Addictive Disorders

MEDICAL CONSEQUENCES OF SUBSTANCE ABUSE

Michael D. Stein MD

Rhode Island Hospital Department of Medicine and Brown University Medical School, Providence, Rhode Island

Address reprint requests to
Michael D. Stein, MD
Director of HIV Services
Rhode Island Hospital
593 Eddy Street
Providence, RI

Since the advent of HIV epidemic in the early 1980s, the medical care of illicit drug users has become central to national and local public health planning. Drug users are at high risk for acquiring and transmitting HIV to their social network via needle sharing, trading sex for drugs, sexual relations with steady partners, and perinatally. The association between alcohol abuse and high-risk behaviors for acquiring AIDS has more recently been demonstrated by the finding of a substantial prevalence of HIV infection among clients of alcohol-addiction treatment programs. [3]

Before HIV disease, life-threatening events were not new to populations of drug and alcohol abusers. [10] [66] Indeed, injection-drug addicts have been found to die at seven times the rate of comparable age groups in the general population. [33] Population studies have shown that heavy drinkers have an increased risk for death from cirrhosis, motor vehicle accidents, suicide, homicide, certain malignancies, and hemorrhagic cerebrovascular disease. [36] Behaviors and environment often dictate health, and most addicts still reside in high-risk neighborhoods. That they die drug-related and violence-related deaths comes as no surprise.

Although research on HIV disease has focused attention on injection-drug use, other routes of drug administration may lead to equally pernicious medical complications. This article is

divided into four parts. The first discusses the complications of alcohol, the most commonly abused substance in the United States. The second involves the complications of injection-drug use, focusing on those illnesses that are specifically caused by needle use. Most of this literature derives from series of

---

opiate abusers. The third section focuses on the complications of cocaine use. Cocaine produces toxicity apart from its route of administration, and these illnesses are highlighted. Finally, the complications of HIV disease that have been described in persons who use illicit drugs are presented. Because the complications that bring addicted persons to seek medical care are mostly caused by alcohol, opiate, or heroin abuse, these three drugs are the focus of this article, and discussions of other classes of drugs, including tobacco, are not included.

The spectrum of disease related to drugs of abuse is broad and often insidious. Health care providers must actively consider drug use when obtaining patient histories, performing physical examinations, and considering differential diagnoses to identify drug users before severe complications occur. [29] Preventive health care requires the early identification of those at risk for drug-related complications. When drug-related complications occur, providers may have a special opportunity to direct patients who are particularly receptive into drug treatment. [23]

The literature concerning the range of medical complications caused by alcohol, opiates, and cocaine is based on case series and individual case reports. Few large surveys documenting the long-term natural history of the complications of opiates or cocaine use exist. [31] Therefore, to assess the precise toxicity of drugs of abuse is difficult because most reports do not, and cannot, report standard doses because patient histories are often unreliable and because concomitant multidrug use is common among chemically dependent persons.

ALCOHOL

Although continued disagreement about the risk levels of alcohol consumption exists, after a medical complication of alcohol use has occurred, it may serve as an aid in breaking though patients' denial of their problem drinking. Higher-than-expected rates of care seeking for digestive disorders and traumatic injuries are associated with heavy alcohol use across broad populations of patients, although many other health problems have been described among heavy users. [54] Population studies have shown that heavy drinkers have an increased risk for death from cirrhosis, motor vehicle accidents, suicide, homicide, certain malignancies, and hemorrhagic cerebrovascular disease. [1] [36] The importance of controlling for cigarette smoking, a strong correlate of alcohol use and a predictor of death from several of these causes, is well known. Nonetheless, the risk for death among heavy drinkers is at least 50% higher than the risk among

light drinkers, and this risk is increased more for women than for men. [2] Alcoholic men who achieve stable abstinence return to age-, sex- and race-matched mortality experience. [5]

A direct relationship generally exists between alcohol consumption level, or duration of use, and clinical problems. Frezza et al [19] noted that women have higher blood alcohol levels than do men given an equivalent

dose of alcohol, most likely because of their smaller size and less first-pass gastric metabolism.

Long-term heavy alcohol use is associated with protean medical complications. [39] A wide range of symptoms, physical findings, and laboratory abnormalities have been described. The medical signs and symptoms of alcohol use include the following:

Nausea

Vomiting

Anorexia

Diarrhea

Tremor

Myalgia

Abdominal pain

Weight loss

Muscle weakness

Dizziness

Confusion

Headache

Physical findings among heavy alcohol users include the following:

Spider angiomata

Palmar erythema

Gynecomastia

Parotid gland enlargement

Polyneuropathy

Hepatomegaly

Splenomegaly

Tachycardia

Hypertension

Dupuytren's contracture

Proximal myopathy

Periorbital edema

Jaundice

Heme-positive stool

Lab abnormalities caused by alcohol abuse include the following:

Hyponatremia

Hypokalemia

Hypomagnesemia

Hyperamylasemia

Hyperbilirubinemia

Prolonged prothrombin time

Thrombocytopenia

Hypophosphatemia

Transaminitis

Anemia

Leukopenia

Many of the disorders that are described in heavy drinkers can be halted or reversed by cessation of alcohol intake. The most common disorders associated with alcohol are described, with focus on clinical findings, treatments, and prognosis.

Gastrointestinal Symptoms

The most common complaints related to alcohol use are gastrointestinal: pain, bloating, nausea, and vomiting. Alcohol slows gastric emptying, stimulates gastric secretions, and injures gastric mucosa. Although symptoms often subside with the cessation of intake, for even moderate drinkers the risk for gastritis and ulcers is not trivial. Heavy, long-term drinking is associated with acute and chronic pancreatitis. Diarrhea is common for a variety of reasons, including exacerbation of lactase deficiency.

The liver is the organ most severely affected by alcoholism. Right upper quadrant pain is a common presentation of patients with liver disease and often occurs in persons consuming modest quantities of alcohol (20-40 g/d). It may signify fatty liver (the most common histologic abnormality on biopsy), hepatitis, cholestasis, or portal hypertension. Alcoholic hepatitis may be asymptomatic or florid and life-threatening, usually developing over weeks with vomiting, weight loss, and possibly jaundice. In mild cases, the course is benign, but the prognoses of many persons worsen despite abstinence and nutritional care. The clinical, biochemical, and histologic consequences of hepatic injury may occur separately or in combination, although poor correlation exists between clinical syndromes and pathologic abnormalities.

An early diagnosis of liver complications is important because both fatty liver and alcohol hepatitis are reversible, but cirrhosis is not. Cirrhosis occurs in 10% to 20% of long-term, heavy alcohol users (120-180 g/d for more than 15 y) but is discovered in only 25% of patients antemortem. More than half of those with cirrhosis die within 4 years. Women may have a greater susceptibility to cirrhosis. [65] Non-alcoholic-related liver disease must be considered even among heavy alcohol users. Finally, alcohol abuse is associated with cancers of the alimentary tract because alcohol enhances the mutagenesis of tobacco-derived products and induces a deficiency of vitamin A. [39]

Cardiovascular Symptoms

Long-term alcohol abuse is associated with a variety of cardiovascular disorders, including hypertension, stroke, heart failure, and sudden death. Alcoholic cardiomyopathy may be subclinical. Clinical decompensation typically occurs in persons who have ingested at least 80 g/d for at least 10 years. [6] Alcoholic cardiac myopathy that is diagnosed early responds to the cessation of alcohol intake. Cardiomyopathy and myopathy

---

are more common in female alcoholics than in male alcoholics. In one study, [68] the threshold dose for the development of cardiomyopathy was considerably lower for women, and the slope of decrease in ejection fractions was steeper for women, indicating that women are more sensitive than men to the toxic effects of alcohol on striated muscle.

Cardiac arrhythmias, mostly atrial, can occur during intoxication, withdrawal, and even moderate intake in persons without cardiomyopathy. Atrial fibrillation is the most common presenting rhythm, and electrolyte levels are usually normal. [13] Cardioversion is often required to return patients to sinus rhythm. An increased risk for sudden cardiac death among persons who abuse

alcohol but who do not have known heart disease has been noted in cohort studies and case-control series. [56]

Epidemiologic studies have also indicated a positive association between the amount of alcohol consumed and cerebral vascular accident, including subarachnoid hemorrhage and stroke. [36] This increased risk may be mediated via alcohol-induced hypertension. Primary care providers should consider alcohol consumption as a potential cause of hypertension because 5% to 10% of hypertensive cases are thought to be caused by alcohol intake. Certainly, the response to antihypertensive agents is decreased by active alcohol use. For heavy drinkers (six drinks per day) the prevalence of hypertension is double that of abstinent individuals. [35] Light to moderate drinking has been found to lower total mortality rates for men and women largely because of the reduced risk for fatal coronary disease. [21]

Hematologic Symptoms

The hematologic disorders related to alcohol result from the direct effects of ethanol, secondary nutritional deficiencies and from hepatic disease. [30] A spectrum of hematologic problems involving erythrocytes, leukocytes, platelets, and other hemostatic factors are relatively common. The production of erythrocytes, leukocytes, and platelets can all be suppressed by alcohol. In patients with severe alcoholism, anemia with macrocytosis is a common finding. In alcohol users without marked liver disease, folate deficiency, reticulocytosis, and macrocytosis predominate, often without anemia. As many as 75% of heavy alcohol users may have bone marrow hypofunction, and half of these cases are related to folate deficiency caused by poor intake, decreased capacity to store folate, and impaired jejunal folate absorption. The anemia of alcohol users is the result of multiple causes, including iron deficiency (from gastrointestinal bleeding), decreased erythrocyte survival, defects of marrow production, and nutritional deficiencies.

Persistent leukopenia and thrombocytopenia are markers of long-term alcoholism. A minority of alcoholics have neutropenia, although this may be more common among those with acute infections. Thrombocytopenia, which may be present in as many as 25% of acutely intoxicated patients, is likely caused by the decreased production and survival

of platelets; a return to normal platelet counts occurs after 2 to 4 weeks after drinking cessation. Coagulation does not change after acute alcohol ingestion; fibrinolytic and coagulation factor changes occur only with long-term alcohol intake.

Gynecologic Symptoms

Numerous gynecologic and obstetric complications are associated with heavy alcohol consumption. Specifically, amenorrhea, dysfunctional uterine bleeding, dysmenorrhea, infertility, and premenstrual syndrome have been described. [11] The obstetric complications of alcohol consumption include spontaneous abortion, stillbirth, premature labor, and low birth

weight infants. An estimated one third of infants born to women drinking more than six alcoholic beverages per day during pregnancy have fetal alcohol syndrome. [11]

Metabolic Symptoms

The metabolic disturbances caused by acute alcohol intoxication are complex. Metabolic acidosis from vomiting and dehydration; respiratory alkalosis from withdrawal, sepsis, or pain; and metabolic ketoacidosis all may be superimposed. [74] Electrolyte disturbances, including hypokalemia, hyponatremia, hypomagnesemia, and hypophosphatemia, are not uncommon, particularly when persons with long-term alcohol abuse and malnutrition start binge drinking.

On average, ethanol (with its high energy content) accounts for half of an alcoholic person's daily caloric intake. [39] Therefore, malnutrition commonly occurs as a result of an inadequate intake of folate, thiamine, and other vitamins, as well as through malabsorptive complications, such as pancreatic insufficiency and impaired hepatic metabolism of nutrients.

Central Nervous System Symptoms

Neurologic disorders constitute a large, diverse, and devastating subset of medical complications of alcoholism. [2] Complications involve every level of the nervous system and may be caused by a combination of direct neurotoxic effects, nutritional factors, and genetics. Alcohol intoxication (with blood levels reflecting levels in the brain) first affects vestibular and cerebellar functions, causing nystagmus, dysarthria, and ataxia; additional intake may lead to mild confusion, stupor, respiratory suppression, and coma. Comatose alcoholic patients pose an array of diagnostic possibilities that include mixed-drug overdose, head trauma, hypoglycemia, meningitis, and ketoacidosis. Although intoxication is legally defined in most places as 100 mg/dL, levels as low as 47 mg/dL are associated with an increased risk for motor vehicle accidents. Long-term

tolerance (thought to be caused by adaptive changes in membrane lipids, neuromodulators, neurotransmitter receptors, ion channels, and G proteins) permit alcoholic patients to remain sober in the face of extremely high ethanol concentrations.

Heavy alcohol intake for a short periods of time, or lower level ingestion over prolonged periods, leads to physical dependence. Cessation of drinking or reduction in intake in physically dependent persons may lead to a withdrawal syndrome. [67] This syndrome is characterized by autonomic hyperactivity, nausea and vomiting, insomnia, tremor, agitation, and perceptual disturbance that includes visual or auditory illusions. Symptoms begin within hours of withdrawal onset, peak at 24 to 36 hours, and may be suppressed by resumption of drinking, beta-adrenergic receptor blockade or alpha$_2$ -adrenergic blockade. A minority of persons (10%-20%) undergoing withdrawal have generalized tonic-clonic seizures early in withdrawal. For patients who have seizures after the first 24 hours of withdrawal and who have focal neurologic deficits or signs of head trauma, brain imaging is required to evaluate for treatable abnormalities, such as a subdural hematoma. The most severe and delayed (day 2-4) manifestation of

withdrawal is delirium tremens. Approximately 5% of those hospitalized for withdrawal develop delirium tremens, which is characterized by profound confusion and agitation and severe autonomic hyperactivity, including tachycardia and fever. Frequently precipitated by other illnesses (e.g., pancreatitis or complications of trauma), delirium tremens resolves in 80% of cases within 72 hours, but 5% of patients may die. These outcomes have not changed significantly over the past 2 decades despite the widespread use of benzodiazepines to limit the discomfort of withdrawal.

Wernicke's encephalopathy, caused by thiamine deficiency, classically includes the triad of encephalopathy, ophthalmoplegia (i.e., nystagmus and lateral rectus palsies), and ataxia. Although only one third of patients with acute Wernicke's encephalopathy have all three signs, a majority are profoundly disoriented. [2] But only a subset of thiamine-deficient alcoholic patients have Wernicke's encephalopathy; how thiamine deficiency leads to the characteristic brain lesions is unclear. With prompt repletion of thiamine (100 mg/d of thiamine for at least 5 d), ocular signs improve within hours and ataxia and cognitive signs within days, most likely representing biochemical improvement rather than the reversal of a structural lesion. Most of these patients are left with Korsakoff syndrome, a disabling anterograde and retrograde memory disorder.

Many long-term, heavy alcohol users have impaired performance on neuropsychological tests even when sober, which may be caused by premorbid intellectual deficits, ethanol neurotoxicity, head trauma, and nutritional deficiencies. A long-term cerebral degeneration may occur after 10 or more years of heavy use, although this condition does not correlate with daily or lifetime consumption patterns, and the cause remains unknown. [2] It is usually of subacute onset, with gait ataxia as the prominent symptom.

358

Alcoholic patients also have a high incidence of peripheral nerve disorders, most commonly polyneuropathies, thought to be caused by thiamine deficiency and other vitamin B deficiencies. Gradually progressive, the clinical findings are usually symmetric and distal, including numbness, paresthesias, cramps, weakness, and loss of tendon reflexes. Improved nutrition and abstinence often result in improvement.

Alcoholic myopathy may present acutely or more slowly. The acute form, which is rare, develops over hours (often during a binge) and is characterized by weakness, tenderness, and swelling of the affected muscle. Most often involving proximal muscles, an elevated serum creatinine kinase level is present, as is myoglobinuria, and necrosis of muscle fibers is present on biopsy. Chronic myopathy includes muscle weakness and atrophy affecting the hip and shoulder groups. The cessation of drinking leads to improvement in most patients.

Trauma

The degree of alcohol intake is predictive of traumatic death. [1] Younger drinkers are known to be more likely to be involved in alcohol-related accidental deaths than are older persons. [45] But

alcohol is also associated with nonfatal injury, and minor trauma may be a clue to excessive drinking.

Drug Interactions

Alcohol interacts with hypnosedatives (e.g., antihistamines, barbiturates, and benzodiazapines), phenothiazines, and opiates to cause respiratory depression. With warfarin, alcohol can increase anticoagulant potency. With therapeutic amounts of acetaminophen, hepatotoxic metabolites can cause liver necrosis. Alcohol may interact with tricyclic antidepressants to increase the risk for seizures and arrythmias; similarly, cocaine is converted to toxic metabolites. Disulfiram-like reactions can occur with chlorpropramide, metronidazole, isoniazid, and some cephalosporins. Acute and long-term alcohol ingestion causes a significant increase in circulating estradiols, particularly in women using estrogen-replacement therapy. [25] The potential health risks and benefits of this finding are being evaluated.

INJECTION-DRUG USE

Illicit drug use leads to approximately 20,000 deaths each year in the United States. [43] These deaths result from overdose, suicide, homicide, injuries caused by motor vehicle accidents, pneumonia, hepatitis and endocarditis, and HIV disease. [24]

Before AIDS, medical epidemics penetrating this population included hepatitis and tetanus. In the 1950s in New York City, 8.3% of deaths among addicts were caused by tetanus. In the late 1960s, acute hepatitis was "the foremost cause of addicts admissions to municipal hospitals." [66] Over the past decade, novel infectious and noninfectious syndromes have been identified among injection-drug users, [10] [66] including the following:

Infectious

Endocarditis

Pneumonia

Cellulitis

Cutaneous abscess

Gas gangrene

Infected false aneurysm

Osteomyelitis

Septic arthritis

Sexually transmitted diseases

Tuberculosis

Tetanus

Malaria

HIV infection

Epidural abscess

Subdural abscess

Brain abscess

Hepatitis A, B, C, and D viruses

Noninfectious

Nephrotic syndrome

Glomerulonephritis

Renal failure

Arrhythmia

Mycotic aneurysm

Talc granuloma

Pulmonary edema

Pneumothorax

Pneumomediastinum

Pulmonary fibrosis

Pulmonary hypertension

Motility disorders

Constipation

Stroke

Myositis

Overdose

Trauma

Needle embolus

Necrotizing angiitis

Amenorrhea

Thrombocytopenia

Drugs injected by addicts include heroin, cocaine, meperidine, hydromorphone, pentazocine, tripelennamine, and barbiturates. [66] These are used individually or are mixed and before injection are usually liquefied and then filtered through cotton into syringes. Opiates are sold in "bags" that are sold with a wide range of purity. Users' lack of awareness of the exact dose injected may be one cause of overdoses. Even in the era of AIDS, drug overdoses remain the leading cause of death among injection-drug users. [53]

Soft Tissue Infections

The possibilities of contamination between bag and bloodstream are both chemical and microbial. Skin infections are among the most common complications of drug injection. [28] Quinine, used as a dilutant, may produce anaerobic skin abscesses. An addict's skin flora is the likely source of the infecting organism, as is demonstrated by the microbiology of soft tissue infections, such as cellulitis and skin abscesses. [50] Skin flora may be expected to differ among institutions as well as according to individuals' injection sites. beta-hemolytic streptococci and *Staphylococcus aureus* account for the majority of microbial cases, although anaerobes predominate in some series. [51] [72] Wound botulism is an unusual, potentially lethal infection caused by spores from *Clostridium botulinum*[52] HIV infection is an independent risk factor for skin abscesses.

Fever

Fever is a common reason for hospital admission among injection-drug users and can be a manifestation of both common and unusual medical conditions. The major concern in the evaluation of a febrile injection-drug user is differentiating severe illnesses (e.g., endocarditis) from less-severe illnesses that can be managed without hospitalization. Two studies have examined consecutive series of febrile injection-drug users. [40] [59] Although in most cases the cause of fever is clinically apparent after a physical examination and initial testing (e.g., pneumonia or cellulitis), in roughly one third of cases, the cause of fever is not apparent. Neither of two studies [40] [59] could identify clinical or laboratory features that might assist clinicians in identifying severe illnesses in this group. Therefore, hospitalization is often recommended for febrile injection-drug users to ensure adherence with follow-up examinations and to initiate parenteral antibiotics for those with occult bacteremia.

Endocarditis

A history of injection-drug use creates the endothelial valvular damage and platelet fibrin deposition thought necessary for bacterial

endocarditis. Endocarditis is diagnosed by the presence of persistently positive blood cultures and cardiac valve involvement. [4] The incidence of bacterial endocarditis is estimated at 2 cases per 1000 addicts per year. An affinity between particular organisms and particular valves may exist. [60] *S. aureus* remains the most common isolate in endocarditis and affects the left and right sides of the heart with approximately equal frequency. [42] Patients with right-sided endocarditis generally have good prognoses, with septic pulmonary emboli being the major complication. *Streptococcus* sp., the next most common organism, may have a proclivity for left-sided valves, where systemic embolization more often leads to fatal outcomes. Echogenic vegetations are predictive of endocarditis, and their presence may persist after bacteriologic cure. Clinical prediction of the infecting species is difficult, and directed antibiotic therapy remains of greatest importance. Approximately 20% of patients require surgery, most often for congestive heart failure. [42]

Pulmonary Symptoms

Dyspnea is another common complaint of injection-drug users and results from common diseases or syndromes unique to this population. For instance, talc granulomatosis is unique to addicts who dilute their drug of choice with talc. Deposition of talc crystals in pulmonary arterioles leads to granuloma formations and chronic dyspnea. Acute onset of shortness of breath suggests a toxic drug response. Cotton, used as a filter, can cause granulomatous pulmonary reactions. [66] Bronchospasm has been reported after intravenous opiate use. Pulmonary edema from heroin use may also occur, although the proposed mechanisms remain speculative and include allergic reaction, opiate-induced histamine release, and a CNS effect. [66]

Pneumonia, caused by typical community-acquired organisms such as *Hemophilus influenzae* and *Streptococcus pneumoniae*, is common among injection-drug users. Alcohol use, in addition to cigarette smoking and drug injection, increases the risk for aspiration. Consideration of opportunistic pulmonary infections is important even in the absence of documented HIV seropositivity. [44]

The resurgence of tuberculosis in general and among injection-drug users in particular geographic areas has been alarming over the past 5 years. Latent tuberculosis has been found in as many as 25% of selected urban drug-using populations. [20] Alcohol has been associated with the reactivation of tuberculosis in part because of malnutrition and poor compliance with antituberculous chemotherapy. The possibility of tuberculosis must be considered with any pulmonary infiltrate. Respiratory precautions, before a definitive diagnosis is made, are appropriate for injection-drug users admitted to the hospital with abnormal chest radiographs in high-risk areas.

Hepatitis

Injection-drug users are at high risk for various forms of infectious and toxic hepatitis. Approximately two thirds of short-term injectors have serologic evidence of hepatitis B virus and hepatitis C virus infection. [22] Acute and chronic liver disease (in particular, hepatitis C disease) may be exacerbated by concomitant alcohol abuse. Outbreaks of delta hepatitis leading to fulminate liver failure have been described among drug injectors. [37] Clinically important cytomegalovirus or Epstein-Barr virus hepatitis is rare among addicts. The progression from chronic, persistent hepatitis to chronic, active hepatitis may be more common among injection-drug users than among those who do not use drugs, perhaps because continued viral exposure and increased viral load. The majority of alcohol-using parenteral drug users have histologic evidence of chronic liver disease ranging from chronic, persistent hepatitis to cirrhosis.

Sexually Transmitted Diseases

Sexually transmitted infections have been associated with substance abuse because of the exchange of sex for drugs and the finding that sexual impulsivity has been associated with psychoactive substance use, particularly cocaine and alcohol. [46] Infections that cause genital ulceration facilitate the transmission of HIV infection. The high false-positive rate of nontreponemal tests for syphilis in injection-drug users justifies the use of specific treponemal tests. [26] The recommendation and distribution of latex condoms may prevent infections.

Renal Disease

A variety of chronic renal conditions have been reported among drug injectors. Urinalysis commonly demonstrates mild to moderate proteinuria and hematuria. Nephrotic syndrome (heroin nephropathy) is most often caused by focal or diffuse glomerulosclerosis and may progress to end-stage renal disease. [55] Renal amyloidosis occurs in addicts who inject subcutaneously or have repeated skin ulceration or abscesses. [47]

Withdrawal

For opiate users, hospitalization for any of the aforementioned complications puts them at risk for withdrawal syndromes. In patients with known or suspected substance abuse, a detailed substance-use history and toxicologic screening may be useful in anticipating the development of withdrawal syndromes. Heroin withdrawal typically

begins 3 to 5 hours after the last heroin use. [48] Other opiates have different withdrawal courses depending on the half-lives of the drugs. Left untreated, heroin withdrawal typically peaks at 3 days and may last up to 2 weeks. Unlike alcohol withdrawal, heroin withdrawal is not associated with severe morbidity or mortality. Symptoms of withdrawal include piloerection, perspiration, lacrimation, nausea, myalgia, yawning, and restlessness. Physical findings include tachycardia, hypertension, fever, and diarrhea. Mild withdrawal symptoms may be treated effectively with clonidine, which suppresses those

manifestations of autonomic nervous system dysfunction. Persons with moderate to severe withdrawal may require methadone, which can be tapered over 5 to 7 days. [48]

COCAINE

During the past 2 decades, with the escalation of cocaine use and the arrival of "crack" cocaine, the medical complications of cocaine use have been amplified. [71] Although many of the complications of cocaine are caused by needle use and are therefore similar to those described among opiate users, others are caused by direct drug toxicity. Complications associated with cocaine use include the following:

Cardiac

Chest pain

Myocardial infarction

Arrhythmias

Cardiomyopathy

Myocarditis

Endocrine

Hyperprolactinemia

Gastrointestinal

Intestinal ischemia

Gastroduodenal perforations

Head and neck

Dental enamel erosions

Gingival ulceration

Keratitis

Corneal epithelial defects

Chronic rhinitis

Perforated nasal septum

Altered olfaction

Optic neuropathy

Neurologic

Headaches

Seizures

Cerebral hemorrhage

Cerebral vasculitis

Pulmonary

Pneumothorax

Pneumomediastinum

"Crack lung"

Pulmonary edema

Exacerbation of asthma

Psychiatric

Anxiety

Depression

Paranoia

Delirium

Psychosis

Suicide

Overdose

Withdrawal

Renal

Rhabdomyolysis

Obstetric

Placental abruption

Lower infant weight

Prematurity

Microencephaly

The most common complaints that bring cocaine users to emergency rooms are cardiac (e.g., chest pain and palpitations) and neurologic (seizures). These complications are most likely caused by the primary physiologic effect of the drug, vasospasm. [57] Psychiatric symptoms, such as suicidal intent, are also a common presentation. No pathognomonic feature of cocaine abuse exists so that identifying those complications ascribed to cocaine can only be confirmed by history or toxicology studies.

Cardiac Symptoms

Cocaine use has been associated with sudden death. Hypothesized mechanisms include arrhythmias (e.g., ventricular fibrillation or asystole), with or without cocaine-induced cardiomyopathy and myocardial ischemia. Angiographic studies of patients with cocaine-related myocardial infarctions have demonstrated both disease and normal coronary vasculature. In those one third of persons who have normal coronary arteries, vasospasm, enhanced platelet aggregation, and increased myocardial oxygen demand caused by cocaine-related tachycardia and hypertension may be the cause of infarction. The onset of ischemia may occur minutes to 36 hours after cocaine use. Silent ischemia has been documented in cocaine users undergoing withdrawal.

Neurologic Symptoms

The most common symptom reported by regular cocaine users is headaches. High levels of cocaine may lead to cerebral vasospasm and

strokes, particularly with crack use. [38] The injection of cocaine has been associated with hemorrhagic stroke. Long-term cocaine users may develop cerebral atrophy. Cerebral vasculitis has also been described. [18]

Pulmonary Symptoms

Inhalation of cocaine commonly causes wheezing and exacerbations of asthma. Pain, hemoptysis, and diffuse alveolar infiltrate, known as "crack lung," may result from a hypersensitivity reaction to cocaine or an unknown cocaine dilutant. [17] Smoking cocaine has been associated with pulmonary edema (possibly because of altered capillary permeability) and barotrauma, leading to pneumothorax. The long-term effects of regular cocaine smoking remain unknown. Smoking of cocaine has also been found to be a risk factor for bacterial pneumonia.

Other Complications

Acute renal failure as a result of rhabdomyolysis has been described. [73] Most patients have mild or no neuromuscular symptoms with cocaine-associated rhabdomyolysis. In one series, one third

of patients developed acute renal failure, and half of these patients died. Aggressive, supportive care is necessary, often including dialysis.

Intestinal ischemia has been reported after cocaine use. Otolaryngologic complications include gingival ulceration, erosion of dental enamel, and perforated nasal septae.

The use of cocaine during pregnancy has been associated with an increased risk for low infant birth weights, prematurity, microcephaly, and placental abruption. [70] Cocaine has also been associated with violence. Forty percent of homicide victims in one study tested positive for cocaine. [27] In New York, 21% of suicide victims younger than age 60 years tested positive at autopsy. [41]

Human Immunodeficiency Virus Disease

Injection-drug use has been established as an important risk factor for infection with HIV. The proportion of AIDS cases related to injection drug use has steadily increased and constitutes half of all cases among women. Two issues remain in question. First, does HIV disease progress faster or slower among injection-drug users compared with other HIV-positive persons, and are the relative prognostic measures of HIV disease stage the same? Second, are the clinical manifestations that characterize HIV disease different in drug users compared with other populations?

Human Immunodeficiency Virus Disease Progression

Two studies [12] [15] early in the HIV epidemic suggested that injection-drug users had a more rapid decrease in CD4 lymphocyte counts than that reported in homosexual men [12] [15] ; however, these studies were limited by small cohort size and short duration of follow-up. Other studies [69] have demonstrated a slow depletion of CD4 lymphocytes among injection-drug users, however, and at rates no different from those of cohorts of homosexual men. These epidemiologic studies [69] also suggest that opiate use does not significantly affect CD4 cell count decrease. Studies of other indices of AIDS progression have not been fully evaluated. [69]

Clinicians now use two measures, CD4 cell counts and plasma viral load, each reflecting different parameters of HIV infections, to predict AIDS morbidity. [58] These measures also direct antiretroviral therapy. [7] The same relationship between virologic and immunologic factors holds in injection drug users as in other HIV transmission risk groups, namely that plasma HIV viral load, independently and in combination with CD4 cell counts, predicts progression to AIDS and death. [69] Nondetectable plasma viral load and higher CD4 cell counts are associated with prolonged survival. Unfortunately, even when combination HIV therapy is available, large numbers of HIV-infected drug users remain untreated because of a variety of factors, including limited access to services. [64]

Fewer studies have attempted to describe the relationship between use of psychoactive drugs or alcohol and the subsequent occurrence of AIDS in HIV-infected persons. A large cohort study of homosexual men demonstrated that neither alcohol nor other classes of commonly used substances (e.g., cocaine, nitrites, phencyclidine, amphetamines, or barbiturates) were important cofactors for the development of AIDS. [34] Certainly drug and alcohol use may lead to those complications described in the earlier parts of this article, unrelated to HIV disease, or may influence behavior that leads to the dissemination of HIV infection, but the immunologic expression of HIV infection seems unchanged.

Human Immunodeficiency Virus Disease Manifestations

Injection drug users have a pattern of HIV-related disease that is largely similar to those seen in other populations with AIDS [49] ; however, several distinctions are worthy of note. Injection-drug users were known to be at risk for bacterial pneumonia before the AIDS epidemic. [44] Several studies have documented a risk for bacterial pneumonia more than four times as high in seropositive drug users as that noted in seronegative drug users. [61] *Streptococcus pneumoniae* and *Hemophilus influenzae* are the most commonly found organisms, suggesting the importance of vaccination for these infections early in the course of HIV infection. Higher rates of bacteremia are found in HIV-infected persons with pneumonia, although response to treatment is similar.

367

HIV-associated tuberculosis has been related to injection-drug use. [63] Extrapulmonary mycobacterial disease (i.e., meningitis or bone involvement) is not uncommon in drug users with advanced HIV infection, representing between 25% and 70% of cases. The classic finding of upper lobe involvement and cavitation are in fact uncommon in patients with AIDS. The risk for active tuberculosis is high in drug users with positive skin tests, suggesting the importance of antituberculosis therapy. [62] Such therapy (i.e., isoniazid) must be monitored closely because of the high frequency of underlying liver disease. After a diagnosis of active tuberculosis is made, four or five drug therapy is recommended, often with direct observation of patient compliance, to prevent the development of drug resistance, which is a growing problem. [16]

Because drug use has long been associated with sexually transmitted infection, and because most women with AIDS in the United States have a history of injection-drug use, women with human papillomavirus are at high risk for cervical dysplasia and cancer. Regular surveillance with Papanicolaou smears in this group is important. [14]

Although cancers of the nasopharynx, larynx, and esophagus have a higher incidence in heavy drinkers and smokers, the observation of increased mortality from solid malignancies has been made in HIV-infected drug users.

Recommendations for HIV treatments, including prophylaxis of opportunistic infections and antiretroviral therapy, should not be different for drug abusers than for other HIV-infected

populations. [8] The importance of early medical intervention in injection drug users has been amply demonstrated. [32]

Finally, clinicians must be aware that the effects of substance abuse can mimic the symptoms of HIV disease. [49] Anorexia, weight loss, fatigue, and nightsweats may indicate HIV-related symptoms, tuberculosis, endocarditis, or drug withdrawal. Similarly, alterations in mental status may result from HIV-related opportunistic infections of the CNS, as well as acute intoxication or withdrawal. Toxicologic screening of urine should, therefore, be routinely incorporated into the care of HIV-infected drug users presenting for medical care.

SUMMARY

Given the preceding review, differentiating the complications of parenteral drug use, HIV disease, and the toxicity of the drugs such as alcohol or cocaine may be a difficult matter for clinicians. The risk for coexisting morbidities is high. Thus, obtaining accurate and complete medical histories is of paramount importance. Drug-abuse treatment and follow-up medical care after an acute complication often involves multiple health care providers. The integration of primary prevention plans with the reinforcement of drug abstinence requires time, commitment, and the coordination of services. This integration should be a priority for individual patients as well as for public health planning.

References

1. Anda RH: Alcohol and fatal injuries among US adults: Findings from the NHANES I Epidemiologic Study. JAMA 260:2529-2532, 1988

2. Andreasson S, Allebeck P, Romelsjo: Alcohol and mortality among young men: Longitudinal study of Swedish conscripts. Br Med J 296:1021-1025, 1988   Abstract

3. Avins AL, Woods WJ, Lindan CP, et al: HIV infection and risk behaviors among heterosexuals in alcohol treatment programs. JAMA 27:515-518, 1994   Abstract

4. Bayer AS, Ward JI, Ginzton LE, et al: Evaluation of new clinical criteria for the diagnosis of infective endocarditis. Am J Med 96:211-218, 1994

5. Bullock KD, Reed RJ, Grant I: Reduced mortality risk in alcoholics who achieve long-term abstinence. JAMA 267:668-672, 1992 Abstract

6. Burch GE, Gilles TD: Alcoholic cardiomyopathy: concern of the disease and its treatment. Am J Med 50:141-145, 1971   Citation

7. Centers for Disease Control and Prevention: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. MMWR Morb Mortal Wkly Rep 47:1-82, 1998   Abstract

8. Chaisson RE, Moore RD: Prevention of opportunistic infections in the era of improved antiretroviral therapy. JAIDS HR 16(suppl):14-22, 1997

9. Charness ME, Simon RP, Greenberg DA: Ethanol and the nervous system. N Engl J Med 321:442-452, 1989   Citation

10. Cherubin CE, Sapira JD: Medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. Ann Intern Med 119:1017-1028, 1993   Abstract

11. Cyr MG, Moulton AW: Substance abuse in women. Obstet Gynecol Clin North Am 17:905-923, 1990   Abstract

12. Desjarlais DC, Friedman SR, Mamor M, et al: Development of AIDS, HIV seroconversion, and potential cofactors for T4 cell loss in a cohort of intravenous drug users. AIDS 1:105-111, 1987

13. Engel TR, Luck JC: Effect of whisky on atrial vulnerability and "holiday" heart. J Am Coll Cardiol 1:816-818, 1983   Abstract

14. Feingold AR, Vermun SH, Burk RD, et al: Cervical cytologic abnormalities and papilloma virus in women infected with human immunodeficiency virus. J AIDS 3:896-903, 1990

15. Fernandez-Cruz E, Desco M, Montes MG, et al: Immunological and serological markers predictive of progression to AIDS in a cohort of HIV-infected drug users. AIDS 4:987-994, 1990   Abstract

16. Fischl MA, Uttamchandani RB, Daikos GL, et al: An outbreak of tuberculosis caused by multiple-drug-resistant tubercle bacilli among patients with HIV infection. Ann Intern Med 117:177-283, 1992   Abstract

17. Forrester JM, Steele AW, Waldron JA, et al: Crack lung: An acute pulmonary syndrome with a spectrum of clinical and histopathologic findings. Ann Rev Respir Dis 142:462-467, 1990

18. Fredericks RK, Lefkowitz DS, Challa VR, et al: Cerebral vasculitis associated with cocaine abuse. Stroke 22:1437-1439, 1991
Abstract

19. Frezza M, Dipadova C, Pozzato G, et al: High blood alcohol levels in women. N Engl J Med 322:95-99, 1990   Abstract

20. Friedman LN, Sullivan GM, Bevilacqua RP, et al: Tuberculosis screening in alcoholics and drug addicts. Am Rev Respir Dis 136:1188-1192, 1987   Abstract

21. Fuchs CS, Stampfer MJ, Colditz GA, et al: Alcohol consumption and mortality among women. N Engl J Med 332:1245-1250, 1995
Abstract

22. Garfein RS, Vlahov D, Galai N, et al: Viral infections in short-term injection drug users: The prevalence of hepatitis C, hepatitis B, human immunodeficiency virus, and human T-lymphotropic viruses. Am J Public Health 86:655-661, 1996   Abstract

23. Gerstein DR, Lewin LS: Treating drug problems. N Engl J Med 323:844-848, 1990   Citation

24. Ghodse AH, Sheehan M, Taylor C, et al: Deaths of drug addicts in the United Kingdom 1967-81. BMJ 290:425-428, 1985

25. Ginsburg ES, Mello NK, Mendelson JH, et al: Effects of alcohol ingestion on estrogens in postmenopausal women. JAMA 276:1747-1751, 1996   Abstract

26. Gourevitch MN, Selwyn PA, Davenny K, et al: Effects of HIV infection on the serologic manifestations and response to treatment of syphilis in intravenous drug users. Ann Intern Med 118:350-355, 1993   Abstract

27. Hanzlick R, Gowitt GT: Cocaine metabolite detection in homicide victims. JAMA 265:760-761, 1991   Abstract

28. Haverkos HW, Lange WR: Serious infections other than human immunodeficiency virus among intravenous drug abusers. J Infect Dis 5:894-902, 1990   Citation

29. Haverkos HW, Stein MD: Illicit drug use. Am Fam Physician 52:2029-2035, 1995   Abstract

30. Herber V: Hematologic complications of alcoholism. Semin Hematol 17:83-176, 1980   Citation

31. Hser YI, McCarthy WJ, Anglin MD: Tobacco use as a distal predictor of mortality among long-term narcotic addicts. Prev Med 23:61-69, 1994   Abstract

32. Jewett JF, Hecht FM: Preventive health care for adults with HIV infection. JAMA 269:1144-1153, 1993   Abstract

33. Joe GW, Simpson DD: Mortality rates among opioid adicts in a longitunidal study. Am J Public Health 77:347-348, 1987   Abstract

34. Kaslow RA, Blackwelder WC, Ostrow DG, et al: No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals. JAMA 261:3424-3429, 1989   Abstract

35. Klatsky AL: The cardiovascular effects of alcohol. Alcohol Alcohol 22:117-124, 1987   Abstract

36. Klatsky AL, Armstrong MA, Friedman GD: Alcohol and mortality. Ann Intern Med 117:646-654, 1992   Abstract

37. Lettau LA, McCarthy JG, Smith MH, et al: Outbreak of severe hepatitis due to delta and hepatitis B viruses in parenteral drug abusers and their contacts. N Engl J Med 317:1256-1261, 1987   Abstract

38. Levine SR, Brust JC, Futrell N, et al: Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. N Engl J Med 323:699-704, 1990   Abstract

39. Lieber CS: Medical disorders of alcoholism. N Engl J Med 333:1058-1064, 1995   Citation

40. Marantz PR, Linzer M, Feiner CJ, et al: Inability to predict diagnosis in drug abusers. Ann Intern Med 106:823-828, 1987   Abstract

41. Marzuk PM, Tardiff K, Leon AC, et al: Prevalence of cocaine use among resident of New York City who committed suicide during a one-year period. Am J Psychol 149:371-375, 1992

42. Mathew J, Addai J, Anand A, et al: Clinical features, site of involvement, bacteriologic featres, and outcomes of infective endocarditis in intravenous drug users. Arch Intern Med 155:1641-1648, 1995   Abstract

43. McGinnis JM, Foege WH: Actual causes of death in the United States. JAMA 270:2207-2212, 1993   Abstract

44. Mientjes GHC, Spijkerman IJB, van Ameijden ETC, et al: Incidence and risk factors for penumonia in HIV-infected and non-infected drug users. J Infect 32:181-186, 1996   Abstract

45. Miller NS, Giannini J, Gold MS: Suicide risk associated with drug and alcohol addiction. Cleve Clin J Med 59:535-538, 1992   Abstract

46. Nelson KE, Vlahov D, Cohen S, et al: Sexually transmitted disesase in a population of intravenous drug users: Association with seropositivity to the human immunodeficiency virus (HIV). J Infect Dis 164:457-463, 1991   Abstract

47. Neugarten J, Gallo GR, Buxbaum J, et al: Amyloidosis in subcutaneous heroin abusers. Am J Med 81:635-640, 1986   Abstract

48. O'Connor PG, Samet JH, Stein MD: Management of hospitalized intravenous drug users: Role of the internist. Am J Med 96:551-558, 1994   Abstract

49. O'Connor PG, Selwyn PA, Schottenfeld RS: Medical care for injection drug users with human immunodeficiency virus. N Engl J Med 331:450-459, 1994   Citation

50. Orangio GR, Della Latta P, Marino C, et al: Infection in parenteral drug abusers, further immunologic studies. Am J Surg 146:738-741, 1983

51. Orangio GR, Pitlick SD, Della Latta P, et al: Soft tissue infections in parenteral drug abusers. Ann Surg 199:97-100, 1984   Abstract

52. Passero DJ, Werner SB, McGee J, et al: Wound botulism associated with black tar heroin among injecting drug users. JAMA 279:859-863, 1998   Abstract

53. Perucci CA, Davoli M, Rapiti E, et al: Mortality of intravenous drug users in Rome: A cohort study. Am J Public Health 81:1307-1310, 1991   Abstract

54. Putnam S: Alcoholism, morbidity and care-seeking: The inpatient and ambulatory service utilization and associated illness experience of alcoholics and matched controls in a health maintenance organization. Med Care 20:97-121, 1982   Abstract

55. Rao TKS, Nicastri AD, Friedman EA: Natural history of heroin associated nephropathy. N Engl J Med 290:19-23, 1974   Citation

56. Regan TJ: Alcohol and the cardiovascular system. JAMA 264:377-381, 1990

57. Rich JA, Singer DE: Cocaine-related symptoms in patients presenting to an urban emergency department. Ann Emerg Med 20:616-621, 1991   Abstract

58. Saag MS: Use of virologic markers in clinical practice. JAIDS HR 16(suppl):3-13, 1997

59. Samet JH, Shevitz SA, Fowle, Singer DE: Hospitalization decision in febrile intravenous drug users. Am J Med 89:53-57, 1990   Abstract

60. Scheld WM, Zak O, Vosbeck K, et al: Bacterial adhesion in the pathogenesis of infective endocarditis: Effect of subinhibitory antibiotic concentration on streptococcal adhesion in vitro and the development of endocarditis in rabbits. J Clin Invest 68:1381-1384, 1981   Abstract

61. Selwyn PA, Alcabes P, Hartel D, et al: Clinical manifestations and predictors of disease progression in drug users with human immunodeficiency virus. N Engl J Med 327:1697-1703, 1992   Abstract

62. Selwyn PA, Hartel D, Lewis VA, et al: A prospective study of the risk of tuberculosis among intravenous drug users with HIV infections. N Engl J Med 320:545-550, 1989   Abstract

63. Selwyn PA, Sckell BM, Alcabes P, et al: High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. JAMA 268:504-509, 1992   Abstract

64. Sherer R: Adherence and antiretroviral therapy in injection drug users. JAMA 280:567-568, 1998   Citation

65. Stein MD, Cyr MG: Women and substance abuse. Med Clin North Am 81:979-998, 1997   Full Text

66. Stein MD: Medical complications of intravenous drug use. J Gen Intern Med 5:249-257, 1990   Citation

67. Turner RC, Lichstein PR, Peden JG, et al: Alcohol withdrawal syndromes. J Gen Intern Med 4:432-444, 1989   Citation

68. Urbano-Marquez A, Estruch R, Fernandez-Sola J, et al: The greater risk of alcoholic cardiomyopathy and myopathy in women compared to men. JAMA 274:149-154, 1995   Abstract

69. Vlahov D, Graham N, Hoover D, et al: Progostic indicators for AIDS and infectious disease death in HIV-infected injection drug users: Plasma viral load and CD4 sup + cell count. JAMA 279:35-40, 1998   Abstract

70. Volpe JJ: Effect of cocaine use on the fetus. N Engl J Med 327:399-407, 1992   Citation

71. Warner EA: Cocaine abuse. Ann Intern Med 119:226-235, 1993   Abstract

72. Webb D, Thadepol A: Skin and soft tissue polymicrobial infections from intravenous abuse of drugs. West J Med 130:200-204, 1979
Citation

73. Welch RD, Todd K, Krause GS: Incidence of cocaine-associated rhabdomyolysis. Ann Emerg Med 20:154-157, 1991   Abstract

74. Wrenn KD, Slovis CM, Minion GE, et al: The syndrome of alcoholic ketoacidosis. Am J Med 91:119-128, 1991   Abstract