

## Medical Disorders in Substance Abuse Patients

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### INTRODUCTION

Comorbid medical disorders in patients with substance use disorders are a major concern of both patients and practitioners. Before HIV disease surfaced, a great deal was written about the many medical disorders that occur as a result of substance abuse. In the health care system, it is often these disorders that bring substance abuse to the attention of caregivers. Medical disorders can result directly from the use of specific substances or as the result of the route of administration of a substance (e.g., intravenous or inhaled). In addition, certain medical disorders can be indirectly related to substance abuse, such as in the case of tuberculosis in injection drug users. This chapter reviews the major medical disorders associated with substance use (other than HIV disease, which is covered in Chapter 15) by considering four major substances of abuse: alcohol, cocaine, opioids, and cannabis, as well as the specific routes of administration commonly employed for these substances.

### COMORBIDITY ASSOCIATED WITH SPECIFIC SUBSTANCES

#### Alcohol

Although patients may be “asymptomatic,” alcohol is known to cause a variety of social and behavioral problems along with medical

comorbidity that can serve as a clue to the presence of problem drinking.

### Social and Behavioral Problems

Social and behavioral complications may be the earliest and most common presenting manifestations of alcoholism seen by health care providers. These behaviors can be diverse and include aspects of psychiatric disease (discussed elsewhere in this book), family dysfunction, legal and employment problems, and frequent accidents. For example, a cross-sectional survey of homeless adults in California demonstrated that they were two to four times more likely to suffer from alcoholism than were those who were non-homeless (1).

A variety of studies have shown a strong link between alcohol use and behaviors resulting in accidents or trauma. Trauma patients seen in emergency rooms are often found to have a clear causal link between the injury or trauma and alcohol (2). While acute alcohol intoxication has been shown to lead to trauma, chronic alcohol abuse increases both the risk of trauma-related complications and mortality (3). A prospective study of 301 patients admitted to a level 1 trauma center found evidence of acute and/or chronic alcohol use in 48% of cases (4). In addition, alcohol abuse is associated with an increased risk of readmission for recurrent trauma, a finding which emphasizes the need to identify and treat all trauma patients who have alcohol abuse histories (5). There is evidence that acutely intoxicated patients, particularly those that are severely injured or incapacitated, are not always readily identified in the emergency room setting (6). Burn patients are also more likely to be alcohol dependent; in one study, alcohol dependence was found in 57% of patients admitted to a burn unit (7). The association of alcohol abuse with injuries and trauma has led to the development of efforts to prevent alcohol-related accidents (8). While these efforts require thorough evaluation, it is clear that both emergency rooms and trauma units must play a major role in establishing the potential link between alcohol and trauma and intervening to prevent recurrent problems in identified patients (9).

### Medical Problems (see Table 1)

**Gastrointestinal:** Patients with alcohol dependence have been shown to experience frequent gastrointestinal symptoms such as heartburn, nausea, vomiting, and diarrhea (10). Chronic esophagitis, Mallory–Weiss tears, esophageal varices and malignancies have all been associated with alcohol use (11). Presenting symptoms can include difficulty swallowing, heartburn, hematemesis, and weight loss. In addition to causing mucosal abnormalities,

**Table 1** Medical Comorbidity Associated with Alcohol Use

Organ system/disease	Comorbid problems <sup>a</sup>	Common symptoms
Gastrointestinal	Esophageal disease	
	Esophagitis	Difficult/painful swallowing
	Mallory–Weiss tear	Pain, hematemesis
	Varices	Hematemesis
	Stomach/duodenum	
Liver	Gastritis	Nausea, vomiting, pain
	Peptic ulcer disease	Nausea, vomiting, pain
	Fatty liver	Abdominal discomfort
	Alcoholic hepatitis	Nausea, vomiting, fever, pain
	Cirrhosis	Jaundice, weight loss, edema, bleeding
Pancreas	Acute pancreatitis	Abdominal pain, nausea, vomiting, fever
	Chronic pancreatitis	Pain, weight loss, diarrhea
Nervous system	Central	
	Dementia	Cognitive dysfunction
	Withdrawal	Cognitive dysfunction, seizures
	Stroke	Fixed deficits (motor, sensory)
	Peripheral neuropathy	Paresthesias, numbness, weakness
Cardiac	Hypertension	Usually none
	Cardiomyopathy	Dizziness, syncope (due to arrhythmias), shortness of breath (due to heart failure)
Malignancies	Esophagus	Difficult/painful swallowing
	Pharynx, larynx	Pain, hoarseness
	Liver	Jaundice, weight loss
	Pancreas, colon, breast?	
Hematopoetic system	Thrombocytopenia	Bleeding, rash (petechiae)
	Anemia	Fatigue, dizziness
	Neutropenia	Infections
Metabolic/ endocrine	Ketoacidosis	Mental status changes
	Osteoporosis	Fractures
	Menstrual dysfunction	Abnormal periods, infertility

<sup>a</sup>Patients may be asymptomatic or symptomatic for many of these problems.

alcohol has also been associated with abnormal primary and secondary contractions, resulting in esophageal symptoms (12).

Alcohol has also been associated with nausea, vomiting, and abdominal pain due to acute gastritis (11). Although cigarette smoking has been linked to ulcer disease, the association of peptic ulcer disease with alcohol is less clear (13). Unrelated to the type or amount ingested, alcohol facilitates the development of gastroesophageal reflux disease by reducing the pressure of the lower esophageal sphincter and esophageal motility (14). Chronic alcohol use may also lead to malnutrition, due to either poor eating habits or malabsorption. Alcohol-dependent individuals are at higher risk of inadequate intake or absorption of several vitamins (15). These nutritional deficiencies can be evident in a patient who presents with weight loss, peripheral neuropathy due to folate deficiency, and Wernicke's encephalopathy due to thiamine deficiency. However, the exact mechanism of vitamin deficiency in alcoholics is somewhat controversial. For example, alcoholic patients receiving adequate doses of thiamine and other vitamins may still be deficient, possibly due to malabsorption or interference with vitamin metabolism (16). One study suggests that in patients in earlier stages of alcohol dependence, it is the cumulative lifetime exposure to alcohol, and not current nutritional status, that is associated with peripheral neuropathy (17).

**Liver:** In the United States, alcohol abuse is an important cause of morbidity and mortality from liver disease (18). Acute alcohol intake is associated with "fatty liver," which may be asymptomatic or associated with nonspecific symptoms including abdominal discomfort and anorexia. It is thought to occur in up to 90% of "heavy" drinkers (19).

Alcoholic hepatitis, which may be seen in up to 40% of "heavy" drinkers, represents more advanced acute liver disease as manifested by nausea, vomiting, fever, abdominal pain, and liver dysfunction (20). Alcoholic hepatitis may be clinically indistinguishable from viral hepatitis, and therefore the diagnosis relies on obtaining an accurate alcohol consumption history. Laboratory evaluation can also be helpful with patients with alcoholic hepatitis typically presenting with mild-to-moderate elevations in serum aminotransferases with relatively higher serum aspartate aminotransferase (AST) levels. Alcoholic hepatitis responds well to abstinence, although a significant proportion, approximately 30%, will progress to cirrhosis (21). Viral hepatitis, particularly hepatitis C, may be more prevalent among some patients with alcoholic liver disease (22). In one study of alcohol-dependent subjects, 30% of heavy drinkers were hepatitis C positive, a finding that was associated with a higher prevalence of alcoholic liver disease (23). A history of previous injection drug use, a significant risk factor

for acquisition of the hepatitis C virus, may be a major contributor to this phenomenon in alcoholic patients (24).

Cirrhosis is the eighth leading cause of death in the United States, resulting in over 25,000 deaths in 1988 (25). Although often asymptomatic, patients with more advanced liver disease experience significant morbidity and may present with jaundice, weight loss, and evidence of hepatic dysfunction, such as bleeding. Interestingly, women may be more susceptible to cirrhosis than men. Clinical studies have shown that cirrhosis occurs more rapidly in women and at lower relative levels of alcohol consumption than in men (26,27). In addition to end-stage liver disease, patients with alcoholic cirrhosis face the risk of the subsequent development of hepatocellular carcinoma (28).

The association of alcoholism with life-threatening liver disease has raised the controversial issue of liver transplantation in alcoholic patients. Many would argue that alcoholism should be a contraindication to transplantation, given the high risk of relapse and the scarcity of available organs. Uniform guidelines need to be developed that include an assessment of the prognosis of individual patients, including an estimate of the likelihood of success in treating the alcohol dependence (29).

**Pancreas:** Among the most dramatic manifestations of alcoholism is acute pancreatitis, a condition in which patients can present with significant abdominal pain, nausea, vomiting, and fever. The diagnosis of acute pancreatitis is often based on the appropriate presenting clinical picture in the setting of a history of alcohol dependence. In addition, a history of high levels of alcohol consumption may be correlated with a more severe initial episode of acute pancreatitis (30). Laboratory evaluation may aid in the diagnosis of alcoholic pancreatitis. One study suggests that serum lipase is more reliable than amylase (31), with the serum lipase being a more specific and sensitive index of pancreatic disease (32). In addition, the serum lipase:amylase ratio has been proposed as an effective way to differentiate alcoholic from nonalcoholic pancreatitis (33,34). Serum carbohydrate-deficient transferrin (CDT) and trypsin levels have also been identified as markers of chronic alcoholism and have been shown to have utility in differentiating alcoholic from non-alcoholic acute pancreatitis (35).

Patients with recurrent acute pancreatitis may develop chronic pancreatitis, which can manifest as chronic intractable abdominal pain and malabsorption with weight loss or diarrhea. Although chronic pancreatitis is thought to be irreversible once it develops, there are data to suggest that abstinence from alcohol is associated with decreased morbidity and mortality (36).

**Nervous system:** Alcohol can have acute and chronic toxic effects on both the central and the peripheral nervous systems (37). While acute central nervous system effects, such as intoxication and withdrawal, are commonly seen in emergency room settings, primary care physicians and psychiatrists may also face these issues in managing patients. Chronic alcohol use may be associated with mild-to-severe cognitive impairment, including impaired short- and long-term memory, along with deficits in functioning in activities of daily living. Later stages of alcoholic dementia may resemble Alzheimer's disease. There may be similar biological mechanisms involved in the effects of alcohol abuse and Alzheimer's disease on the brain but there is still limited evidence that alcohol increases the risk of the development of Alzheimer's disease (38–40). Both direct toxicity of alcohol and thiamine deficiency are possible etiologies for alcoholic dementia (41).

Alcohol withdrawal seizures are a well-described phenomenon, although their diagnosis and treatment can be challenging (42). Generally these are considered benign in the absence of other neurologic disease, and they respond well to abstinence (42). The relationship between alcohol consumption and the risk of stroke is controversial, with some studies showing a modest increase in the risk of stroke (43) while other studies showed no overall significant association between total alcohol intake and stroke, and in fact showed a protective effect of alcohol amongst older subjects (44). Cerebellar degeneration presenting as gait ataxia can also result from chronic heavy alcohol use.

Peripheral neuropathy is also a major comorbidity of alcoholism (45). Presenting symptoms include paresthesias, numbness, weakness, and chronic pain. Similar to dementia, there is evidence that both direct toxicity and vitamin deficiency may play a role in the development of peripheral neuropathy (45). The results of one study showed that alcohol-related neuropathy is a frequent condition and is mostly characterized by axonal degeneration of peripheral nerve fibers and earlier involvement of sensory fibers and the lower extremities. Alcoholic disease duration and total lifetime dose of ethanol could be more important than malnutrition in leading to neuropathy (46).

**Cardiovascular system:** Common cardiovascular manifestations of alcohol use include hypertension, acute supraventricular arrhythmias or "holiday heart," and chronic cardiomyopathy (47). Evidence suggests that moderate-to-high levels of alcohol intake are associated with hypertension and that decreased alcohol intake may lower blood pressure (48,49). In addition, hypertensive alcoholics may be more prone to left ventricular hypertrophy than hypertensive patients who are not alcoholic (50). The data from one study suggested that there is a dose-dependence effect, with

chronic alcohol consumption exceeding 29 ml per day leading to the development of left ventricular hypertrophy in patients with hypertension, while lighter drinkers exhibited less end-organ damage and a risk of cardiovascular disease (51). Despite the evidence of the harmful cardiovascular effects of alcohol, other data suggest that moderate alcohol intake may have beneficial cardiac effects (52). These data have been derived from retrospective studies and any benefit to the heart may be outweighed by the risks of the other alcohol-related complications. Alcoholic cardiomyopathy presents clinically with congestive heart failure and arrhythmias. It responds to abstinence and to the usual treatments for congestive heart failure (47). Heavy alcohol intake has also been linked to sudden cardiac death. In one study, heavy drinkers (i.e., those consuming >6 drinks daily) were 1.7 times more likely to die suddenly than controls (53).

**Malignancies:** Alcohol has been associated with cancer of the upper digestive and respiratory tract, the liver, and, in at least one study, the prostate, pleura, and cervix (54). Alcohol-related malignancies of the mouth, oropharynx, and esophagus are thought to be in part related directly to alcohol and in part due to increased tobacco use in alcohol-dependent individuals (55,56). Other cancers that have been postulated to be associated with alcohol dependence include cancer of the pancreas, colon, and breast, although data for these have been less convincing (56–58). There is evidence that in patients with colorectal adenomas, excessive alcohol intake increases the likelihood of developing high-risk adenomas or colorectal cancer (59).

**Hematopoietic system:** Alcoholism may present with bleeding as a result of dysfunction of hepatic synthesis of clotting factors. Alcohol may also cause bleeding or petechiae due to thrombocytopenia. All bone marrow cell lines are susceptible to the toxic effects of alcohol. In addition, immune dysfunction has been attributed to excessive alcohol intake, potentially making alcoholics more susceptible to infections such as pneumonia and tuberculosis (60).

**Metabolic and endocrinological problems:** Acute metabolic ketoacidosis represents an acute and treatable manifestation of binge drinking (61). Alcohol consumption may also cause more subtle metabolic and endocrinologic abnormalities. For example, the potentially reversible disruption of bone metabolism, potentially leading to osteoporosis, has been documented in male alcohol-dependent patients (62). Alcohol-associated osteopenia appears to be both a direct effect of alcohol on bone cells and an indirect effect through mineral-regulating hormones (63). Alcohol has also been associated with disturbances in lipid metabolism (64). Endocrinologic abnormalities such as menstrual problems, anovulation, infertility, and

early menopause have all been linked to alcohol abuse (65). Similarly, male gonadal function is impaired by alcohol intake. Moderate consumption of alcohol may affect semen quality, and high alcohol consumption may result in serious disorders of spermatogenesis (66). Finally, the toxic effects of alcohol on thyroid and adrenal function have also been demonstrated (67).

**Other medical issues:** Toxic effects of alcohol on the kidney are generally subclinical or secondary to other alcohol-related effects (68). Gout is associated with alcohol consumption and may occur in alcoholics at lower serum urate levels than in nonalcoholics (69). In addition to the dermatologic manifestations of chronic liver disease, alcohol has been related to other important skin conditions including psoriasis and dermatologic malignancies (70,71). A high prevalence of dental and periodontal disease has also been documented in alcohol-dependent patients (72).

### Cocaine

Similar to all forms of substance use, cocaine use is associated with social and behavioral problems. Cocaine use is also associated with a unique spectrum of comorbid medical problems (see Table 2).

**Table 2** Medical Comorbidity Associated with Cocaine Use

Organ system	Comorbid problems <sup>a</sup>	Common symptoms
Nervous	Nonspecific symptoms	Headache, tremor, vertigo, dizziness, syncope, etc.
	Cerebrovascular disease	
	Hemorrhage	Headache, mental status changes, focal deficits
	Infarct	Focal deficits
Cardiovascular	Seizures	Generalized and partial
	Ischemic heart disease	
	Ischemia	Chest pain
	Infarction	Chest pain, dizziness, shortness of breath
	Arrhythmias	Palpitations, dizziness, syncope
	Cardiomyopathy	Fatigue, shortness of breath
Other medical complications	Aortic dissection	Chest pain
	Intestinal ischemia	Abdominal pain
	Acute renal failure	Agitation, altered mental status

<sup>a</sup>Patients may be asymptomatic or symptomatic for many of these problems.

### Acute Intoxication

Cocaine hydrochloride is a water-soluble salt and thus easily injected or absorbed through mucus membranes. "Freebase" cocaine is an alkaloid which is insoluble in water but soluble in alcohol, acetone, oils, and ether and vaporizes at high temperatures without decomposing, thus allowing it to be smoked (73). The time course of the physiological and subjective effects of a single dose of cocaine are closely correlated with the route of administration and blood levels achieved. Injected and smoked cocaine is absorbed immediately, while there are delayed effects with cocaine used by nasal inhalation. An intravenous infusion of lethal doses of cocaine in animals produces a predictable sequence of physiological events, which can be seen in humans as well. Such infusions cause an increase in heart rate, blood pressure, cardiac output, and body temperature. When combined with a fall in blood pH, these phenomena can cause severe metabolic acidosis (74), leading to the development of generalized seizures, cardiopulmonary collapse, and multiorgan failure.

Central nervous system stimulation may result in irritability, restlessness, emotional lability, paranoia, and, in severe cases, paranoid psychosis and violent behavior. Hyperthermia and grand mal seizures may accompany stimulant toxicity (75). A recent study of cocaine-induced hyperthermia concluded that in humans a major mechanism by which cocaine raises the body temperature is by impairing heat dissipation, affecting sweating and cutaneous vasodilation, as well as by impairing heat perception (76). Stimulation may be followed by central nervous system depression, which is characterized by paralysis of motor activity, hyperreflexia with eventual areflexia, coma, loss of vital functions, and potentially death.

In the case of cocaine intoxication, supportive measures and symptom-based treatments are indicated. Agitation may respond to benzodiazepines, psychosis to haloperidol, and hyperthermia to cooling measures. Acidification of urine will hasten excretion of cocaine and seizure activity can be controlled with the use of diazepam (77). Withdrawal from cocaine may be accompanied by hypersomnia, depression, fatigue, and apathy, all of which are usually transient (78).

### Nervous System

Cocaine use has been associated with neurological symptoms and diseases, including severe headaches, tremor, vertigo, nonspecific dizziness, syncope, blurred vision, ataxia, tinnitus, transient ischemic attacks with transient hemiparesis of unknown origin, choreiform movements, seizures, confusional states, cerebral hemorrhage, cerebral infarction and spinal cord ischemia, and toxic encephalopathy. In one study, Lowenstein et al. reported

that the most frequent neurological complications observed at one hospital were seizures, focal neurological deficits, headaches, and transient loss of consciousness (79).

Potential mechanisms of cocaine-related neurological comorbidity have been proposed. The enhanced sympathetic activity, cerebral vasoconstriction or vasospasm, accompanied by a sudden surge of blood pressure following cocaine use, may precipitate ischemic symptoms and even spontaneous bleeding in a previously normotensive person (80). Cocaine has been shown to decrease cerebral metabolism *in vivo* and may thus cause a decrease in cerebral blood flow. Because serotonin is a potent vasoconstrictor, the cocaine-induced increase in serotonin levels at the synapse may contribute to the neurological effects of cocaine (81). Cocaine also leads to an enhanced response of platelets to arachidonic acid, resulting in increased thromboxane production and platelet aggregation (82,83).

Headaches from cocaine use may be related to the combination of disturbed sympathetic, serotonergic, and platelet functions similar to dysfunctions that have been reported in patients with migraine headaches. Migraine headache or migraine-like symptoms have been associated with cocaine use (84). In acute cocaine encephalopathy, hyperpyrexia and metabolic acidosis ensue, which, along with the effect of the drug on neurotransmitters, may contribute to the development of neurological complications.

**Cerebrovascular accidents:** According to a retrospective review by Kaku and Lowenstein (85), cocaine use is frequently associated with cerebrovascular accidents in stroke victims aged 17 to 44. Recent studies support the findings that cocaine abuse significantly increases the risk of ischemic stroke (86). The main mechanism of cocaine-induced cerebral ischemia is vasospasm, primarily mediated by increased levels of extracellular dopamine, which also has an effect on regulation of cerebral blood flow. There is evidence that cocaine-induced hypoperfusion and the resultant cognitive deficits can persist even after six months of abstinence. The dihydropyridine class of calcium channel antagonists is being investigated as potential therapeutic agents for preventing cocaine-induced cerebral ischemia.

Klonoff et al. (87) reviewed 47 known cases of cocaine-related stroke and concluded that the incidence of stroke related to cocaine use is increasing, that stroke may occur following any route of cocaine administration, with onset occurring from within minutes to as long as a day after use, and that stroke after cocaine use is frequently associated with cerebrovascular abnormalities. In addition, they concluded that in cocaine-associated strokes the frequency of intracranial hemorrhage exceeds that of cerebral infarction.

This finding is in contrast to stroke in the general population, where cerebral infarction is most common. Clinical presentations of subarachnoid and intracerebral hemorrhage related to cocaine use have been similar, with varying combinations of headache, altered mental status, lateralized deficits, and seizures. Sudden death is also a presenting feature. In addition to thrombotic and hemorrhagic cerebrovascular disease in two cases, cerebral vasculitis has been presumptively linked to cocaine use (86,88,89).

**Seizures:** Seizures following cocaine use are a well-recognized comorbidity. Seizures associated with smoking crack cocaine have been described in adolescents (90,91). In humans, seizures from cocaine use are generally brief, with generalized tonic-clonic features, although complex partial status epilepticus has also been reported (92–94). The interval between most recent cocaine use and the seizure may vary from minutes to 12 hours and seizures may occur in first-time users, induced after a single dose of cocaine, as well as in chronic users (95).

Cocaine-related seizures may occur in association with anatomic lesions, cerebral hypoperfusion secondary to cardiac events, and in association with metabolic derangements such as hyperpyrexia and metabolic acidosis (96). Of the traditional anticonvulsants, only diazepam and barbiturates have been found to have any preventive effect. Cocaine-induced status epilepticus may be refractory to standard anticonvulsants and may require aggressive treatment, including induction of a phenobarbital coma (96).

#### Cardiac Complications

Increasingly, a variety of cardiovascular problems have been recognized to be associated with cocaine use, including hypertension, tachycardia, arrhythmias, acceleration of atherosclerosis, myocardial ischemia and infarction, cardiomyopathy, myocarditis, aortic dissection, and sudden death (97). Cardiac consequences are seen with all routes of cocaine administration, often occur in the absence of underlying heart disease, and can occur at relatively low doses of cocaine administered. Published case reports have documented myocardial infarction and ventricular fibrillation in individuals, including previously healthy young women, who received cocaine from physicians during otolaryngologic procedures (98–100).

**Ischemic heart disease:** Acute non-Q wave and Q wave myocardial infarctions (MIs) have been associated with cocaine abuse (101,102). Acute chest pain is the typical presenting symptom and ischemia and myocardial infarction may occur in the absence of significant underlying coronary artery disease (103–105). Affected patients may be young, without evidence of hyperlipidemia, diabetes mellitus, or hypertension, and may be stricken on initial use of cocaine (106,107). The Third National Health and Nutrition

Examination Survey, which collected data from a sample of 10,085 U.S. adults aged 18 to 45 years, showed that regular cocaine use was associated with approximately one of every four nonfatal MIs in persons in the age group surveyed (108). The mechanism of cocaine-induced ischemia is controversial, but may relate to an increase in cardiac workload and coronary artery vasospasm. In one review of case reports of cocaine-related infarction, 55% of patients had abnormal cardiac catheterizations, suggesting that cocaine may uncover previously unrecognized disease (109). The Cocaine Associated Chest Pain (COCHPA) study prospectively followed a cohort of 246 patients presenting to emergency departments with cocaine-associated chest pain and found that 5.7% had myocardial infarctions and 0.8% died (110). The authors found no clinical features predictive of infarction in these patients and thus recommended that all such patients be evaluated for myocardial infarction (110).

In some cases it is postulated that thrombosis in normal or near-normal arteries may result from prolonged spasm and intimal damage (111,112). In patients with fixed coronary artery disease, cocaine causes a dose-related increase in heart rate and blood pressure secondary to the adrenergic output, and thus predictably increases myocardial oxygen demand, potentially leading to myocardial ischemia and infarction (97). "Street" cocaine may be mixed with a variety of diluents including lidocaine, procaine, antihistamines, lactose, and amphetamines, which may contribute to the cardiac dysfunction (97). The cardiovascular effect of mixed substance abuse, especially that of cocaine and alcohol, has not been well studied.

The treatment of cocaine-related acute myocardial ischemia/infarction generally includes the standard protocols for cardiac ischemia (113). With regard to newer approaches, Smith et al. found thrombolytic therapy to be successful, whereas Bush cautioned against the use of thrombolytics in intravenous drug abusers because of the risk of intracranial bleeding secondary to the increased risk of mycotic aneurysm in this population (114,115). In a report from Hollander et al., no significant complications were seen among 25 patients with cocaine-related myocardial infarction who received thrombolytic therapy (116).

**Cardiac arrhythmias:** Cocaine-associated cardiac arrhythmias may occur alone or in the setting of ischemia and may include sinus tachycardia, supraventricular and ventricular tachycardias, ventricular fibrillation, and asystole (97,117,118). Arrhythmias may occur during acute cocaine intoxication or in the context of metabolic acidosis from prolonged seizures or hyperpyrexia. Arrhythmias related to myocardial ischemia and infarction are frequently described, and arrhythmic effects of cocaine may not be limited to adults. A study of children exposed to cocaine during the prenatal period

documented supraventricular arrhythmias and ventricular ectopy in excess of that seen in a historical control cohort (119).

**Cardiomyopathy:** Patients who suffer coronary artery ischemia secondary to cocaine use may develop an ischemic cardiomyopathy, with a reduction in left ventricular ejection fraction and resultant congestive heart failure (120). An additional mechanism that has been proposed on the basis of animal and human data is that cocaine may produce cardiomyopathy through direct toxic effects, with a depressed left ventricular function due to the effects of high levels of circulating catecholamines on myocardial cells (121,122). Acute myocarditis related to the long-term use of freebase cocaine has been demonstrated by endomyocardial biopsy. While the association of myocarditis with cocaine use has not been clearly established, one case report demonstrated that the inflammation from myocarditis could successfully be treated with prednisone and azathiaprine (118).

**Aortic dissection:** Several cases of acute aortic dissection attributed to cocaine abuse have been reported. These cases include examples of involvement of both the ascending and thoracic aorta (123,124). Similarly to the case of ischemic heart disease, these patients generally presented with substernal chest pain. Successful management included emergency surgical intervention (125,126). Mechanisms for cocaine-induced aortic dissection may include underlying hypertensive disease, in addition to the acute elevation of systemic blood pressure and catecholamine release following cocaine use (127,128).

#### Obstetric Complications

As high as 15% of a sample of pregnant women in an urban setting who were evaluated by urine toxicology screening were found to have abused cocaine (129–131). When compared with non-users, cocaine abusers have been found to be less likely to receive prenatal care, have decreased pregnancy weight gain, increased previous history of spontaneous abortions, more sexually transmitted diseases, and an increased number of prior low birthweight infants (132–134). Studies have documented preterm labor and delivery and an increased risk of abruptio placentae and intrapartum placenta previa in association with cocaine use (135–137).

Adverse perinatal outcomes associated with in utero cocaine exposure include fetal distress in labor with stained amniotic fluid, low gestational age, low birthweight, low birth length, and small head circumference (138–140). A neonatal withdrawal syndrome described in infants with positive cocaine toxicology includes tachycardia, tremulousness, poor feeding, and seizures (141). In utero cocaine exposure has also been associated with an increased incidence of congenital malformations of the genitourinary

tract and heart (142). Maternal cocaine abuse has also been associated with congenital syphilis, intrauterine and neonatal death, and sudden infant death (143,144).

Negative neurological and developmental outcomes have been identified in infants with perinatal cocaine exposure. One study reported that infants exposed to cocaine only in the first trimester had birthweight, birth length, and head circumference similar to drug-free controls, but those exposed to cocaine throughout pregnancy had significantly smaller measurements (131,144). Another study confirmed the association between cocaine use and lower mean weight and head circumference, but did not demonstrate significant differences in motor tone or mental and psychomotor development (145). Cocaine users have been reported to be more likely to use other drugs, including opiates, marijuana, tobacco, and alcohol, thus increasing the risk of negative outcomes related to these drugs (146). A more recent study of infants prenatally exposed to cocaine revealed that, at three months of age, they demonstrated no significant cognitive effects and only mild psychomotor abnormalities (147). In a study of newborns in New York City, Joyce et al. (148) demonstrated that infants exposed to cocaine and other illicit drugs were hospitalized seven days longer than infants not exposed, at a cost of over \$7500.

Despite prior compelling data, a recent systematic review looking at outcomes in early childhood after prenatal exposure to cocaine found that, amongst children aged 6 years or younger, there was no significant evidence that prenatal cocaine exposure was associated with adverse developmental effects that are different from those associated with prenatal exposure to other risk factors such as alcohol, tobacco, or marijuana (149).

Nevertheless, given the prevalence of cocaine abuse during pregnancy and the existing evidence of adverse perinatal outcomes associated with its use, screening of women for cocaine use during pregnancy is key. Identification of cocaine use during pregnancy should lead to intensive prenatal care and substance abuse and social service referral for these women. In addition, infants with a documented cocaine exposure history should have neurodevelopmental follow-up.

### Other Complications

Gastrointestinal complications of cocaine have been described in case reports (150). Intestinal ischemia and perforation have been associated with cocaine use (151–153) and should be considered in cocaine users who present with severe abdominal pain. Cocaine-induced hepatotoxicity has been well documented in experimental animals (154,155) and has also been reported in humans (156,157). It is postulated that cocaine may cause direct hepatotoxicity through its interaction with the cytochrome P-450 system and

through the production of free radicals (158). Acute myoglobinuric renal failure has been reported in cocaine users (159,160) who may present with agitation, seizure, hyperthermia, tachycardia, tachypnea, altered mental status, metabolic acidosis, renal failure with rhabdomyolysis, and multi-system failure.

### **Opioids**

Unlike alcohol and cocaine, opioid use has not been associated with major organ-specific comorbid conditions. The major comorbidities associated with opioid use are those associated with acute intoxication and withdrawal and those associated with injection drug use (as discussed in the next section).

Opioid intoxication and toxicity, which can result from either an accidental or intentional overdose, typically presents with the triad of lethargy or coma, pinpoint pupils, and respiratory depression (161). Depending upon the severity of toxicity, patients are usually managed with a combination of supportive measures such as fluids, respiratory support including mechanical ventilation, and the use of naloxone (161,162). Unlike alcohol withdrawal, opioid withdrawal is associated with minimal morbidity (162). Common signs and symptoms, including abnormalities in vital signs, rhinorrhea, diaphoresis, muscle cramps, and craving may be managed with clonidine or opioid substitution with methadone or buprenorphine (162,163).

Although relatively uncommon, heroin use has been associated with medical comorbidities including renal disease (i.e., glomerulosclerosis, amyloidosis, or rhabdomyolysis-induced renal failure) (164–166), hypotension (167), seizures (168), hypersensitivity reactions (169), and acute myelopathy (170). With the exception of renal disease, which is described primarily in injection drug users, most of the complications have been described only in case report format. Heroin has also been associated with problems in pregnancy (171), as well as with a neonatal abstinence syndrome (172) and child developmental difficulties (173). Other than the neonatal abstinence syndrome, many of the difficulties related to heroin use in pregnancy may be more the result of various factors such as high-risk behaviors, polysubstance use, and poor nutrition, which are correlated with drug use in general rather than with the heroin use itself.

### **Cannabis**

Similar to the case of opioids, the literature on the comorbid medical complications of cannabis use is sparse (174). Other than the psychiatric disorders discussed elsewhere in this book and the route-related

complications noted in the next section, cannabis use has been associated with little specific medical comorbidity (175). For example, cannabis has been implicated as a cause of temporary decreases in serum testosterone and sperm count (175) as well as gynecomastia in males (176) and motor vehicle accidents (177).

### DISORDERS ASSOCIATED WITH ROUTE OF ADMINISTRATION

The comorbidities associated with the oral consumption of alcohol were reviewed earlier in this chapter. This section will focus on the comorbidities associated with injection and inhaled drug use (see Table 3).

**Table 3** Comorbidity of Substance Abuse Associated with Specific Routes of Administration

Route	Comorbidity <sup>a</sup>	Symptoms
Injection	Bacterial infections	
	Skin	
	Cellulitis	Redness
	Abscess	Swelling
	Heart (endocarditis)	Fatigue, shortness of breath
	Lungs (pneumonia)	Cough, shortness of breath
	Bone (osteomyelitis)	Bone pain
	Joints (septic arthritis)	Joint pain/swelling/redness
	Brain (meningitis, abscess)	Headache, mental status changes
	Viral infections	
	Acute hepatitis (A, B, C, delta)	Fatigue, anorexia, nausea, etc.
	Chronic hepatitis (B, C)	Fatigue, edema, bleeding
	HIV	See Chapter 15
	Other infections	
	Tuberculosis	Cough, shortness of breath
Syphilis	Genital sores	
Gonorrhea/chlamydia	Genital discharge, pain	
Inhalation	Atelectasis	Dyspnea, cough, sputum production
	Pneumomediastinum	Chest pain
	Pneumothorax	
	Hemothorax	
	Talc granulomatosis	
	Asthma	

<sup>a</sup>Patients may be asymptomatic or symptomatic for many of these problems.

## Injection Drug Use

In addition to HIV infection, a number of other important medical comorbidities have long been associated with injection drug use (178). These conditions typically include a variety of infectious diseases related to the penetration of the skin with the introduction of contaminants, the results of local trauma, and lifestyle-related comorbidities.

### Bacterial Infections

Bacteria from contaminated needles or from skin may enter through the bloodstream and implant on abnormal cardiac structures, such as valves, resulting in endocarditis (179). Typically, persons with endocarditis present with an acute febrile illness, a variety of non-specific constitutional symptoms, and possibly a new cardiac murmur. Blood cultures are typically positive and echocardiography may reveal valvular, usually right-sided, vegetations. The tricuspid valve is the primary site of infection in injection drug users and in these cases infective endocarditis is not associated with peripheral emboli; instead, patients will present with clinical manifestations of septic pulmonary emboli (180). *Staphylococcus aureus* is the most common organism isolated, although streptococcal and gram negative organisms may also be found (181). Therapy for endocarditis is directed towards the organisms isolated on blood culture. While there is evolving discussion regarding the choice and duration of antibiotic therapy, recent data support the use of nafcillin or oxacillin with the addition of gentamycin for two weeks in the treatment of right-sided staphylococcal endocarditis (182–184). During therapy, patients need to be monitored closely for complications such as valvular failure and systemic emboli.

A high proportion of patients may present with bacteremia without clinical evidence of endocarditis (185). IDUs are well known to be at increased risk for other serious bacterial infections, such as pneumonia, osteomyelitis, and central nervous system infections that may be associated with bacteremia (186). Bacterial pneumonia is typically caused by *Streptococcus pneumoniae* or *Haemophilis influenzae* and is among the most common causes of fever in this group of patients (187).

Bacterial infections in IDUs may be localized to soft tissues such as skin, subcutaneous tissue, and muscle, without being associated with bacteremia. Frequently, these infections occur at injection sites and result in cellulitis or abscesses. The bacteria causing these skin infections usually exist as normal skin flora, but they can also be more unusual organisms from contaminated needles. One study of the bacteriology of skin and soft tissue infections in IDUs found that 67% of isolates from IDUs originated from the oropharynx, compared to 25% of controls. In addition, a wider variety

of organisms was identified in IDUs (188). While skin and soft tissue infections are amongst the most common causes of fever in this population, one study found that only 42% of patients with a skin or soft-tissue infection had fever and 19% had bacteremia (189). Localized infection can often be treated with oral antibiotics such as dicloxacillin while skin abscesses frequently require surgical drainage. Patients with localized infection that does not respond to oral antibiotics, or patients with signs of systemic infection, may need treatment with intravenous antibiotics. Patients who use hygienic injection techniques, such as skin cleansing with alcohol, may protect themselves from these infections (190).

### Hepatitis

The viral hepatitises including hepatitis A (HAV), B (HBV), and C (HCV), are important medical comorbidities among IDUs. Patients with acute hepatitis complain of fatigue, anorexia, nausea, vomiting, dark urine, and light stools. Patients with chronic hepatitis may present with more nonspecific symptoms, complications of advanced liver disease, or they may be asymptomatic.

While HAV is transmitted primarily via the fecal–oral route, studies have shown that the transmission of HAV is associated with needle sharing (191). There is evidence, however, that the lower socioeconomic status of IDUs may be a stronger contributing factor to the transmission of HAV than the drug use itself (192). Although infection with HAV does not have a chronic course, 15% of individuals infected with this virus will have relapsing symptoms for six to nine months following infection. Given the high rate of coinfection of HAV with HBV and HCV in IDUs, found in one study (191) to be 43% and 81%, respectively, and given the increased risk of complications, particularly with HAV and HCV coinfection, routine HAV vaccination is recommended in IDUs.

IDU is a significant risk factor for the transmission of HBV, accounting for 15% of the cases in the U.S. HBV is an important cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. In the U.S., there are 1.25 million individuals with chronic HBV infection, approximately 300,000 new HBV infections per year, 15,000–30,000 of them developing chronic infection each year, and two to three patients per 1000 dying annually secondary to fulminant hepatitis (193). Still, it is estimated that 50% of active IDUs have serological evidence of prior exposure to HBV, and the majority of these cases show evidence of active viral infection. In addition, approximately 70% of IDUs are infected with HBV within five years of their injecting drugs (194). One study of 255 IDUs in Europe demonstrated a 61% seropositivity for hepatitis B surface antibody (indicating past exposure) and a 7% incidence of hepatitis B surface antigenemia (indicating current infectivity) (195).

The hepatitis D virus (HDV) or delta virus is dependent on HBV for replication (196). Hepatitis caused by the delta virus is the least common form of chronic viral hepatitis, but the one most likely to progress to cirrhosis (197). HDV can co-exist with HBV either as a coinfection, with acquisition at the same time as the HBV infection, or as a superinfection of a chronic HBV carrier, typically an injection drug user (198,199). Coinfection with HDV carries a higher risk of severe acute disease but a lower risk of chronic infection, while superinfection with HDV carries a higher risk of severe and chronic disease. While HDV accounts for a minority of the cases of HBV-related acute hepatitis, it has been estimated that more than 50% of cases of acute liver failure in patients with HBV are due to delta virus rather than HBV alone (200). The risk factors for HDV infection are similar to those for HBV, particularly injection drug use. Since HDV requires the presence of HBV infection, HDV can be prevented either by HBV vaccination or post-exposure prophylaxis in the cases of exposure to HBV.

Recently hepatitis C has emerged as a major viral pathogen, particularly in the subpopulation of IDUs. Formerly designated non-A, non-B hepatitis (NANBH), HCV is the most common chronic blood-borne infection in the U.S., with HCV antibodies detected in 1.8% of the U.S. population (201). Of the approximately four million people in the U.S. who have a positive antibody status, 74% have a detectable HCV ribonucleic acid (RNA). There are an estimated 36,000 new infections reported each year, and HCV has become the most common cause of chronic liver disease, with 40% of chronic liver disease being HCV-related (201). In the U.S., HCV infection is the primary reason for liver transplantation and accounts for 8000 to 10,000 deaths per year (202).

The majority of patients with acute HCV infection are asymptomatic. Seventy-five to 80% of patients with acute HCV will become chronically infected (201). Progression of chronic HCV is variable and typically follows an indolent course, with the time from exposure to manifestation of clinical disease often being many years (203). Progression depends in part on the presence of coinfection with other viruses such as HIV or HBV, as well as exposure to alcohol or other hepatotoxins. There is abundant data to support the finding that heavy alcohol consumption has a deleterious effect on the course of chronic HCV infection. One study revealed a 34% increase in the rate of progression of liver fibrosis in individuals consuming > 50 g/day of alcohol (204). A further study not only found a two- to threefold greater risk of cirrhosis and decompensated liver disease in patients with significant alcohol intake (> 40 g/day for women, > 60 g/day for men), but also noted a more rapid rate of development of cirrhosis in the subjects with greater alcohol consumption (205). In general, cirrhosis develops in 20% of all patients with chronic HCV within 20 years (206).

Hepatocellular carcinoma develops in one to five percent of patients with chronic HCV infection, and in one to four percent of patients per year in the setting of cirrhosis (201). In patients with evidence of compensated cirrhosis, the five-year survival is 91%, which is reduced dramatically to 50% in those with decompensated cirrhosis.

IDU is the major risk factor for HCV transmission in the U.S., accounting for 60% of new cases and 20 to 50% of cases of chronic infection (201,207). Approximately 80% of injection drug users will develop positive HCV antibodies after one year of drug use. As many as 90% of users are infected with HCV after five years of injecting drugs (194). In the setting of sharing needles and injection paraphernalia, nearly all injection drug users will become infected after eight years of use.

Because of the common risk factors for acquiring HCV and HBV in the IDU population, many injection drug users will have antibodies to both viruses, with approximately five percent of them having both infections and active liver disease (199). The coexistence of HCV and HBV viruses is a common cause of acute and chronic liver disease. Coinfection with HBV and HCV has also been shown to increase the rate of progression of liver disease in these patients, with evidence of increased severity of the histological lesions on biopsy. One study examining the prevalence of coinfection with HCV and HBV found that 33% of patients with HCV had occult HBV infection, and 33% of those patients had cirrhosis. In contrast, 19% of patients who had HCV infection alone had cirrhosis (208). Studies have shown that the two viruses appear to inhibit each other at the molecular level while enhancing the cytopathic effects, thereby increasing the severity of the histological lesions (209,210). One survey revealed that HBV core antibody, a marker of past infection, was detected in 80% of IDUs and that HCV antibody was found in 90% of these patients, indicating the high prevalence of both viruses in IDUs and the need for education on routes of transmission (211).

Management of hepatitis in IDUs involves careful assessment and close medical follow-up. Individuals with chronic liver disease (i.e., chronically elevated liver enzymes) need to be followed longitudinally, with a focus on avoiding, when possible, potential hepatotoxins (e.g., alcohol, some medications). All drug users should be screened carefully for hepatitis with serologic studies and liver function tests. A critical aspect of preventive care for patients with hepatitis is vaccination for other viral hepatitis. On the basis of serological results, the patient should be vaccinated to prevent superinfection with HAV or HBV, leading to further hepatic injury (212). One prospective study showed that, while patients with chronic HBV who acquired HAV infection had a relatively benign course, patients with HCV who were superinfected with HAV had a significant risk

of developing fulminant hepatic failure (213). Therefore, vaccination against HAV is recommended in HCV-infected patients without detectable HAV antibody (214).

Patients without evidence of HBV surface or core antibodies should receive the HBV vaccination series. Coinfection with HBV and HCV can increase the rate of progression of liver disease, with biopsy evidence of increased severity of the histological lesions (209). Given that the majority of IDUs have antibodies to HCV and are at risk for coinfection with HBV, vaccination against HBV is indicated (215). The FDA recently approved a combined HAV and HBV vaccine consisting of inactivated HAV and recombinant HBV surface antigen protein (Twinrix). The use of this new vaccine, which combines components previously used in the single antigen vaccines, is indicated in IDUs (216). Other recommended vaccinations include pneumococcus, influenza, and tetanus (212,217,218).

### Tuberculosis

Although substance abuse in general is associated with an increased risk of tuberculosis, there is a greater concern for tuberculosis in IDUs, particularly those with HIV disease (219). Substance use-related factors that contribute to the increased risk of tuberculosis include malnutrition, poor and crowded living conditions, and alcohol abuse, along with IDU and HIV disease. For example, alcoholism has been thought to promote the reactivation of tuberculosis in infected individuals through malnutrition and alcohol-induced immune dysfunction. In addition, patients with alcohol dependence are likely to be noncompliant with therapies for tuberculosis (220). Drug use itself was recognized as a risk factor for tuberculosis before the recognition of HIV disease in drug users (221). One study found that, in the absence of AIDS, substance abuse might account for additional deaths among patients with tuberculosis (222).

Managing tuberculosis in IDUs with HIV disease is a particularly complex issue. Tuberculosis infection is more difficult to diagnose because skin testing is less reliable in individuals with immune dysfunction (219). In addition, in this setting active tuberculosis may present atypically, such as in the case of extrapulmonary disease (223). Compliance with both prophylactic therapy, in the case of a positive purified protein derivative (PPD) skin test, and therapies for active disease can also be problematic in drug users. Drug treatment programs such as methadone maintenance may be an effective means by which to enhance compliance with tuberculosis therapies in this population (219,224).

All patients with substance use disorders should be screened annually for tuberculosis. Latent tuberculosis is defined as a skin test with a positive PPD but without active disease, as evidenced by a negative chest radiograph

and negative sputum culture. Those individuals with evidence of latent infection should be offered prophylactic therapy. Treatment options for latent tuberculosis include isoniazid (INH) for 9 months (for HIV seronegative or seropositive patients); INH for 6 months, rifampin and pyrazinamide for 2 months; or rifampin for 4 months. Current guidelines also advocate the use of rifampin and pyrazinamide daily for 8 weeks as an effective alternative regimen (225). Patients infected with both HIV and latent tuberculosis have a much greater risk of progression from latent infection to active disease and, therefore, should be treated early in the latency stage. Patients with active disease require therapy with multiple drugs and thus need to be followed very closely, in some cases with directly observed therapy (DOT) (219).

Active tuberculosis is defined as having a positive PPD and a positive chest X-ray or sputum culture. The choice of medications and the duration of treatment are dependent on the level of drug resistance in the region in which the patient lives. Treatment options for active tuberculosis in areas with less than 4% INH resistance include INH, rifampin, and pyrazinamide daily for 8 weeks, followed by INH and rifampin daily for 16 weeks. In areas with greater than 4% INH resistance, patients should receive INH, rifampin, and pyrazinamide for 8 weeks and INH and rifampin for the following 16 weeks, with the addition of ethambutol or streptomycin until the susceptibility pattern of the organism is known (226).

#### Fever in Injection Drug Users

When a patient who is actively injecting drugs presents with a febrile illness, the clinician faces the challenging task of finding the source. A thorough history and physical examination, along with laboratory studies such as a complete blood count, liver enzymes, cultures of body fluids, and chest radiograph, are often required to fully evaluate the patient. Even when these steps are taken, a source may not be found. In a study done in the Boston City Hospital emergency department, physicians had significant difficulty predicting which patients were bacteremic or had endocarditis (227). Often, when initial evaluation is unrewarding, close follow-up, including hospitalization, may be necessary until a source is found. Other less acute sources of fever such as tuberculosis, viral illnesses including HIV and hepatitis, and opportunistic infections in HIV-infected patients, need to be considered as well.

#### Inhaled Drug Use

After injection use, inhalation is the second most common route of administration of illicit drugs. Both cocaine and heroin can be smoked by mouth or "snorted" intranasally. While not as prevalent as that seen as a result of tobacco use, the comorbidities associated with inhalation of illicit

drugs are important. In addition, although most of the published literature on the complications of inhaled drug use describes problems seen in cocaine users, the documented shift of heroin use from injection to inhalation is likely to result in more reports of similar problems in heroin users (228).

Chest pain, dyspnea, cough, sputum production, and hemoptysis are important pulmonary symptoms with which users of free-base or “crack” cocaine present for medical evaluation. Chest radiographs have been helpful in the diagnosis of underlying pulmonary abnormalities, and findings such as atelectasis, pneumomediastinum, pneumothorax, and hemopneumothorax have been reported (229). Toxic combustion products from using crack cocaine have been shown to reduce mucociliary clearance and cause bronchiolar damage in both animals and humans, resulting in atelectasis. In addition to these toxic effects, immunologically mediated adverse effects of cocaine have also been postulated (230). Cannabis inhalation has also been associated with pulmonary toxicity (231).

Spontaneous pneumothorax and pneumomediastinum due to inhalation of cocaine have been described. Pneumothorax may result from rupture of visceral pleural blebs, whereas pneumomediastinum may occur when air dissects centrally along the bronchiovascular sheaths into the mediastinum. Pulmonary talc granulomatosis and exacerbation of asthma have also been associated with cocaine inhalation (232,233).

Inhalation of both heroin (234) and marijuana (235) has also been associated with asthma. In addition, marijuana has been shown to contain many of the same carcinogens seen in tobacco (175), leading to a concern about the potential of widespread cases of lung cancer in marijuana smokers. This concern has not yet been realized, perhaps due to the small number of marijuana smokers and the fact that they tend to smoke relatively few marijuana cigarettes per day (175).

Intranasal cocaine use can cause nasal symptoms that mimic allergic or vasomotor rhinitis. In more severe cases, septal perforations may occur as a result of “snorting” (236,237). Irritation from adulterants, ischemia secondary to the vasoconstrictive effects of cocaine, and direct trauma may lead to these sino-nasal complications. In a study using a logistic-regression analysis, intranasal cocaine use was found to be a significant risk factor for HCV infection among the HCV-positive subjects (238), with possible etiologies including sharing of straws or episodes of epistaxis during cocaine use.

## **MODELS OF MEDICAL CARE FOR SUBSTANCE ABUSERS**

The medical comorbidity seen in substance users provides a major challenge to the health care system with respect to how to approach the multiple

problems in this patient population. Preoccupation with the acquisition and use of drugs and the impaired judgment that results from drug use make it exceedingly difficult to provide both disease treatment and preventive services to patients with substance use disorders. In addition, given the fragmented and chaotic lives of many substance abusers, receiving treatment for their substance use disorder as well as for their concurrent medical or psychiatric conditions may not realistically be possible. Therefore, the benefits of linkage of treatment of substance use, medical, and psychiatric disorders would address the problems that arise when the substance use disorder is not addressed in the primary care or mental health setting, when the comorbid medical or psychiatric conditions are not addressed in the substance abuse treatment setting, or when the patient receives care in all these settings but there is a lack of communication between them (239).

Three health “systems” approaches that have applicability to substance users as a whole (240) have been described to address the medical needs of HIV-infected drug users. In the “distributive” model, which is currently widely used, patients with substance use disorders are distributed to a variety of sites throughout the health care system. “Mainstreaming” of patients has appeal, in that these systems already exist and nothing new is required. However, this “usual care” approach is generally recognized as inadequate for many substance abusers. Barriers to the effectiveness of this approach include provider–patient mistrust and provider uncertainty of how to manage substance use disorders.

Two other models have been described that include innovative approaches to providing primary care to substance-using populations. In the “primary assessment and triage” model, special programs have been developed in which substance abusers receive a comprehensive substance abuse and medical evaluation at one site and are then referred for ongoing drug abuse treatment and primary medical care at selected programs in the community (241). In the “drug treatment linked to primary care” model, both types of services are provided “under one roof” (242). Both of these models recognize the need for comprehensive and coordinated services for this population. The “linked” model provides for initial and longitudinal care for patients. A recent randomized controlled trial looking at the provision of primary medical care within an addiction treatment program found that subjects with substance abuse-related medical conditions treated in the integrated model had a significantly higher rate of abstinence than patients treated in the usual treatment model in which primary care and substance abuse treatment were provided separately (243).

An extension of the “linked” model is the practice of providing substance abuse treatment within a primary care office-based setting. This model has been shown to be successful in patients with alcohol problems in

terms of primary-care physicians providing screening, brief interventions, and longitudinal care (244–246). In addition, this model has proven to be a feasible and effective option in the treatment of opioid dependence. The Food and Drug Administration's recent approval of buprenorphine for maintenance treatment of opioid dependence provides an additional viable option for treatment in the primary care setting (247). Two randomized controlled trials looking at the provision of office-based opioid dependence treatment (248,249) found equal or superior results with methadone or buprenorphine in this setting when compared with those seen in the provision of care offered in a traditional narcotic treatment program. Therefore, this model of care provides integration of treatment for substance use disorders and related medical conditions while aiming to broaden access to care by bringing new patients into treatment. Ultimately, the determination of which model is best will depend on the level of need and access to services for individual patients.

## **CONCLUSIONS**

Comorbid medical disorders are of major importance in the care of substance-using patients. The presence of medical comorbidities is commonly the stimulus for patients to seek treatment and, as such, needs to be addressed as part of the treatment plan. Clinicians providing services to substance abusers need to be aware of these problems, be able to recognize them when they occur, and have access to the resources necessary to address them. Models of medical care for substance users have been developed in which drug treatment and medical services are provided in an integrated fashion. Careful attention to the medical needs of patients with substance use disorders will benefit both their substance use behavior and their general medical wellbeing.

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