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Abstract

Drugs of abuse often have important effects on the cardiovascular system, some of which are life-threatening. An understanding of the intersection between addictive and cardiovascular disorders, therefore, is increasingly relevant to general practitioners and psychiatrists. The effects of illicit drugs vary depending upon the agent, dose, route of administration, and its potential interaction with other prescription medications. Cardiovascular consequences can range from innocuous side effects, such as mild tachycardia and hypertension, to life-threatening ventricular arrhythmias and myocardial infarction.

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Hemodynamic alterations are common with both active drug abuse and withdrawal and are frequently mediated by the autonomic nervous system.

Sympathomimetic drugs like amphetamines and cocaine often result in an increase in blood pressure and heart rate. In addition, they may cause substantial cardiotoxicity including arrhythmia, stroke, myocardial infarction, heart failure, and death. These stimulant drugs often increase the propensity for developing atherosclerosis. Some of this is mediated by increases in blood pressure and lipids, but may also occur due to proinflammatory effects or increased hypercoagulability. By contrast, some drugs such as opioids lead to small reductions in pulse and blood pressure. Most naturally occurring opioids do not alter cardiac rhythm; however, synthetic opioids, such as methadone, may result in QTc interval prolongation and torsades de pointes, a form of life-threatening ventricular arrhythmia. In this chapter we review the cardiovascular effects of common drugs of abuse including cocaine, amphetamines, nicotine, opioids, alcohol, marijuana, and anabolic steroids.

100.1 Introduction

Drugs of abuse have a myriad of cardiovascular effects. Depending on the drug, dose, and route of administration, cardiovascular consequences can range from innocuous side effects, such as mild tachycardia and hypertension, to life-threatening ventricular arrhythmias and myocardial infarction (Table 100.1). Hemodynamic alterations are common with drug use and most often are mediated through interactions with the autonomic nervous system (Ghuran and Nolan 2000). Sympathomimetic drugs like amphetamines cause an increase in release of peripheral catecholamines stimulating increases in heart rate, systemic vascular resistance, and cardiac contractility, thus resulting in augmentation of cardiac output and blood pressure. In contrast, several drugs are directly cardiodepressant in the acute setting, and many drugs of both types are cardiotoxic causing cardiomyopathy and congestive heart failure with long-term use.

Changes in the balance of myocardial oxygen supply and demand with drug use can lead to myocardial ischemia (Ghuran and Nolan 2000). For example, cocaine augments oxygen demand in the myocardium by increasing heart rate, afterload, and contractility while simultaneously decreasing supply by inciting epicardial coronary vasoconstriction. Modulation of lipid profiles, coagulation factors, platelet function, and inflammation further heighten the risk of cardiac ischemic events in patients using these drugs.

Many recreational drugs are arrhythmogenic in the acute setting or during abstinence/withdrawal. Mechanisms of arrhythmias are complex and likely result from interplay between the direct effects of drugs, electrolyte derangements, sympathetic nervous alterations, and cardiac ischemia. Of particular importance is the interaction of several drugs, especially the synthetic opioids, with a subunit of a voltage-gated potassium channel coded by the human Ether-à-go-go-Related Gene (hERG) (Katchman et al. 2002). Inhibition of this subunit causes alterations

Table 100.1 Cardiovascular effects of various drugs of abuse

Drug	Cardiovascular effect
Ethanol	Hypertension
	Arrhythmias – holiday heart
	Dilated cardiomyopathy
	Coronary artery disease
	Stroke
Cocaine	Tachycardia
	Hypertension
	Myocardial depression
	Prothrombotic risk
	Atherosclerotic risk
	Chest pain
	Angina pectoris
	Myocardial infarction
	Arrhythmias
	Left ventricular hypertrophy
	Dilated cardiomyopathy, myocarditis
	Aortic dissection
	Infective endocarditis
Stroke	
Mesenteric ischemia	
Amphetamines	Tachycardia
	Hypertension
	Chest pain
	Myocardial infarction
	Arrhythmias
	Sudden cardiac death
	Aortic dissection
	Cardiomyopathy
	Infective endocarditis
	Stroke
	Premature coronary artery disease
Opioids	Orthostatic hypotension
	Ischemic preconditioning
	Ventricular arrhythmia
	Infective endocarditis
Nicotine	Coronary artery disease
	Worsens angina pectoris
	Myocardial infarction
	Stroke
	Prothrombotic risk

(continued)

Table 100.1 (continued)

Drug	Cardiovascular effect
Cannabis	Tachycardia
	Bradycardia
	Hypertension
	Orthostatic hypotension
	Syncope
	Worsens angina pectoris
	Myocardial infarction
	Ischemic stroke
	Arrhythmias
Anabolic steroids	Prothrombotic risk
	Hypertension
	Dyslipidemia
	Myocardial infarction
	Ischemic stroke
	Ventricular hypertrophy

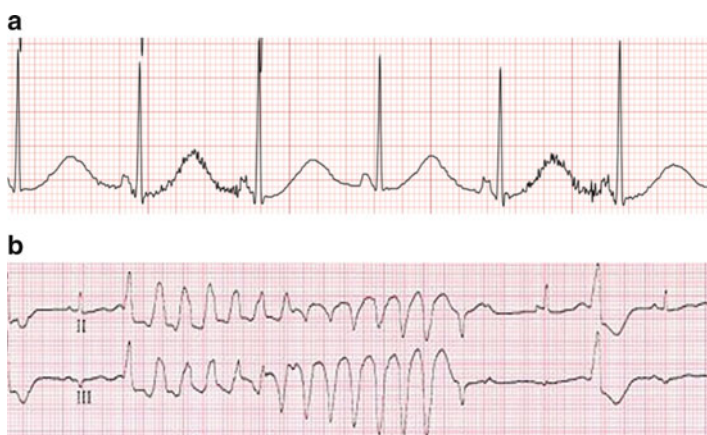


Fig. 100.1 (a) Prolonged rate-corrected QT interval (QTc). (b) Torsades de pointes, a type of polymorphic ventricular tachycardia

in repolarization during phase 3 of the action potential, which can lead to acquired prolongation of the rate-corrected QT (QTc) interval, augmenting the risk of the ventricular arrhythmia, torsades de pointes, and sudden cardiac death (Fig. 100.1).

This overview highlights the variety of short-term and long-term cardiovascular consequences of abused drugs, with a particular focus on cocaine, opioids, and alcohol employing a clinical vignette format.

100.2 Mechanisms and Cardiovascular Consequences of Abused Drugs

100.2.1 Alcohol

Alcohol (ethanol) is widely used throughout the world with an estimated two billion users representing nearly half of the world's population. Light to moderate alcohol consumption has been associated with a reduced risk of atheroembolic vascular events including myocardial infarction and ischemic stroke, but chronic heavy alcohol use is clearly cardiotoxic and is associated both directly and indirectly with a number of cardiovascular consequences including hypertension, atrial fibrillation, stroke, and cardiomyopathy. Adverse cardiovascular effects begin to appear with consumption of two to three standard drinks/day or more and increase thereafter in a dose-dependent fashion (Lange and Hillis 2012). In comparison with moderate regular drinking, binge drinking is also associated with increased risk of complications such as atherosclerosis, atrial fibrillation (AF), and stroke (Liang et al. 2012). Alcohol is directly toxic to cardiomyocytes via a number of mechanisms including uncoupling of the excitation-contraction system, impairment of calcium sequestration in the sarcoplasmic reticulum, reduction of mitochondrial respiratory ratio, and increased interstitial protein synthesis (George and Figueredo 2011; Lange and Hillis 2012). In addition, alcohol increases sympathetic tone producing elevated heart rate and blood pressure (Mandyam et al. 2012), impairs vagal tone, may precipitate electrophysiologic changes in atrial tissue (Kodama et al. 2011), and is associated with endothelial dysfunction (Goslowski et al. 2013), each of which may contribute to adverse cardiovascular outcomes.

Abstinence often results in rapid improvement in many of cardiovascular consequences and in some cases may be the only intervention necessary in the long term to address alcohol-associated cardiovascular risk. However, acute alcohol withdrawal delirium tremens in particular can precipitate cardiovascular changes that may be fatal. Hypertension and tachycardia are classic symptoms of acute alcohol withdrawal, and though they improve within 3–4 days of alcohol cessation, they may precipitate ischemic or hemorrhagic stroke, acute decompensated heart failure, or cardiac ischemia in the setting of coronary artery disease. Fatal arrhythmias may also be precipitated by adrenergic surge, electrolyte deficiencies, or QT interval prolongation. Management of patients with acute alcohol withdrawal who have known cardiovascular disease is further complicated by potential exaggerated hemodynamic responses to beta-blockers, calcium channel blockers, and long-acting nitrates early in the course of withdrawal (Kahkonen 2006). There is little direct evidence regarding management of cardiovascular complications of acute alcohol withdrawal in the setting of specific cardiac conditions, but propranolol and clonidine are most commonly suggested to treat withdrawal-related autonomic instability as well as aggressive replacement of potassium, magnesium, and phosphate. Because of the potential exaggerated effects on cardiac output and peripheral vascular resistance of both medications, particular caution must be taken in the setting of dilated cardiomyopathy and valvular disease such as advanced aortic stenosis.

Vignette A 48-year-old man is evaluated in the emergency department on January 2 for intermittent palpitations and chest pressure over the preceding 48 hours. He does not regularly receive medical care and takes no medications. He smokes cigarettes but uses no other drugs. He reports drinking up to 12 packs of beer per day normally and consumed up to double his normal amount during the week prior to presentation. He is noted to have an irregular heart rate of 130, a blood pressure of 140/90, and moderate pedal edema.

100.2.1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia among older adults and is categorized as paroxysmal (intermittent, not exceeding 7 days), persistent (episodes exceed 7 days or require treatment to terminate), and permanent (continuous, long standing) (Fig. 100.2). AF was the most common arrhythmia identified in 1978 as part of the “holiday heart syndrome” that was defined as hospital admission for dysrhythmia immediately following binge drinking in the setting of chronic alcohol use, classically following a weekend, vacation, or year-end holiday (Ettinger et al. 1978). Since then, moderate to heavy drinking has been associated with both new onset AF and exacerbation of existing paroxysmal AF, and it is suspected that alcohol is a causative factor in up to two-thirds of patients ≤ 65 years of age with AF (Samokhvalov et al. 2010; Kodama et al. 2011; Liang et al. 2012; Mandyam et al. 2012). However, the mechanisms underlying this association remain unclear, though clear electrophysiologic changes have been noted in atrial tissue exposed to ethanol including shortening of the action potential duration and refractory period, each of which may trigger dysrhythmia. The increased incidence of atrial fibrillation may also be due to other factors such as heightened sympathetic tone or electrolyte disturbances. Alcohol consumption is often associated with hypokalemia and hypomagnesemia, which both lead to QTc interval prolongation in experimental models. Heavy alcohol consumption has also been associated with left atrial enlargement and left ventricular enlargement (Singh et al. 2013), both of which may increase the risk of developing AF.

Acute AF related to alcohol and/or illicit drug use will often revert to sinus rhythm without requiring electrical cardioversion in young patients (Krishnamoorthy et al. 2009). However, if the patient is likely to continue to use alcohol, they will remain at an elevated rate of future episodes of paroxysmal AF that may become permanent. There are no specific recommendations regarding management of AF related to alcohol use. β -blockers have a theoretical advantage over calcium channel blockers for rate control in light of the adrenergic excess



Fig. 100.2 Atrial fibrillation

thought to contribute to alcohol-related AF. Alcohol and drug abuse have been associated with a lower likelihood of treatment with warfarin, and it remains important to risk stratify all patients using a validated risk score such as the CHADS₂ or CH₂ADS₂-Vasc score when deciding whether to initiate prophylactic antiplatelet or anticoagulation therapy (Camm et al. 2010). Unlike warfarin, newer agents such as rivaroxaban, dabigatran, or apixaban offer the advantage of not requiring routine monitoring, which may be useful in the setting of questionable compliance (Camm et al. 2012). These agents were associated with lower rates than warfarin of intracerebral hemorrhage and gastrointestinal bleeding, both of which occur more frequently in alcoholics than nonalcoholics, but there is no direct evidence to determine whether they provide a safe alternative for anticoagulation in AF in the setting of alcohol abuse.

100.2.1.2 Hypertension and Vascular Disease

Alcohol has been associated with dose-dependent increase in blood pressure both acutely and chronically in both men and women in several large studies (Marmot et al. 1994; Yoshita et al. 2005; Wakabayashi and Araki 2010). While the effect was seen at all ages, it was more prominent in the elderly where the propensity for hypertension is elevated. Furthermore, abstinence has been associated with clinically meaningful reductions in blood pressure comparable with effects of antihypertensive medications (Estruch et al. 2005). The mechanism of the association between alcohol and hypertension is incompletely understood, although evidence of vascular dysfunction has been observed even in young binge drinkers (Goslowski et al. 2013). Marked endothelial dysfunction is observed in alcoholics that is only partially reversed with abstinence, suggesting a persistent risk of cardiovascular morbidity and mortality. Furthermore, patients may continue to demonstrate exaggerated blood pressure response to stress for many weeks. Nevertheless, complete abstinence has been associated with reduction in systolic blood pressure of 7–12 mmHg approximating the effects of the most potent antihypertensive drugs. Therefore, abstinence remains a primary recommendation for all patients with hypertension who use alcohol.

The association between alcohol and vascular disease including coronary artery disease and stroke is J-shaped, with small to moderate amounts of ethanol producing reductions in several cardiovascular outcomes due in part to favorable effects on high-density lipoprotein cholesterol and apolipoprotein A-I levels, inhibition of platelet aggregation, increased antioxidant activity, decreased serum fibrinogen, anti-inflammatory effects, and improved fibrinolysis. However, heavy alcohol use is associated with increases in atherosclerotic coronary artery disease (McElduff and Dobson 1997; McClelland et al. 2008; Ruidavets et al. 2010), ischemic stroke, and cerebral hemorrhage (Leppala et al. 1999) compared with moderate drinkers. The mechanism of this association remains controversial but is likely due in part to increased serum triglycerides, hypertension, decreased nitric oxide synthesis, and increased inflammation (Cahill and Redmond 2012). In particular, risks of both coronary and cerebrovascular events have been repeatedly shown to be increased by binge drinking (Snow et al. 2009; Ruidavets et al. 2010), and an acute increase in

stroke risk within 1–24 h of heavy alcohol use has been observed. This may be due to reactive thrombocytosis and increased platelet aggregation during alcohol withdrawal, and we speculate that increased adrenergic activity may also play a role. Paradoxically, the observed association between alcohol and hemorrhagic stroke may relate to impaired coagulation function as well as weakening of cerebral arteries. The increased risk of both stroke and death due to ischemic heart disease appears to return toward baseline in former heavy drinkers (Hillbom et al. 1999; Roerecke et al. 2011), and apart from abstinence, there are no specific risk reduction strategies recommended apart from standard cardiovascular risk reduction. Elimination of tobacco abuse may be a particularly important risk factor given that it is often used in the setting of social alcohol consumption and is itself a potent atherosclerotic risk factor.

100.2.1.3 Cardiomyopathy

Although light to moderate alcohol consumption has been associated with a lower rate of heart failure than nondrinkers, chronic heavy alcohol use is a well-known cause of left ventricular diastolic and systolic dysfunction. In fact, alcohol may be the leading etiology of nonischemic dilated cardiomyopathy in industrialized nations. Most men who develop alcoholic cardiomyopathy have consumed ≥ 8 standard drinks/day for ≥ 5 years. Women appear to be more sensitive to the cardiotoxic effects of alcohol and may develop cardiomyopathy with a smaller comparative exposure. Evidence of cardiotoxicity may be apparent long before the emergence of symptoms, as 30–50 % of alcoholics have echocardiographic evidence of left ventricular hypertrophy and/or diastolic dysfunction and 30 % of asymptomatic alcoholics have evidence of systolic dysfunction as measured by reduced left ventricular ejection fraction (LVEF). Direct myocardial damage may be mediated by acetaldehyde, the first metabolite of ethanol. Acetaldehyde levels are particularly elevated in heavy drinkers, in part due to reduced hepatic aldehyde dehydrogenase activity (Zhang et al. 2004). Chronic activation of the renin-angiotensin-aldosterone system and sympathetic nervous system and nutritional deficiency (especially thiamine) may also contribute to progression of myocardial dysfunction by potentiating alcohol- and acetaldehyde-induced cell death.

Abstinence can result in significant improvement in left ventricular systolic function if achieved early during the progression of myocardial dysfunction. It has been shown that “controlled” intake of two to six standard drinks/day has also been associated with improvement in LVEF within months, but because controlled drinking is generally not possible for alcoholics, total abstinence remains the primary recommendation. Long-term survival in patients with alcoholic cardiomyopathy who achieve abstinence is the same or better than patients with idiopathic dilated cardiomyopathy, whereas patients who continue to drink have a lower survival (Prazak et al. 1996). As for all dilated cardiomyopathies, neurohormonal blockade with β -blockers and renin-angiotensin-aldosterone system inhibitors is the cornerstone of medical therapy. Additional considerations in the setting of alcoholic cardiomyopathy are nutritional and vitamin supplementation, particularly vitamin B12 and folate.

Vignette *During his hospitalization, the patient is noted to be in atrial fibrillation and to have reduced LVEF of 40 %. Cardiac catheterization reveals no coronary artery disease. He is counseled on abstinence; started on β -blockers, an angiotensin-converting enzyme (ACE) inhibitor, warfarin, and loop diuretics; and then discharged to an addiction treatment center. He leaves treatment after 21 days of a 30-day program and is found dead two weeks later in a hotel room. Although there are empty bottles of alcohol in his room, his blood alcohol level is found to be zero. Autopsy revealed an enlarged, hypertrophic heart but no evidence of acute ischemia, consistent with sudden cardiac death.*

100.2.1.4 Sudden Cardiac Death

Large studies have demonstrated an elevated risk of sudden death associated with heavy drinking (>6 drinks/day), even in patients without preexisting ischemic or structural heart disease (Wannamethee and Shaper 1992). Electrophysiologic studies have demonstrated that alcohol increases susceptibility to ventricular arrhythmias as well as supraventricular arrhythmias. However, sudden death may also occur during periods of abstinence or withdrawal. The QTc interval is may be prolonged in up to 63 % of cases during alcohol withdrawal (Cuculi et al. 2006) and normalizes with remission of abstinence symptoms. Electrolyte abnormalities, catecholamine excess, impaired vagal control of heart rate, myocardial fibrosis, and sleep apnea may also contribute to a heightened risk of arrhythmia (Laonigro et al. 2009).

In addition to correction of electrolyte abnormalities, particularly hypokalemia and hypomagnesemia, it is therefore important to consider cardiac monitoring of patients during the early stages of withdrawal, particularly in the setting of underlying structural heart disease and severe symptoms including delirium tremens. Furthermore, caution should be taken in administration of QTc-prolonging medications such as antipsychotics, even if the patient has previously been taking them, as there appears to be acute, transient prolongation of the QTc interval and increased QT variability during alcohol withdrawal. There is currently no recommendation for prophylactic antiarrhythmic therapy or continuing therapy after alcohol withdrawal has subsided.

100.2.2 Cocaine

Vignette *A 44-year-old man presents to the emergency department with complaints of mid-sternal chest discomfort of moderate severity, which has been unremitting for the past 3 hours and radiates to his shoulders. He notes palpitations, feelings of uneasiness, and resting dyspnea. He is a long-standing smoker and has untreated bipolar disorder. He denies illicit drug use but became more agitated when this line of questioning was pursued. Examination reveals an alert male somewhat apprehensive but with normal cognition. Blood pressure is 178/90 mm Hg and pulse rate is 95 beats per minute, while respiratory rate, temperature, and oxygen saturation are within normal limits. Cardiovascular exam reveals normal*

jugular venous pressure and a soft systolic murmur. Lung auscultation is normal. Urine toxicology is positive for benzoylecgonine. ECG demonstrates ST segment elevation in leads V2–V5 with peaked T-waves. QRS duration and rate-corrected QT (QTc) intervals are prolonged. Chest x-ray and serum chemistries (including cardiac troponin) are unremarkable. Upon sharing these results, the patient confides that he and his girlfriend consumed an “eight-ball” (3.5 grams) of cocaine by intranasal route.

Cocaine (benzoylecgonine) is a crystalline alkaloid, derived from the coca plant that is among the most widely abused drugs worldwide. It is consumed via intranasal insufflation, inhaled vapor from smoking a freebase combination with sodium bicarbonate, or the intravenous route. Cocaine incites a wide array of cardiovascular consequences ranging from acute alterations in hemodynamics to myocardial ischemia, ventricular arrhythmias, and dilated cardiomyopathy (Table 100.1). The extensive effects on the cardiovascular system result from its numerous mechanisms of action. Cocaine is a potent sympathomimetic that augments central sympathetic outflow and has the ability to increase peripheral catecholamine concentration. Cocaine also exhibits antiarrhythmic-like inhibition of voltage-gated sodium channels and potassium channels and has complex, poorly understood interactions with L-type calcium channels (Ramirez et al. 2012).

100.2.2.1 Hemodynamics

Cocaine incites a range of hemodynamic alterations. Sympathomimetic activity dominates at low to moderate doses resulting in tachycardia, systemic vasoconstriction, and coronary vasospasm. However, at higher doses, cocaine's sodium and potassium channel inactivation can lead to cardiodepression, tachy- and bradydysrhythmias, and even vasodilation (Egashira et al. 1991a; Schwartz et al. 2010).

When taken at low doses (~0.35 mg/kg) through the intranasal route, cocaine ingestion simply results in slight elevation of systolic blood pressure, while higher doses (~1.3 mg/kg) will cause an increase in systolic and diastolic blood pressure (~30/15 mmHg) and elevation of the heart rate (~20 bpm). The onset of these alterations occurs at 2 min and peaks at 5–10 min (Resnick et al. 1977). Moderate cocaine doses (2–3 mg/kg) have a positive inotropic effect, resulting in an increase in left ventricular contractility and cardiac index (Boehrer et al. 1992). In sum, low to moderate doses of cocaine result in tachycardia and in hypertension via a rise in both systemic vascular resistance and cardiac output.

The mechanism of catecholamine response is dependent on the route of cocaine administration. Experimentally, intravenous infusion of cocaine in humans blocks the reuptake of catecholamines peripherally, thereby increasing available norepinephrine in the heart and vascular smooth muscle (Muscholl 1961; Tuncel et al. 2002). However, when consumed by the intranasal route, peripheral norepinephrine levels are not elevated (Tuncel et al. 2002). Therefore, the mechanism of hypertension in acute cocaine intoxication following intranasal is due to an increase of central sympathetic outflow (Vongpatanasin et al. 1999).

Tachycardia is mediated through β -adrenergic receptor interactions as nonselective β -blockade with propranolol abolishes the increase in heart rate caused by cocaine (Kenny et al. 1992). Hypertension is partially mediated through α -adrenergic receptors as α -blockade with prazosin experimentally prevents vasoconstriction (Egashira et al. 1991a). However, positive inotropic effects facilitated through β -adrenergic stimulation contribute to hypertension caused by cocaine, as propranolol attenuates the rise in mean arterial pressure by diminishing the cocaine-mediated rise in left ventricular contractility. Combined α - and β -blockade with labetalol eliminates cocaine's chronotropic effect on the heart and significantly blunts the increase in blood pressure (Kenny et al. 1992).

Cocaine use has also been implicated in epicardial coronary artery vasospasm. Animal studies demonstrate that intravenous cocaine administration results in coronary vasoconstriction with a decrease in coronary diameter of 15–46 % (Benzaquen et al. 2001). In addition to α -adrenergic stimulation, cocaine causes vasospasm by increasing the expression of the potent vasoconstrictor endothelin and decreasing levels of nitric oxide (Mo et al. 1998; Wilbert-Lampen et al. 1998). Denuded endothelium that simulates atherosclerotic coronary artery disease exhibits a mean greater degree of narrowing compared to healthy coronary arteries experimentally (Egashira et al. 1991b). Human data have corroborated these observations. In several studies employing a recreational dose of cocaine (2 mg/ml) intranasally in humans, coronary caliber has been shown to decrease (Benzaquen et al. 2001). In a study of patients with and without coronary artery disease undergoing diagnostic catheterization, coronary diameter decreased more than twice as much in diseased arteries (>50 % stenosis) versus normal arteries (Flores et al. 1990). The time course of coronary vasospasm does not simply follow peak serum levels of cocaine. In fact, coronary vasoconstriction was found to occur at a greater magnitude at 90 min post administration when cocaine metabolites were highest compared to 30 min when serum cocaine levels peaked (Brogan et al. 1992). The degree of vasospasm is augmented by concurrent cigarette smoking with 19 % reduction in coronary diameter seen with simultaneous cocaine and smoking and 7 % reduction seen with cocaine alone in one study (Moliterno et al. 1994). The risk of coronary events is further heightened by cocaine's ability to activate platelets and provoke shear stress.

Cocaine infusion has been shown to be directly cardiodepressant in animal models and in vitro human cardiomyocytes (Egashira et al. 1991a; Perreault et al. 1993). This cardiodepression occurs independently of alterations in coronary blood flow (Morcos et al. 1993). The negative inotropic effect of cocaine is paralleled by a decrease in ventricular myocyte intracellular calcium concentration. The mechanism responsible for direct cardiodepression is hypothesized to result from decreased intracellular sodium concentration caused by voltage-gated sodium channel inactivation by cocaine. This results in less sodium available for the sodium-calcium exchanger in the sarcoplasmic reticulum, less calcium storage in the myocytes, and therefore lower intracellular calcium concentrations during depolarization (Perreault et al. 1993). In fact, it has been found that when cocaine's sympathomimetic action on the heart is blocked with β -adrenergic receptor

antagonists, cocaine's direct effect on the heart is unmasked and left ventricular contractility is significantly reduced (Kenny et al. 1992).

100.2.2.2 Myocardial Ischemia

Cocaine is responsible for 57 % of illicit drug-related emergency department visits in the United States, and chest pain is the most common presenting symptom (Finkel and Marhefka 2011). Cocaine-related chest pain is typically described as pressure-like in quality and is frequently associated with dyspnea, diaphoresis, nausea, palpitations, and anxiety (McCord et al. 2008). The reported incidence of acute myocardial infarction (MI) in patients with cocaine-related chest pain ranges between 0.7 % and 6 %. There is a 24-fold increased risk of acute MI within the first hour of cocaine use. However, myocardial injury can also occur hours after use presumably due to cocaine metabolites (Mittleman et al. 1999; McCord et al. 2008). Cocaine is estimated to play a role in one out of four MIs in patients between the ages of 18 and 45, and half of patients with cocaine-related MIs have no evidence of atherosclerotic coronary artery disease on angiography (Lange and Hillis 2001; Qureshi et al. 2001). All routes of administration appear to carry a similar risk of acute MI.

The diagnosis of myocardial infarction in those with recent cocaine use is difficult. There are no historical factors useful for distinguishing MI from chest pain without myocardial injury in this population. Specific characteristics of pain such as onset, location, quality, and duration are not predictive, nor are histories of chest pain, myocardial infarction, or risk factors for atherosclerotic coronary artery disease (Hollander et al. 1994). Furthermore, in the presence of cocaine, electrocardiograms (ECGs) can exhibit abnormal repolarization in the absence of ischemia. Presenting ECGs are abnormal in approximately 55–85 % of cocaine users, and up to 43 % of patients with cocaine-related chest pain meet diagnostic criteria for ST-elevation MI (as defined by >0.1 mV elevation in contiguous leads) (Gitter et al. 1991; Chakko et al. 1994; Hollander et al. 1994). The positive predictive value of ECG for MI in this population is reportedly only 18 % with a sensitivity of approximately 36 % (Hollander et al. 1994). Serum levels of creatinine kinase can be misleading presumably due to rhabdomyolysis (Gitter et al. 1991). However, serum troponin assays remain effective in detecting myocardial injury in cocaine users (Lange and Hillis 2001; Finkel and Marhefka 2011).

Myocardial ischemia is caused by misbalance of oxygen supply and demand. The sympathomimetic actions of cocaine augment myocardial oxygen consumption by increasing heart rate, blood pressure, and myocardial contractility (Lange and Hillis 2001). Simultaneously, coronary artery vasoconstriction, which occurs more dramatically in segments with significant atherosclerosis, decreases oxygen supply. Habitual cocaine use has been linked to premature coronary artery disease in postmortem studies, which is thought to result from increase vascular permeability to LDL and amplified expression of leukocyte adhesion molecules (Lange and Hillis 2001). Acute cocaine use is also associated with intracoronary thrombus formation, which may result from cocaine's ability to activate and trigger aggregation of platelets and augment levels of fibrinogen, von Willebrand factor, and

plasminogen activator inhibitor, without a corresponding increase in plasmin (Heesch et al. 2000; Lange and Hillis 2001; Siegel et al. 2002).

To our knowledge, there have been no randomized, placebo-controlled trials addressing improving outcomes in cocaine-related MIs (McCord et al. 2008). Those with chest pain in the setting of cocaine use should receive IV benzodiazepines as early management, as their use relieves chest pain and mitigates hemodynamic alterations. Nitroglycerin reverses cocaine-associated coronary vasoconstriction and should also be given as a first-line agent. Calcium channel blockers are recommended after benzodiazepines and nitroglycerin have failed. Although they can reverse coronary vasospasm, use of calcium channel blockers in ACS in the absence of cocaine has not been shown to improve survival and may even increase mortality rates in those with decreased left ventricular function. Phentolamine, an α -adrenergic blocker, may also be administered as a second-line agent, as it reverses coronary vasoconstriction.

Recent guidelines for unstable angina and non-ST-elevation MI caution against the use of β -blockers in patients using cocaine, because unopposed α -adrenergic stimulation can potentially exacerbate coronary vasoconstriction and worsen arterial hypertension (McCord et al. 2008; Anderson et al. 2011). β -blockers have been shown to reduce mortality when given orally in the first 24 h in acute coronary syndrome not related to cocaine. However, the mortality rate in cocaine-related MI is lower, which alters the risk/benefit ratio of this intervention (McCord et al. 2008). There have only been two studies that prospectively evaluated the effect of β -blockers on coronary artery vasoconstriction in the setting of cocaine use (Lange et al. 1990; Boehrer et al. 1993; Finkel and Marhefka 2011). These two small studies included only nine to ten patients each and evaluated the effects of only propranolol and labetalol, yet are the basis for the recommendation against β -blockers in cocaine-related chest pain patients (Finkel and Marhefka 2011).

In opposition, recent retrospective studies have evaluated outcomes in patients with cocaine-related chest pain who were given β -blockers prior to the discovery of their recent cocaine use. It was found that β -blocker therapy was associated with a lower incidence of MI without change in the rate of adverse outcomes or peak levels of troponin (Dattilo et al. 2008; Rangel et al. 2010; Ibrahim et al. 2013). In one study, there was a trend toward decreased post-hospital mortality in those receiving β -blockers (Rangel et al. 2010). The 2011 updated AHA guidelines state that it is reasonable to consider administering a combined α - and β -blocker like labetalol in situations when patients are hypertensive and tachycardic and have received a vasodilator such as nitroglycerin or a calcium channel blocker in close temporal proximity (Anderson et al. 2011). Much is still unknown about the potential benefit and harm of β -blockers in patients with cocaine-related myocardial ischemia, and caution should be taken with their use until further investigation has been conducted.

Due to the risk of coronary thrombus formation, patients should be given aspirin, and those with proven MI should receive unfractionated heparin or low molecular weight heparin if there are no contraindications (McCord et al. 2008). Fibrinolytics should be used with caution, as there are reports of devastating complications in

cocaine users, and the diagnosis of STEMI is challenging in this population due to baseline ECG abnormalities (Lange and Hillis 2001; McCord et al. 2008). Percutaneous coronary intervention is the preferred management of intracoronary thrombus, but fibrinolytics can be used in cases of persistent ST segment elevation after nitroglycerin and calcium channel blockers have been given if there are no contraindications and coronary angiography is not available (McCord et al. 2008; Anderson et al. 2011).

Outcomes are generally better in cocaine-related MI compared to MI not related to cocaine (McCord et al. 2008). The incidences of ventricular arrhythmias, congestive heart failure, and death are 4–17 %, 5–7 %, and <2 %, respectively (Lange and Hillis 2001). The better outcomes are presumably due to the overall younger age of patients experiencing MI while using cocaine. However, those who experience cocaine-related MI are at high risk for recurrent ischemic events as more than half will continue to use cocaine and up to 58 % will have recurrence of ischemia (McCord et al. 2008).

100.2.2.3 Cardiac Conduction and Arrhythmia

Cocaine can cause a wide range of electrocardiographic alterations owing to its sympathomimetic actions and antiarrhythmic properties (Ramirez et al. 2012). Cocaine acts similar to class I antiarrhythmic by blocking voltage-gated sodium channels (I_{Na}) in the inactive state. Cocaine also blocks the *hERG*-coded voltage-gated potassium channel responsible for the rapid delayed rectifier potassium current (I_{Kr}) that allows for repolarization. Together, the inhibition of I_{Na} and I_{Kr} slows the rapid upstroke of the action potential during phase 0 and prolongs the action potential duration by delaying phase 3. Electrocardiographically, this results in widening of the QRS complex and prolongation of the QT interval.

Clinically, cocaine use is associated with a variety of arrhythmias (Table 100.2) (Lange and Hillis 2001). The most common alteration is sinus tachycardia, but an assortment of other supraventricular rhythm disturbances has been temporally related to cocaine use, including nonsustained supraventricular tachycardia, atrial fibrillation, and sinus bradycardia (Ramirez et al. 2012). Excluding torsades de pointes, prospective studies on patients consuming cocaine have not consistently demonstrated an increase risk of ventricular arrhythmias other than frequent premature ventricular contractions. However, the literature contains frequent case reports of monomorphic ventricular tachycardia and ventricular fibrillation in cocaine users. These associations are often confounded by polysubstance use and electrolyte derangements, especially acidosis.

A prospective trial demonstrated that when habitual users smoke cocaine, the rate-corrected QT interval (QTc) modestly increases (Magnano et al. 2006). Furthermore, a retrospective report found that QTc interval prolongation is present in approximately 4 % of chronic cocaine abusers, 26 % of patients treated for cocaine toxicity in the ED, and 75 % of cases of cocaine-related mortality (Chakko et al. 1994). In addition to its ability to prolong the QT interval, cocaine has been shown to induce early afterdepolarizations, further increasing the risk of the ventricular arrhythmia torsades de pointes (Kimura et al. 1992). In the case report

Table 100.2 Arrhythmias and ECG abnormalities associated with cocaine

Arrhythmia	ECG abnormality
Sinus tachycardia	PR interval shortening
Sinus bradycardia	PR interval lengthening (first-degree AV block)
Supraventricular tachycardia	
Atrial fibrillation	QRS widening
Atrial flutter	Nonspecific intraventricular block
Second- and third-degree AV block	Right bundle branch block
Accelerated idioventricular rhythm	Left bundle branch block
Torsades de pointes	Left anterior fascicular block
Ventricular tachycardia	QT interval prolongation
Ventricular fibrillation	ST segment elevation/depression
Asystole	T wave peaking, flattening, inversion
	Acquired Brugada syndrome
	ST elevation, down-sloping ST segment, and T wave inversion

literature, QT prolongation is frequently reported, and associated torsades de pointes occurred in almost half of these cases (Ramirez et al. 2012).

Cocaine has seemingly contradictory interactions with atrioventricular conduction (Ramirez et al. 2012). Several small observational studies have shown that cocaine use is associated with PR segment shortening, which would suggest that cocaine enhances conduction through the AV node. However, the case report literature is incongruent with these results and contains several cases of PR prolongation with various degrees of AV block. QRS interval widening reportedly occurs in up to 6 % of patients using cocaine, which is most commonly due to nonspecific intraventricular conduction delay or right bundle branch block. It is important to note that many of these cases may be confounded by electrolyte derangements and concomitant ingestion of other substances.

There have been cases of acquired Brugada pattern associated with cocaine use (Ramirez et al. 2012). However, electrophysiologic testing did not induce sustained ventricular arrhythmias in any of these cases, and it is unknown if cocaine-associated Brugada pattern confers any additional risk of sudden cardiac death.

100.2.2.4 Other Effects: Cardiomyopathy, Endocarditis, Aortic Dissection, and Stroke

Cocaine can cause left ventricular hypertrophy and systolic dysfunction (Lange and Hillis 2001). Administration of cocaine in animal models acutely results in left ventricular dilation and decreased contractility, while intracoronary administration in humans has been shown to be negatively inotropic (Perreault et al. 1993; Schwartz et al. 2010). There are reports of dilated cardiomyopathy in long-term cocaine users as well as acute, reversible, profound left ventricular dysfunction after acute cocaine binge use (Lange and Hillis 2001). Additionally, transient left

ventricular apical ballooning syndrome (takotsubo cardiomyopathy) has been temporally related to acute cocaine intoxication (Schwartz et al. 2010). One study found that left ventricular dysfunction is present in 7 % of apparently healthy, asymptomatic cocaine users (Bertolet et al. 1990).

In those with congestive heart failure, stimulant use (cocaine and amphetamines) is associated with an increased incidence of hospitalization and reduced ejection fraction (Diercks et al. 2008). Cocaine cessation leads to improved cardiac function, and cocaine relapse can cause recurrence of decompensated heart failure (Schwartz et al. 2010). The possible mechanisms of cocaine's effects on myocardial systolic dysfunction include myocardial ischemia/infarction, repetitive sympathetic stimulation of the myocardium (similar to cardiomyopathy associated with pheochromocytoma), hypersensitivity to adulterants or infectious agents leading to myocarditis, alteration of intracellular calcium concentration, and stimulation of cytokine production resulting in remodeling and myocyte necrosis (Lange and Hillis 2001).

As with any substance used by the intravenous route, there is a risk of bacterial endocarditis with IV cocaine use (Lange and Hillis 2001). For unknown reasons, cocaine seems to increase the risk of endocarditis compared to other drugs. Left-sided valves are more frequently involved with cocaine than other IV drugs.

Aortic dissection is well described in the setting of cocaine intoxication (Eagle et al. 2002). The prevalence of cocaine use in aortic dissection has been found to range from 0.5 % in a larger multicenter review to 37 % of aortic dissections at a single inner-city hospital. Cocaine-related aortic dissections primarily affect young, black, hypertensive individuals, and there may be a higher risk with crack cocaine use compared to other routes of administration. The mechanism of cocaine's association with aortic dissection is thought to involve arterial hypertension and tachycardia with a resulting increase in arterial shear stress. Cocaine is associated with decreased aortic elasticity, increased smooth muscle cell apoptosis, and premature atherosclerosis, all of which play a role in increasing dissection risk (Eagle et al. 2002; Finkel and Marhefka 2011).

Cocaine use confers a twofold increase in the risk of ischemic and hemorrhagic stroke (Schwartz et al. 2010). Compared to the general population, former cocaine users experience a higher proportion of subarachnoid hemorrhage, while current cocaine users have higher ratios of both subarachnoid hemorrhage and intracerebral hemorrhage. Subarachnoid hemorrhage most commonly results from rupture of arterial aneurysms, and intracerebral hemorrhagic strokes are thought to result from large spikes in blood pressure. Compared to those not using cocaine, cocaine users with hemorrhagic strokes have worse functional outcomes and increase mortality (Martin-Schild et al. 2010). Overall, cocaine is widely considered the most cardiotoxic among drugs of abuse.

100.2.3 Amphetamines

Amphetamines are a group of drugs that are derived from a β -phenylethylamine core structure, a structure also shared by catecholamines. They cause an increase in

catecholamines concentrations both centrally and peripherally by stimulating their release, blocking their reuptake, and inhibiting their metabolism by monoamine oxidase (Fleckenstein et al. 2007). The degree of peripheral and central sympathetic activation varies between the different types of amphetamines (Kaye et al. 2007). Given their sympathomimetic mechanism of action, it is not surprising that amphetamines share many of the adverse cardiovascular effects associated with cocaine. This section focuses on three commonly abused amphetamines: amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA).

As would be expected with a sympathomimetic drug, amphetamines cause tachycardia, vasoconstriction, and hypertension (Carvalho et al. 2012). In healthy subjects, oral amphetamine administration results in a dose-dependent increase in both systolic and diastolic blood pressure that peaks in 1–2 h (Mas et al. 1999). There is a biphasic heart rate response; the baroreceptor reflex blunts the initial rise in heart rate, but heart rate quickens again 3–4 h later when blood pressure begins to lower.

The most common clinical presentations of amphetamine users requiring hospitalization are chest pain syndrome, cardiac arrhythmias, palpitations, and hypertension (Kaye et al. 2007). Acute coronary syndrome and acute MI are particular concerns in this population. One series found that 25 % of patients using methamphetamine that presented with chest pain to the emergency department were diagnosed with an acute coronary syndrome (Turnipseed et al. 2003). Indeed, there are an abundance of reports of acute MI in amphetamine users presenting to the ED and in postmortem series (Kaye et al. 2007; Carvalho et al. 2012). Furthermore, patients suffering acute MI associated with amphetamine use are often young. For example, a 15-year-old boy with no previously known cardiac abnormalities had an MI after starting extended-release amphetamine salts for attention deficit disorder (Sylvester and Agarwala 2012). The pathogenesis of cardiac ischemia in the setting of amphetamines results from an increase in myocardial oxygen demand, through augmentation in chronotropy, wall stress, and afterload, with a reduction in coronary blood flow secondary to vasoconstriction (Kaye et al. 2007; Carvalho et al. 2012). The risk of ischemia may be further increased in long-term users, as postmortem and angiographic data suggests that amphetamines may cause premature coronary atherosclerosis (Kaye et al. 2007).

Amphetamines have been associated with sudden cardiac death and ventricular arrhythmias (Bennett and Walker 1952; Kaye et al. 2007; Carvalho et al. 2012). Specifically, in animal models, methamphetamine has been shown to inhibit the channels responsible for the transient outward potassium current, inward rectifying potassium current, and L-type calcium current (Liang et al. 2010). In humans, methamphetamine has been shown to prolong the QTc interval in humans increasing the risk of torsades de pointes (Haning and Goebert 2007).

Aortic dissection has been strongly associated with methamphetamine intoxication in case reports (Kaye et al. 2007). In fact, one autopsy series found that after hypertension, methamphetamine use was the most common risk factor for fatal acute aortic dissection (Swalwell and Davis 1999). The pathogenesis of aortic dissection is proposed to be secondary to hypertension, but methamphetamine may also have a direct degenerative effect on the aortic wall (Kaye et al. 2007).

Amphetamine use is linked to cardiomyopathy in the acute and chronic setting (Kaye et al. 2007; Carvalho et al. 2012). Amphetamine-associated cardiomyopathy is usually manifest as the gradual onset of a dilated cardiomyopathy with systolic dysfunction. In some cases, the cardiomyopathy may reverse with abstinence. Additionally, takotsubo cardiomyopathy has been described in the setting of acute amphetamine use (Carvalho et al. 2012). The pathogenesis of cardiomyopathy in these patients is probably multifactorial with contributions from catecholamine-induced toxicity, oxidative stress, and ischemia (Kaye et al. 2007; Carvalho et al. 2012). As with other cardiomyopathies, the cornerstone of therapy is neurohormonal blockade with β -blockers, renin-angiotensin-aldosterone system blockade with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and/or aldosterone antagonists, and possibly vasodilators including long-acting nitrates and hydralazine. β -blockers are not recommended for use in the setting of acute cocaine intoxication, and the safety of their long-term use in patients who continue to use sympathomimetic recreational drugs is unknown. Because of the lack of prospective data, β -blocker therapy may be considered only after careful risk-benefit assessment and ideally after documentation of sustained abstinence (Schwartz et al. 2010). Where available, ivabradine may be an alternative to β -blockers in the setting of ongoing cocaine or amphetamine abuse, as it lowers the heart rate and has been shown to improve outcomes via mechanism unrelated to the adrenergic receptor (van Bilsen et al. 2009).

100.2.4 Opioids

Opioids exert their principal clinical actions of analgesia and euphoria via agonist activity at the μ -opioid receptor in the central nervous system (CNS). Respiratory depression occurs in a dose-dependent manner and represents the principle cause of opioid-related mortality. By contrast, cardiovascular effects tend to be relatively mild, with no direct effect of most opioids on cardiac rhythm or myocardial contractility. However, orthostatic hypotension may occur, presumably secondary to histamine release and vasodilation of peripheral arteriolar vessels. In patients with acute coronary syndromes, opioids are often used intravenously for relief of chest discomfort. Intravenous morphine is most frequently utilized in acute myocardial infarction. It leads to mild venodilatation, which decreases preload and myocardial oxygen consumption in the setting of left ventricular systolic dysfunction and pulmonary edema. Intravenous opioids also result in a small decrease in pulse and blood pressure in the acute coronary syndrome patient. Opioids may also improve myocardial energetics at the cellular level and have been associated with enhancement of "ischemic preconditioning." This phenomenon entails repetitive episodes of noncritical ischemia, which may provide myocardial protection to patients chronically treated with opioids. In support of this theory, an autopsy study evaluated age and gender matched decedents stratified by the presence of opioid detected at autopsy (Marmor et al. 2004).

The authors found a lower burden of coronary artery disease among opioid users and postulated that this may relate to ischemic preconditioning.

By contrast to the potential protective effects of opioids with regard to atherosclerotic coronary artery disease, more recent evidence suggests that synthetic opioids may adversely influence cardiomyocyte electrophysiology and occasionally lead to malignant arrhythmia. Specifically, synthetic opioids may block the delayed rectifier potassium ion current known as I_{Kr} , which is encoded by the *hERG* gene. This blockade may lead to prolongation of the QTc interval in vivo, which is the requisite substrate for drug-induced torsades de pointes, a type of polymorphic ventricular tachycardia (Fig. 100.1).

Vignette *A 34-year-old law school student presents to your psychiatry office with complaints of fevers, malaise, occasional rigors, and fatigue for 10 days. He has been previously treated for major depression but takes no prescription drugs. He has a 7-year history of intermittent recreational opioid abuse. Over the past 6 months he reports escalation in abuse of prescription opioids including oxycodone and hydrocodone cough syrup with dextromethorphan. When he is unable to use opioids, he develops withdrawal symptoms, and 2 weeks ago he admits to a period of intravenous, black-tar, heroin use. His last opioid consumption was 2 hours ago. The patient is in no acute distress. Examination is notable for a temperature of 38.5 degrees Celsius. Blood pressure is 135/70 mm Hg, and pulse is 112 beats per minute. Cardiovascular exam is notable for a grade III systolic murmur at the lower left sternal border accentuated following inspiration. He reluctantly rolled up his sleeves, revealing the presence of healed track marks and a small abscess in the left antecubital fossa. The remainder of his examination is normal.*

100.2.4.1 Heroin

Diacetylmorphine or heroin was originally formulated as an antitussive agent. It is derived from the opium poppy and was extensively marketed by Bayer Corporation before its addictive potential was recognized in the early 1900s (Marmor et al. 2004). Heroin is often injected after heating a liquid solution but increasingly is smoked or nasally insufflated. Like all opioids, its principal medical complication is central nervous system (CNS) depression and respiratory depression.

The effects of heroin on the cardiovascular system are not extensive, which may in part reflect its close derivation from the natural opium poppy. Heroin abuse is associated with acute pulmonary edema, but this is generally non-cardiogenic in origin. The typical hemodynamic findings include normal pulmonary-capillary pressure and a normal or increase cardiac output (Barceloux 2012), suggesting the absence of direct myocardial toxicity. Although moderately elevated pulmonary artery pressures have been described, this is most likely due to direct pulmonary toxicity in the setting of injected impurities or in overdose with hypoxemia leading to subsequent increased pulmonary-capillary leakage.

The most feared cardiovascular complication of heroin abuse is the development of infective endocarditis. Infective endocarditis is diagnosed using the Duke criteria based on a combination of major (bacteremia and valvular vegetation seen on echocardiography) and minor diagnostic criteria including fever, intravenous drug use history, and vascular embolic findings such as nail bed or “splinter” hemorrhages (Durack et al. 1994). Heroin may also result in embolic stroke due to systemic embolization of cardiac valvular vegetations to the brain. Infective endocarditis of the right-sided heart valves (tricuspid and pulmonic) should always alert the clinician to the possibility of surreptitious intravenous drug abuse. Moreover, the type of bacterium isolated from blood cultures may be pathognomonic for intravenous drug abuse. Pyogenic species such as *Staphylococcus aureus* are commonly isolated as this bacterium may be carried on the skin of intravenous drug abusers. In addition, *Pseudomonas* and even fungal organisms have been reported given the potential for suspending heroin in contaminated water. In suspected cases of endocarditis, a complete skin examination is mandatory that includes the neck, groin, and feet, as patients are not always forthcoming in exposing pathognomonic skin lesions associated with injection drug use. Careful cardiac auscultation is essential, and both systolic (tricuspid and mitral valve destruction) and diastolic (aortic and pulmonic valve destruction) regurgitant murmurs may be detected. Cases of potential endocarditis should be confirmed immediately by transthoracic echocardiography, which is often diagnostic particularly for right-sided valvular vegetation. If there is a high clinical suspicion for this disorder, transesophageal echocardiography is increasingly utilized as it offers enhanced visualization, particularly of left-sided valvular structure.

Since the early 1970s, a high incidence of sudden death has been noted among heroin users, some of whom were receiving methadone treatment. One study suggested that QTc interval prolongation occurred more often among individuals receiving methadone (Lipski et al. 1973). However, this study was not designed to prospectively address the effects of methadone, heroin, or both medications on cardiac repolarization. More recently, in a study of 115 active heroin users admitted to an opioid treatment center, the median QTc interval was not significantly different compared with 57 healthy controls (Lysenko et al. 2008), which suggests that heroin is unlikely to be directly associated with cardiac arrhythmia. This clinical finding is consistent with its pharmacologic classification as a natural (esterified morphine), rather than a synthetic, opioid.

Vignette (Continued) *The patient is effectively treated for tricuspid valve endocarditis with 6 weeks of intravenous antibiotics with resolution of symptoms. He returns to school but eventually begins to relapse and abuse heroin. He asks for assistance and it's decided to induce him onto methadone maintenance therapy. It is initiated on 30mg/day and up-titrated to 90 mg daily at which point he feels well and discontinues illicit opioids entirely. One month later he is at the opioid treatment center in a group counseling sessions and develops the sudden onset of tonic-clonic seizures and loss of consciousness. He regains awareness and is referred for neurologic evaluation. Computed tomography of the brain is normal.*

Subsequently, magnetic resonance imaging is performed without focal lesion and an electroencephalography study is similarly unremarkable. He started on low dose anti-epileptic therapy but one month later is involved in a motor vehicle accident after passing out while driving.

100.2.4.2 Methadone and Synthetic Opioids Used in Addiction Treatment

Methadone is the most commonly utilized medication for treating heroin addiction worldwide given its low cost and long terminal elimination half-life. This allows patients to break the cycle of frequent, daily heroin use. Methadone is a synthetic diphenylpropylamine compound with a chemical structure similar to propoxyphene (Marmor et al. 2004). Propoxyphene was recently removed from the market in the United States and a number of other countries due to reports of QTc interval prolongation and ventricular arrhythmias (Food et al. 2011).

To investigate the effect of synthetic opioids on arrhythmia risk, the principal focus is on cardiac repolarization. Repolarization describes the phase in the cardiac cycle where myocytes “reset” and is clinically characterized by the QTc interval on the surface electrocardiogram. Opioids have generally been considered devoid of cardiac activity. However, the cardiac repolarization changes associated with synthetic opioids were characterized in human cells stably transfected with the hERG gene which encodes the I_{Kr} current (Katchman et al. 2002). The ratio of the concentration of drug that blocks 50 % of I_{Kr} channels (IC50%) was divided by the expected maximal plasma concentration (Cmax) in man for the individual drugs yielding the IC50/Cmax. This ratio predicts the likely occurrence of QTc prolongation, with higher numbers suggesting the greatest margin of safety. The IC50/Cmax observed with codeine and morphine (and by extension diacetylmorphine or heroin) was >400 μ M. These “naturally occurring” opioids therefore are not associated with QTc prolongation and torsades de pointes. By contrast, the synthetic opioids fentanyl, meperidine, and buprenorphine exhibited modest blockade with IC50/Cmax ranging from approximately 50 to 200. Notably, the most potent I_{Kr} -blockade was observed with methadone and levacetylmethadol (LAAM), with ratios of 2.7 and 2.2, respectively. This creates a challenging paradox: while synthetic opioids clearly reduce the harm of injection drug use including the risk of hepatitis, HIV infection, and endocarditis, they also have a cardiac safety liability in susceptible individuals.

From a clinical perspective, LAAM was first shown to have a dose-dependent relationship with cardiac repolarization in 2001 (Huber et al. 2001). LAAM, a long-acting methadone derivative was discontinued from the market in Europe, Australia, and the United States in 2003 due to its association with cardiac arrhythmia. This leaves methadone and sublingual buprenorphine as the primary therapeutic choices for opioid-dependent patients. In 2002, a case series of torsades de pointes associated with high-dose oral methadone was first described (Krantz et al. 2002). In the case presented within the clinical vignette, it is likely that the patient’s grand mal seizures and syncope were manifestations of torsades de pointes. Torsades de pointes is a self-terminating arrhythmia in most cases, though it may degenerate

into ventricular fibrillation and lead to sudden cardiac death. A case of methadone-induced arrhythmia masquerading as epilepsy has been previously described (Krantz et al. 2005). This highlights the fact that ventricular arrhythmia if prolonged may result in marked reduction of cardiac output and cerebral hypoxemia and subsequent seizures. Thus, seizures are not always due to epilepsy and should alert clinicians to the possibility of life-threatening arrhythmia.

Many addiction clinicians are unaware of the cardiac arrhythmic properties of synthetic opioids used in treating opioid dependency (Krantz et al. 2007). However, a recent registry study found that ventricular arrhythmia and cardiac arrest are now the most frequent FDA-reported class of methadone-associated adverse events, and reports of QTc prolongation and torsades de pointes have increased sharply in the past decade (Kao et al. 2013). In this study, methadone was associated with a disproportionate signal of torsades de pointes reporting similar to that of drugs with established proarrhythmic properties (such as dofetilide). By contrast, propoxyphene, which was recently withdrawn from the market due to QTc prolongation and dysrhythmia, was not associated with disproportional arrhythmia reporting. Because available evidence definitely suggests that both oral and intravenous methadone hydrochloride cause QTc interval prolongation and torsades de pointes, a consensus guideline suggesting QTc interval screening was developed (Krantz et al. 2009). The guideline emphasized five recommendations for physicians prescribing methadone (Table 100.3). Because the arrhythmia risk associated with methadone is a direct consequence of its effect on cardiac repolarization, the recommendations are applicable to patients either receiving current treatment with methadone or being considered for initiation of methadone treatment for addiction or pain management. Because methadone is now considered an essential medication by the World Health Organization, its utilization is expected to rise, highlighting the need to enhance its cardiac safety.

Table 100.3 Consensus recommendations for QTc interval screening in methadone treatment (Krantz et al. 2009)

Recommendation 1 (disclosure)	Clinicians should inform patients of arrhythmia risk when they prescribe methadone
Recommendation 2 (clinical history)	Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope
Recommendation 3 (screening)	Obtain a pretreatment ECG for all patients to measure the QTc interval and then a follow-up ECG within 30 days and annually. Additional ECG is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures
Recommendation 4 (risk stratification)	If QTc interval is >450 ms but <500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing methadone or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy
Recommendation 5 (drug interactions)	Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone

100.2.5 Nicotine

Cigarette smoking is the leading risk factor for developing cardiovascular disease, increasing risk of coronary artery disease by up to 80–100 % (Law et al. 1997). Secondhand smoke exposure is also harmful, potentially increasing risk of coronary artery disease by up to 30 % (Whincup et al. 2004). Furthermore, pipe smoking, smokeless tobacco, and cigars are all associated with increases in cardiovascular morbidity and mortality (Katsiki et al. 2013). Nicotine is the addictive and primary active component in tobacco products and causes many of the adverse cardiovascular effects of smoking. Nicotine acts in part by stimulating release of norepinephrine from sympathetic nerves and by release of epinephrine from the adrenal glands, which produce increases in heart rate and blood pressure shortly after exposure. Although the precise role of nicotine relative to other components of cigarette smoke is unclear, cigarette smoking is also associated with vasomotor dysfunction mediated by reduced availability of nitric oxide, systemic inflammation that increases adherence of leukocytes to endothelial cells, increases in serum low-density lipoprotein and triglycerides with decreases in high-density lipoprotein, platelet dysfunction, and alteration of thrombotic factors (Ambrose and Barua 2004). Consequently, cigarette smoking is associated with increased rates of all-cause and cardiovascular mortality, first myocardial infarction, recurrent infarction or revascularization in patients with coronary artery disease, sudden death, and stroke (Foody et al. 2001; Prescott et al. 2002; Rodriguez et al. 2002; Goldenberg et al. 2003).

Cessation of smoking is associated with rapid decreases in cardiovascular events including myocardial infarction, stroke, and sudden death, with rates returning to near that of nonsmokers within 3–4 years in many cases (Rea et al. 2002; Gellert et al. 2013). Although the increased risk of cardiovascular events associated with smoking appears to increase with age, the benefits of cessation are independent of age. Despite the clear risks of smoking and benefits of smoking cessation, smoking rates remain relatively stable, and the rate at which physicians in the United States advise patients to stop smoking has actually decreased over the last 10 years (Kruger et al. 2012). Intensive support including structured behavioral modification counseling and pharmacotherapy with either nicotine replacement therapy and/or bupropion appears superior to one-time counseling in patients hospitalized for coronary disease or heart failure, although even a brief statement to outpatients of the risks associated with smoking can result in increases in smoking cessation (Lin et al. 2013).

The acute hemodynamic effects of nicotine withdrawal are poorly characterized, but appear minimal. Blood pressure and heart rate are likely to decrease compared with ongoing tobacco use (Morrell et al. 2008), and withdrawal symptoms are primarily limited to psychosocial changes including prominent irritability. Consequently, abrupt smoking cessation as may occur during hospitalization for myocardial infarction or heart failure is unlikely to adversely affect an individual's hemodynamic status. Theoretical concerns regarding vasoconstrictor activity of nicotine and rare anecdotal reports of myocardial infarction in patients

taking nicotine replacement therapy, particularly those who continue to smoke, have resulted in caution in using nicotine replacement therapy in patients with known coronary artery disease, including immediately post-myocardial infarction (Hubbard et al. 2005; Woolf et al. 2012). However, large studies have failed to show an increased risk of cardiovascular events or death following initiation of nicotine replacement therapy in the setting of cardiovascular disease. Furthermore, effects of continued smoking on platelet activation, hypercoagulability, and other factors suggest that any small increase in atheroembolic risk associated with nicotine replacement therapy is far outweighed by the potential benefits of smoking cessation. There are very few drug-drug interactions between nicotine replacement therapy and cardiovascular medications. Bupropion appears safe to use in patients hospitalized for acute myocardial infarction, but may not be as effective as in chronic, stable outpatients (Eisenberg et al. 2013). Varenicline has not been studied specifically in the acute post-myocardial infarction setting. The use of varenicline in patients with cardiovascular disease is controversial due to some evidence of trends toward a small increase in cardiovascular events in unselected populations (Ware et al. 2013), and the FDA issued an advisory in 2011 that varenicline may increase the risk of adverse cardiovascular events in patients with known cardiovascular disease (US Food and Drug Administration 2011). However, these findings have not been verified, and it is likely that any increased risk is quite small (Prochaska and Hilton 2012). Nonetheless, given the paucity of safety data with varenicline in patients with known cardiovascular disease, patients using varenicline should seek medical attention promptly if their cardiovascular symptoms worsen.

The effects of smoking ordinances that reduce secondhand smoke exposure and the risk of myocardial infarction are an important albeit controversial international public health issue. The biologic effects of secondhand smoke have been well characterized and mirror those of direct tobacco exposure. In particular, coronary arterial plaque destabilization is triggered by nicotine in secondhand smoke; this stimulates the matrix metalloproteinase enzyme that degrades the fibrous cap in coronary plaques (Carty et al. 1996). Secondhand smoke is also associated with impaired coronary endothelial function, increased aortic stiffness (Mahmud and Feely 2003), as well as reduced heart rate variability (15), a marker of abnormal sympathetic nervous system activity. Early studies examining the effect of smoking ordinances found unexpectedly large reductions in myocardial infarction as high as 40 % in Helena, Montana, United States (Meyers et al. 2009). Larger statewide and countrywide smoking studies have been completed including Scotland, England, Italy, the Netherlands, New Zealand, Ireland, and the United States, suggesting an attenuated impact from smoking legislation. In particular, one US analysis found that in contrast to smaller regional studies, smoking bans were not associated with statistically significant short-term declines in mortality or hospital admissions for myocardial infarction or other diseases (Shetty et al. 2010). Regardless of the ultimate impact of smoke-free policy on cardiovascular events, it remains clear that nicotine is among the most highly active substance in tobacco leading to adverse cardiac physiology.

100.2.6 Cannabis

Cannabis (marijuana) is generally thought to be relatively benign by the community despite growing evidence that implicates it in several serious cardiovascular complications including myocardial infarction and ischemic stroke (Bachs and Morland 2001). Cannabis is most commonly smoked and rapidly absorbed through the lungs with physiologic changes appearing shortly after use (Ghuran and Nolan 2000). When consumed through the enteral route, absorption is slower and less predictable. The primary active constituent of cannabis is Δ -9-tetrahydrocannabinol (THC), which interacts with G-protein-coupled cannabinoid receptors (CB1 and CB2) (Pertwee 2006). CB1 receptors are found primarily on neuronal tissue, and their activation at peripheral nerve terminals inhibits neurotransmitter release (Pertwee 2006). In addition, there may be cross talk between CB1 and α_2 -adrenergic receptors on the presynaptic autonomic nerves.

THC causes a biphasic autonomic response. The sympathetic nervous system is activated at low to moderate doses and the parasympathetic nervous system predominates at higher doses (Ghuran and Nolan 2000). This results in tachycardia and augmented cardiac output at lower doses and hypotension and bradycardia at high doses. Even at low doses, cannabis can cause both hypertension and hypotension. Blood pressure alterations during cannabis use are often positional; blood pressure increases while in the seated or supine position and drops while standing (Pratap and Korniyenko 2012). Hypotension can also occur during the act of smoking due to rapid changes in autonomic nervous system output, and orthostatic hypotension with resulting syncope is not an uncommon occurrence. Autonomic changes are generally well tolerated in healthy individuals, and cannabis-induced hypotension usually resolves spontaneously or responds to intravenous fluid boluses (Ghuran and Nolan 2000).

Cannabis use increases myocardial oxygen demand by increasing heart rate, wall stress, and sometimes blood pressure. Additionally, when smoked, it decreases oxygen supply through carboxyhemoglobin formation (Aronow and Cassidy 1974). Cannabis use has been shown to decrease threshold to symptomatic angina pectoris. Furthermore, one study demonstrated that the risk of acute MI is 4.8 times higher within the hour following cannabis use (Mittleman et al. 2001). A follow-up study of these MI patients found that continued marijuana use of more than once per week was associated with a 4.2-fold increased risk of death over a 3.8-year period (Mukamal et al. 2008).

In addition to cardiac ischemia, evidence is emerging that implicates cannabis use with inciting ischemic stroke (Wolff et al. 2013). As of 2013, there have been 59 reported cases of stroke associated with cannabis use. All but one were ischemic in origin and the patients were often young. Cannabis use has been particularly strongly associated with two specific etiologies of ischemic stroke: reversible cerebral vasoconstriction syndrome (RCVS) and multifocal intracranial stenosis (MIS). In a prospective study evaluating cannabis' role in ischemic stroke, a single center enrolled every patient under 45 years of age that presented with ischemic stroke (Wolff et al. 2011). It was found that cannabis use was highly associated with

ischemic strokes caused by multifocal intracranial stenosis. In this study, ten of 11 multifocal intracranial stenosis stroke patients had used cannabis for years, and all had binge-smoked cannabis the day prior to their ischemic events. Caution must be taken with attributing these events solely to cannabis, as all patients also smoked tobacco regularly and half of these patients had binged on alcohol shortly before their ischemic events.

Epidemiological data demonstrates that cannabis users are more likely to feel palpitations than nonusers, which is usually caused by sinus tachycardia (Petronis and Anthony 1989). However, other arrhythmias have also been temporally related to cannabis use such as sinus bradycardia, atrial fibrillation, atrial flutter, ventricular extrasystoles, and second-degree AV block (Fisher et al. 2005; Pratap and Korniyenko 2012). The onset of arrhythmias can begin within a few minutes of cannabis use, peaks at about 30 min, and can last as long as 90 min (Johnson and Domino 1971). The majority of these arrhythmias revert spontaneously to sinus rhythm. If persistent, the American Heart Association and European Society of Cardiology management protocols should be followed (Fisher et al. 2005). There are two cases of cannabis-induced Brugada pattern, neither of which were associated ventricular arrhythmias (Pratap and Korniyenko 2012). Although reports of ventricular arrhythmias are not common with cannabis use, a postmortem case series carried out on six patients with unexplained sudden death with recent cannabis use concluded that causes of death were “acute cardiovascular events,” possibly representing fatal arrhythmias (Bachs and Morland 2001).

100.3 Anabolic Steroids

Anabolic steroids have varying degrees of androgenic properties and are frequently utilized by athletes, weightlifters, and bodybuilders to enhance athletic performance and strength. Anabolic steroids are associated with direct effects such as left ventricular hypertrophy and myocardial fibrosis and indirect effects, including dyslipidemia, hypertension, arrhythmia, and myocardial infarction (Higgins et al. 2012). It is likely that chronic exposure to these agents can result in significant alterations in the cardiovascular system, beyond the expected increase in salt and water retention leading to elevations in blood pressure in susceptible patients.

Cardiomyocytes have testosterone receptors, which may explain the propensity to muscular hypertrophy in the setting of supraphysiologic doses. The most feared complication of anabolic steroids, however, is the increased risk of ischemic cardiovascular events. Numerous reports of myocardial infarction have been described in the literature even among young patients. In addition, there is further concern that anabolic steroids may accelerate the overall atherosclerotic process with ongoing abuse. A framework for understanding this risk has been put forward (Melchert and Welder 1995). Four mechanisms are suggested: (1) atherosclerosis-dyslipidemia model given marked reductions up to 70 % in high-density lipoprotein (HDL) cholesterol, which is responsible for reverse cholesterol transport and >20 % increases in the atherogenic low-density lipoprotein (LDL) cholesterol;

(2) vasospasm model given alterations in the vascular nitric oxide system; (3) thrombosis model involving alterations in platelet and clotting function including increases in plasminogen activator activity; and (4) direct myocardial injury model including impaired myocardial relaxation and diastolic dysfunction. Another factor that enhances the risk of myocardial infarction is polycythemia associated with anabolic steroids. This increases blood viscosity and the risk of thrombosis. As such, a complete blood count should be obtained in patients using anabolic steroids who present with ischemic complications. Beyond the risk of acute myocardial infarction, these agents have been associated with cerebrovascular accident (Garcia-Esperon et al. 2013), suggesting that atheroembolic complications may affect all vascular territories. Furthermore, anabolic steroid use has been associated with supraventricular and ventricular ectopy, atrial fibrillation, ventricular fibrillation, and ventricular tachycardia, and cardiac pathology has been frequently observed in deceased anabolic steroid abusers (Thiblin et al. 2000).

Anabolic steroid use should be considered in young athletes with evidence of hypertension, very low serum HDL and elevated LDL cholesterol levels, atrial or ventricular arrhythmias, and/or left ventricular hypertrophy by electrocardiogram or echocardiogram. There is little data regarding cardiovascular risk reduction associated with anabolic steroid use apart from abstinence. The actual prevalence of significant coronary artery disease among anabolic steroid users is not known, and cardiovascular risk reduction should conform to standard age-appropriate guidelines until additional data is available. Blood pressure and lipid abnormalities will generally resolve after 6–12 months of abstinence, but there is evidence that pathologic left ventricular hypertrophy may persist for years after discontinuation of steroid use, although this persistence may be due to sustained or ongoing strength training (Achar et al. 2010). If blood pressure abnormalities are particularly severe, or do not resolve with abstinence, pharmacologic intervention should be considered. Statin therapy should be initiated for sustained LDL cholesterol levels ≥ 160 mg/dL in accordance with current guidelines. Rosuvastatin in particular appears more effective in raising HDL levels than other statins. Omega-3 fatty acids and niacin have also been associated with increases in HDL cholesterol, but their efficacy in reducing risk of cardiovascular effects is uncertain. Antihypertensive therapy should be considered if the blood pressure is consistently $\geq 140/90$ in accordance with currently guidelines. The optimal antihypertensive agent for steroid-associated hypertension is unclear, although the stimulation of the renin-angiotensin-aldosterone system observed in anabolic steroid users suggests that ACE inhibitors or angiotensin receptor blockers may be particularly effective and are often tolerated well by young patients. β -blockers are typically not used as monotherapy for hypertension, but may be considered if coexisting arrhythmias are present. There is currently no evidence or recommendation for antiplatelet therapy for primary prevention in anabolic steroid use. There is no clear evidence for pharmacologic treatment of LV hypertrophy, although dilated cardiomyopathy as a result prolonged steroid use and/or ischemic events should be treated in accordance with heart failure guidelines using neurohormonal blockade with β -blockers and renin-angiotensin-aldosterone system inhibitors along with vasodilators and/or diuretics according to patient symptoms.

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