show the location of the packets and allow tracking as they move through the GI tract. However, a negative result on plain abdominal radiograph does not rule out body packing, and an abdominal CT scan may be needed to visualize the packets (81).

Most body packers are asymptomatic and can be managed conservatively until the packets have been completely evacuated (81,82). Whole bowel irrigation may assist with passage of the packets. Body packers with signs and symptoms of drug toxicity, in vivo degradation, or GI obstruction require emergent surgical intervention (81).

Cocaine Withdrawal

Psychological and biochemical dependency on cocaine may be intense. Cocaine causes activation of the dopamine system and blocks dopamine uptake, especially in the pleasure centers of the brain (83). The brain becomes dopamine deficient, and even a short period of cocaine abstinence can result in a withdrawal state.

The clinical effects of cocaine withdrawal include depression, fatigue, irritability, sleep and appetite dysfunction, psychomotor agitation or retardation, and craving for more cocaine (30). A period of prolonged somnolence and decreased arousal can occur after the binge use of cocaine and often necessitates evaluations to rule out complications associated with cocaine use (84). A supportive environment and professional drug counseling are warranted.

TABLE 152.4 Classification of Opioid Agents

<table>
<thead>
<tr>
<th>Opioid Agonists</th>
<th>Natural opium derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Codeine</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Semisynthetic opioids</td>
</tr>
<tr>
<td></td>
<td>Heroin</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
</tr>
<tr>
<td></td>
<td>Oxymorphone</td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
</tr>
<tr>
<td></td>
<td>Synthetic opioids</td>
</tr>
<tr>
<td></td>
<td>Diphenoxylate</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
</tr>
<tr>
<td></td>
<td>Levorphanol</td>
</tr>
<tr>
<td></td>
<td>Loperamide</td>
</tr>
<tr>
<td></td>
<td>Meperidine</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td>Propoxyphene</td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pure Opioid Antagonists</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agonists-Antagonants</td>
<td>Naloxone</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
</tr>
</tbody>
</table>

Opioids include all drugs (synthetic as well as natural) that have morphine-like properties and/or bind to opioid receptors. There are at least five opioid receptors with various physiologic roles including analgesia, ventilatory depression, drug dependence, bradycardia, dysphoria, hallucinations, sedation, and miosis. Opioids are classified as receptor agonists or antagonists. Some have combined properties because they stimulate one type of receptor and antagonize another. A classification of opioids is found in Table 152.4. Opioid dependence is characterized by repeated self-administration of drug and encompasses physiologic dependence and addictive behavior. Exposure to opioids causes neural changes that produce tolerance, dependence, and withdrawal (83).

Toxicity

Abuse of prescription opioid pain relievers has been increasing, resulting in overdoses and fatalities (86,87). Heroin is rapidly absorbed by all routes of administration, including IV, intranasal, intramuscular, subcutaneous (skin popping), transdermal (fentanyl patches), and inhalation. Most fatal overdoses occur with IV administration; IV fentanyl extracted from analgesic patches is also associated with fatalities (88). Oral opioids are available illicitly or by prescription, and toxicity depends on the potency of the agent, dose ingested, and tolerance of the individual. Codeine elixir (“syrup”) is abused by adolescents and young adults. The diagnosis of opioid toxicity is made by characteristic clinical findings, exposure history, qualitative toxicology assay, and response to naloxone. Qualitative urine assays may not detect all opioid derivatives (e.g., fentanyl) and have little impact on immediate evaluation and treatment.

Opioid intoxication is characterized by a clinical syndrome of depressed level of consciousness, respiratory depression, and miosis. However, manifestations may be variable depending on the drug used and the presence of other drugs or alcohol. Miosis is not seen with meperidine and propoxyphene toxicity. The primary toxic manifestations of opioids are mediated by the μ- and κ-receptors in the brain, which cause CNS depression. Common clinical effects of these drugs are shown in Table 152.5.

The most worrisome feature of CNS depression is hypventilation. Tidal volume decreases first, and then respiratory rate falls. Although less common, seizures may be associated with meperidine, propoxyphene, and tramadol toxicity or result from hypoventilation and hypoxemia due to other opioids. Arteriolar and venous dilatation with opioid use can precipitate preload reduction, a fall in cardiac output, and hypotension.

An opioid-induced release of histamine from mast cells can precipitate bronchospasm, urticaria, and pruritus. Other respiratory complications include aspiration of gastric contents, noncardiogenic pulmonary edema, asthma exacerbation (heroin), pulmonary hypertension, ARDS, and septic pulmonary emboli (58,89). Intravenously injected illicit opioids may be mixed with microcrystalline cellulose, talc, or cellulose. These fillers are capable of producing angiothrombosis and a foreign body granulomatous reaction in the lung.
 effects last approximately 60 to 90 minutes. The patient may require repeated bolus injections of naloxone or a continuous infusion to maintain adequate respirations, particularly with long-acting opioids. The dose for infusion is one-half to two-thirds of the initial naloxone dose that reversed respiratory depression given on an hourly basis. Adjustments of the dose should be made to achieve clinical end points and avoid withdrawal symptoms. Additional boluses may be required as the infusion is started. Nalmefene, a long-acting opioid antagonist, has also been used to treat opioid overdoses, but prolonged withdrawal symptoms are a concern (92).

Isotonic fluids should be administered for hypotension due to opioids. Patients with significant opioid toxicity should be observed for other potential complications including aspiration pneumonitis and noncardiogenic pulmonary edema. Noncardiogenic pulmonary edema is usually self-limited, resolving in 24 to 36 hours, and managed with supportive care that may include intubation and mechanical ventilation. Seizures unresponsive to naloxone should be treated with IV benzodiazepines. Refractory seizures may suggest either body packing or another complication. The potential for acetaminophen toxicity should be considered in patients ingesting opioids formulated with acetaminophen.

**Acute Opioid Withdrawal**

The chronic administration of exogenous opiates is thought to lead to diminished endogenous opioid peptides. When these exogenous opiates are discontinued, the patient can develop opioid withdrawal. The clinical manifestations of opioid withdrawal are outlined in Table 152.6. The onset of symptoms varies with the drug abused. Symptoms can begin within 6 to 12 hours of the last dose with short-acting opioids such as heroin and within 36 to 48 hours with long-acting opioids.

### Treatment for Acute Intoxication

The most common cause of death in opioid overdose is ventilatory failure, and the immediate priority in acute opioid intoxication is airway management and ventilation (90). If reversal of respiratory depression cannot be accomplished quickly with naloxone, intubation may be necessary. Naloxone, a pure opioid antagonist, reverses all of the opioid-induced CNS and ventilatory depressant effects. The dose required to reverse opioid effects depends on the amount and type of opioid administered. The initial dose of naloxone is 0.4 to 2 mg; the lower dose should be administered initially in patients suspected of chronic addiction to avoid precipitating acute withdrawal symptoms. Additional doses of naloxone can be given based on the patient’s response. Although IV administration is preferred, naloxone can be administered intramuscularly, by sublingual injection, through an endotracheal tube, or by inhalation (91); naloxone kits and self-injectors are now available for home use. The goal of therapy is to restore adequate spontaneous respirations rather than complete arousal. Doses of naloxone up to 10 to 20 mg may be required in patients who have administered large quantities of opioids or opioids such as propoxyphene, pentazocine, methadone, and fentanyl. If CNS depression is not reversed by 20 mg of naloxone, alternate causes should be aggressively evaluated for, such as hypoglycemia, hypothermia, or head trauma. Close observation of the patient after naloxone administration is warranted because its

### Table 152.5 Clinical Manifestations of Opioid Intoxication

<table>
<thead>
<tr>
<th>Central Nervous System</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Gastrointestinal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Histamine release—bronchospasm</td>
<td>Arteriolar and venous dilation</td>
<td>Decreased peristalsis</td>
<td>Histamine release—urticarial, pruritus</td>
</tr>
<tr>
<td>Apathy</td>
<td>Pulmonary edema</td>
<td>Preload reduction</td>
<td>Decreased hydrochloric acid secretion</td>
<td>Muscle rigidity (fentanyl)</td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td>Hypotension</td>
<td>Constipation</td>
<td>Piloerection</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
<td>Restless sleep</td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td></td>
<td></td>
<td>Yawning</td>
</tr>
<tr>
<td>Ventilatory depression</td>
<td></td>
<td></td>
<td></td>
<td>Sneezing</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td>Rhinorrhea</td>
</tr>
<tr>
<td>Emesis</td>
<td></td>
<td></td>
<td></td>
<td>Anorexia</td>
</tr>
<tr>
<td>Misosis</td>
<td></td>
<td></td>
<td></td>
<td>Tremor</td>
</tr>
</tbody>
</table>

A pronounced decrease in GI peristalsis and increased ileocecal and anal sphincter tone are responsible for the constipation frequently seen with opioid use. Urinary retention may be caused by increased detrusor muscle tone. Local infections, endocarditis, and other systemic infections are especially common in the IV user.

### Table 152.6 Clinical Manifestations of Opioid Withdrawal

<table>
<thead>
<tr>
<th>Early</th>
<th>Intermediate</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yawning</td>
<td>Restless sleep</td>
<td>Fever</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Fliberation</td>
<td>Nausea</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>Restlessness</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Irritability</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Sweating</td>
<td>Anorexia</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Flushing</td>
<td>Tachycardia</td>
<td>Difficulty sleeping</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Tremor</td>
<td>Muscle spasm</td>
</tr>
<tr>
<td>Tremor</td>
<td>Hyperthermia</td>
<td>Joint pain</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Involuntary ejaculation</td>
<td>Suicidal ideation</td>
</tr>
</tbody>
</table>
such as methadone. Opioid withdrawal is rarely life-threatening and usually does not require intensive care.

If it is necessary to control withdrawal symptoms, most opioids in sufficient dosage will alleviate symptoms. Methadone, buprenorphine, and clonidine have been used to treat acute opioid withdrawal. In addition, methadone and buprenorphine have been used to treat opioid addiction chronically. Methadone can cause constipation, respiratory depression, dizziness, sedation, nausea, and diaphoresis. Oral buprenorphine has low toxicity in high doses, partly because its μ-antagonistic effects limit the opioid effects of sedation, respiratory depression, and hypotension. Buprenorphine is more effective than clonidine and similar to methadone for management of opioid withdrawal (93).

Clonidine has also been used to suppress the autonomic effects of opioid withdrawal. Doses of 0.1 to 0.3 mg orally can suppress the signs and symptoms of opiate withdrawal within 24 hours and shorten acute withdrawal reactions by 3 to 4 days (94). Side effects are hypotension, drowsiness, dry mouth, and bradycardia.

Heroin Body Packers

Heroin body packers should be managed similar to cocaine body packers (see above). If there is evidence of systemic absorption from leaking packets, opioid toxicity should be treated with a continuous infusion of naloxone.

AMPHETAMINES AND DERIVATIVES

Amphetamines, methamphetamines, and similar derivatives are, along with cocaine, the most commonly abused CNS stimulants. Although there are limited medical uses for these drugs—such as narcolepsy, attention deficit disorder, and obesity—they are usually abused for the euphoric effects or to enhance performance. Amphetamines act by increasing release and inhibiting reuptake of dopamine and serotonin in the brain. Minor chemical substitutions can enhance the hallucinogenic properties of the drug. The ease of production of these drugs from readily available ingredients in clandestine laboratories has resulted in increased supply throughout the United States. Methamphetamine can be made from common ingredients such as rock salt, paint thinner, lantern fuel, battery acid, lye, ammonia, lithium, ether, rubbing alcohol, iodine, and cold medicines containing pseudoephedrine.

Methamphetamine in a crystalline form—commonly called ice, crank, glass, or crystal—is one of the most popular drugs in this class. It can be orally ingested, smoked, snorted, or injected intravenously. An amphetamine-like drug, 3,4-methyldioxymethamphetamine, is a designer drug—commonly known as Ecstasy, XTC, or MDMA—that acts simultaneously as a stimulant and hallucinogen (95). It results in greater serotonin release in the brain with inhibition of serotonin reuptake. It is abused in pill or capsule forms that are orally ingested. MDMA use has been associated with rave parties and is more commonly abused by adolescents and young adults. Most amphetamines are detected on qualitative urine toxicology assays but a negative result does not rule out amphetamine intoxication or abuse.

Toxicity

In general, these drugs cause the release of catecholamines, which result in a sympathomimetic/adrenergic syndrome. Compared to cocaine, the “high” and physiologic effects last longer, hours to several days depending on the agent used. The clinical presentation is characterized by tachycardia, hyperthermia, agitation, hypertension, and mydriasis. Hallucinations—both visual and tactile—hypervigilance, and acute psychoses (often paranoia) are frequently observed. MDMA leads to increased verbosity and sociability. MDMA use is associated with bruxism that is often countered by sucking on a pacifier or lollipop. Amphetamine use is often associated with behaviors resulting in trauma and risky sexual encounters. The acute adverse medical consequences are similar to those seen with cocaine abuse (see above) and include myocardial ischemia and dysrhythmias, seizures, intracranial hemorrhage, stroke, hyperthermia, rhabdomyolysis, necrotizing vasculitis, and death (96). Long-term use of these drugs may result in dilated cardiomyopathy and “meth mouth,” which refers to a pattern of oral signs and symptoms of methamphetamine abuse, thought to include rampant caries and tooth fracture, leading to multiple tooth loss and edentulism (97). Burn injuries from methamphetamine laboratory explosions are associated with a higher incidence of inhalational injury and greater use of critical care resources (98).

Complications of MDMA use are usually a result of the drug effects and nonstop physical activity. The effects of MDMA last for 4 to 6 hours. Medical complications include hyperthermia, hyponatremia, rhabdomyolysis, seizures, renal failure, arrhythmias, syncope, cerebral infarction/hemorrhage, hepatotoxicity, serotonin syndrome, and death (99). Hyponatremia and hepatotoxicity are relatively unique with this agent and the mechanisms leading to these complications are unknown.

Management

Management of amphetamine intoxication is primarily supportive. Gastric lavage is not recommended because absorption after oral ingestion is usually complete when patients present; activated charcoal may be considered if a recent oral ingestion is known to have occurred. Further interventions are dependent on patient complaints and clinical findings. A careful assessment for complications should be made, including measurement of core temperature, obtaining an ECG, searching for evidence of trauma, and evaluating laboratory data for evidence of renal or hepatic dysfunction and rhabdomyolysis. IV hydration for possible rhabdomyolysis is warranted in individuals with known exertional activities pending CPK results. Patients should be placed in a quiet, calm environment and benzodiazepines, often in high doses, are used for controlling agitation. Haloperidol should be reserved for patients who do not have an adequate response to benzodiazepines.

Withdrawal

Acute withdrawal from amphetamines is similar to cocaine and symptoms include fatigue, depression, anxiety, motor retardation, hypersomnia—followed by insomnia—increased eating, and drug craving (100). Although withdrawal is uncomfortable, the manifestations are not dangerous. Patients
may become suicidal during withdrawal and should be evaluated for this possibility. Symptoms may persist for months.

**γ-HYDROXYBUTYRATE**

γ-Hydroxybutyrate (GHB), a naturally occurring metabolite of GABA found in the brain, has limited clinical use in narcolepsy but is more commonly a drug of recreational abuse (101). It is one of several agents characterized as a “date rape” drug and it has been promoted to build muscle, improve performance, produce euphoria, and enhance sleep. The drug is usually available as a colorless, odorless liquid with a mild salty taste that is easy to mask in drinks. GHB is absorbed from the stomach, usually within 10 to 15 minutes, and readily crosses the blood–brain barrier where it interacts with GHB and γ-aminobutyric acid type-B (GABAB) receptors. Stimulatory effects occur from resulting increased dopamine levels in the brain and sedative effects by potentiation of endogenous opioids. γ-Butyrolactone (GBL), also known as 2(3H)-furanone-2,4-dihydro, and 1,4-butanediol (BD), also called tetramethylene glycol, have been abused with the same adverse effects as GHB. Both agents are metabolized systemically to GHB.

**Acute Toxicity**

The manifestations of GHB toxicity are dose related and include agitation, coma, seizures, respiratory depression, and vomiting. Other effects include amnesia, tremors, myoclonus, hypotonia, hypothermia, decreased cardiac output, and bradycardia. A dose of 20 to 30 mg/kg can produce euphoria and sleepiness and coma may result from doses of 40 to 60 mg/kg or more (101,102). Concomitant use of ethanol results in synergistic CNS and respiratory depressant effects. Deaths attributed to GHB and related agents usually result from respiratory depression, hypoxemia, or aspiration. GHB is not routinely detected by urine toxicology assays but can be detected in plasma or urine by gas chromatographic–mass spectrophotometric techniques. Rapid clearance precludes detection beyond 12 hours after a dose (102). Diagnosis is usually determined by the clinical course and history of exposure elicited after the patient recovers. A hallmark of GHB intoxication is rapid onset of toxicity and sudden, rapid recovery rather than a gradual recovery usually seen with ethanol or benzodiazepine intoxication.

**Assessment and Treatment of Acute Intoxication**

There is no antidote for GHB, GBL, or BD toxicity. The primary management for ingestion of these drugs is supportive care with particular attention to airway protection. In some cases, intubation and mechanical ventilation are required. Gastric lavage and activated charcoal are not warranted because of the small amounts involved and the rapid absorption. Naloxone and flumazenil are of no benefit. Atropine may be needed for symptomatic bradycardia. Patients with mild intoxication may be observed in the emergency department and released after symptoms resolve. A rapid recovery of consciousness from an obtunded condition in a few hours is frequently observed. In patients requiring intubation and mechanical ventilation, symptoms can be expected to resolve within 2 to 96 hours unless complications such as aspiration or anoxic injury have occurred. The concomitant use of alcohol may prolong the CNS depression. Although physostigmine has been reported to awaken patients with GHB intoxication, its use is not recommended (101).

**γ-Hydroxybutyrate Withdrawal**

A sedative withdrawal syndrome following high-dose frequent use—every 1 to 3 hours—of GHB, GBL, and BD has been described (101–103). Mild symptoms such as anxiety, insomnia, nausea, vomiting, and tremors begin within 6 hours of the last dose and may progress to severe delirium with autonomic instability, usually mild, requiring hospitalization and sedation. Patients may experience auditory, visual, and tactile hallucinations. The duration of symptoms requiring treatment may be as long as 2 weeks. Benzodiazepines are the initial choice for management and high doses may be required. Propofol and barbiturates have also been used successfully (101–103).

**PHENCYCLIDINE**

Phencyclidine (PCP) is a psychoactive drug used as a hallucinogen that can be administered by oral ingestion, nasal inflation, smoking, or IV injection. PCP is a dissociative agent that blocks the NMDA receptors leading to an inhibition of sensory perception. Sympathomimetic effects result from inhibition of norepinephrine and dopamine reuptake.

**Clinical Manifestations**

Signs and symptoms reported with PCP use are variable depending on the route of abuse, susceptibility of the user, and concomitant drug use (104). Behavioral effects of PCP include coma, catatonia, psychosis, and confusion. Agitation may be intermittent and unexpected. Misperception of reality can lead to violent behavior, risk-taking behavior, and accidents resulting in trauma. Nystagmus—horizontal, vertical, and/or rotatory—and miosis are characteristic findings with PCP intoxication along with ataxia. Medical complications can include hyperthermia, rhabdomyolysis, and seizures; dystonic reactions occur rarely. PCP is usually detected on urine qualitative toxicology tests.

**Management**

Management of a patient with PCP intoxication includes control of agitation using a quiet, nonstimulatory environment and benzodiazepines as needed; haloperidol may be beneficial for frank psychosis. Physical restraints are often needed until adequate sedation is achieved. Tachycardia and hypertension, if present, usually respond to control of agitation. Activated charcoal does adsorb PCP but most patients present after GI absorption is complete following oral ingestion. Although urinary acidification enhances PCP excretion, that intervention is not recommended. The possibility of rhabdomyolysis should be evaluated and early fluid therapy should be considered while awaiting test results.
Key Points

**Alcohol Intoxication and Withdrawal**

- Treatment of acute ethanol intoxication is primarily supportive, but a careful examination is needed to detect complications or concomitant conditions.
- The first priority in treating acute ethanol intoxication is assessment and stabilization of the airway and ventilation.
- Four stages of alcohol withdrawal have been described, but symptoms are a continuum of neuropsychiatric and hemodynamic manifestations. A key distinction is to determine if the patient has an intact or altered sensorium.
- Benzodiazepines are effective in treating minor alcohol withdrawal symptoms, preventing withdrawal seizures and terminating withdrawal seizures.
- High-dose IV benzodiazepines administered at frequent intervals or as a continuous infusion are used to control the hyperadrenergic symptoms of DT.

**Cocaine Intoxication**

- Patients with cocaine intoxication may present with a variety of signs and symptoms related to CNS stimulation and complications involving other organ systems.
- Benzodiazepines are the agents of choice for control of cocaine-induced agitation.
- Aspirin, nitroglycerin, and benzodiazepines are the first line of treatment for cocaine-induced myocardial ischemia.
- Patients with hyperthermia, severe agitation or motor activity, seizures, and obtundation should have fluid resuscitation initiated while they are evaluated for rhabdomyolysis.

**Opioid Intoxication and Withdrawal**

- Opioid intoxication is characterized by a clinical syndrome of depressed level of consciousness, respiratory depression, and miosis.
- The immediate priority in acute opioid intoxication is assessment and stabilization of the airway and ventilation.
- Naloxone can reverse all of the opioid-induced CNS and ventilatory depressant effects but the goal is to administer the appropriate dose to restore adequate spontaneous respirations rather than complete arousal.
- Opioid withdrawal is rarely life threatening and withdrawal symptoms can be managed with administration of opioids in sufficient dosage.

**Amphetamine and Derivative Intoxication**

- Amphetamines and related drugs result in a sympathomimetic/adrenergic syndrome similar to cocaine.
- Management of amphetamine intoxication is primarily supportive with specific interventions dependent on patient complaints and clinical findings.
- Benzodiazepines, often in high doses, are used for controlling agitation.

**γ-Hydroxybutyrate Intoxication and Withdrawal**

- The manifestations of GHB toxicity include agitation, coma, seizures, respiratory depression, and vomiting.
- The primary management for ingestion of GHB is supportive care with particular attention to airway protection.
- GHB withdrawal may manifest with mild symptoms such as anxiety, insomnia, nausea, vomiting, and tremors and may progress to severe delirium with autonomic instability, requiring hospitalization and sedation with benzodiazepines.

**References**