Comorbidity of Mental and Physical Illness: A Selective Review


Physical Diseases and Addictive Disorders: Associations and Implications

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Abstract
Increasingly, the identification, assessment and treatment of unhealthy use of alcohol and other drugs often occur within general medical settings. Within this climate, there is a growing awareness of the physical effects connected to acute or chronic use of substances of abuse. By examining these associations and their purported biological causative mechanisms, greater clinical attention – in the form of screening, identification and treatment – to co-occurring medical conditions as well as to the use of illicit substances itself may be possible. In this review, we examine recent peer-reviewed literature regarding three substances of abuse (cocaine, marijuana and opioids) and their direct associations with physical disorders. We group the association of diseases based on organ systems and critically examine the literature regarding the evidence to supporting those associations and causative mechanisms. There is good evidence to support the association of cocaine, marijuana and opioid use with a variety of physical health conditions. Unfortunately, while the causative evidence of these associations is preliminary, we could conclude that the use of these substances can incite a host of medical illnesses or complicate their treatment. When combined with societal, mental health and public health harms associated with the use of illicit substances, co-occurring or incident physical health conditions associated with substance use may present a substantial healthcare cost to the individual as well as to the healthcare system at large, resulting in a debilitating strain on often limited time and resources.

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Alcohol and illicit drug use and related use disorders impact mental, physical and environmental health. Identification and treatment of addictive disorders are the responsibility of all healthcare providers. Currently, the education and training of healthcare professionals to address co-occurring physical and mental health conditions associated with alcohol and illicit drug use and related use disorders may not be a focus of medical education and training. Because they have not been exposed to sufficient undergraduate or graduate medical education regarding screening, assessment, and treatment of alcohol and illicit drug use, providers may feel inadequately equipped to engage the complex intersection between mental and physical health presented by ongoing alcohol and substance use. In some countries, a concerted
effort has been undertaken in primary care to educate generalist healthcare providers about addiction and alcohol and illicit drug-related physical and medical health disorders [1–4]. While much attention has been devoted to physical conditions resulting from alcohol use [5–8], less attention has been directed to the associations between physical conditions and other illicit drug use [9, 10].

A pressing need exists for better understanding among healthcare providers of the serious health and healthcare implications of illicit substance abuse, particularly for physical health conditions. The purpose of this review is to examine the co-occurring and comorbid relationships between major drugs of abuse and physical illness. Similar to previous efforts, we examined the recent peer-reviewed literature regarding evidence of the associations of illicit substance use on physical health conditions [9, 10]. We investigated the literature to detail physical health issues associated with the use of three of the most common substances of abuse (cocaine, marijuana and opioids). While physical illnesses associated with use of other broad categories of drugs of abuse, such as stimulants and hallucinogens, may mirror the health effects of cocaine (stimulants) or marijuana (hallucinogens), for simplicity and brevity we concentrated our review on only cocaine, marijuana and opioids. Although each substance may invite risk of physical illness due to the nature of taking the substance (e.g. injection or inhalation), or social and environmental problems associated with use (e.g. risky sexual practices, trauma or other criminal activity), we concentrated our review on the direct associations between the substance in question and physical health. For many of these associations, we examined purported pathophysiological reasons for the association with physical ill-health. Thus, we provide a brief description of physical health conditions related to use of these three substances, organized according to generalized bodily systems.

## Immune System

### Cocaine

An increasing body of evidence, both from clinical epidemiological and laboratory studies, points to an association between cocaine use and an altered innate immune response that involves a decrease in monocyte expression of several cytokines [11]. As a weak agonist for sigma receptors, cocaine has also been found to alter cytokine release from both proinflammatory and anti-inflammatory T cells [12]. These studies suggest that cocaine use can have a direct effect on the innate immune system and thus increase the likelihood of greater risk for infectious diseases. Adulterants in cocaine, specifically levamisole, which is found in more than half of the cocaine in the USA [13], has a direct effect on the immune system. Leukopenia (especially neutropenia), agranulocytosis and vasculitis have been associated with levamisole.

### Marijuana

Despite strong evidence that cannabinoid type 2 receptors are found predominantly on cells involved in immunity and inflammation and can decrease activity of immune cells [14], no link has been shown between marijuana use and hematopoietic or lymphatic disorders.

### Opioids

Some of the opioids, including fentanyl, methadone, loperamide and β-endorphin, have been found to increase the levels of interleukin-4 (IL-4) in human type 2 T cells while other opioids, such as morphine and buprenorphine decrease the levels of IL-4 [15]. However, a study of male long-term daily opium users in Iran did not show a change in IL-4 levels compared to controls [16], although there were higher levels of other cytokines associated with either cellular or humoral immunity (interferon-γ, IL-10 and IL-17), indicating that some opioids have an effect on the immune response and the ability to react to infectious agents.
Infection

Cocaine
Besides the effect of cocaine on the innate immune system, cocaine use can increase the risk of infections through risky behavior associated with drug use, e.g. unprotected sex, multiple sexual partners, needle sharing and contaminated drug paraphernalia. Unhealthy living conditions and malnutrition can also influence the risk for infections.

Marijuana
Marijuana users may be more vulnerable to infection than the general public. Combined with cannabinoids’ suppression of the inflammatory response and natural immunity [17], marijuana use may promote greater susceptibility and decreased resistance to a wide array of infections. The common practice of shared or communal use of bongs, pipes and marijuana cigarettes may further promote transmission of airborne and fluid-based diseases, such as tuberculosis [18, 19]. Among other diseases for which marijuana use has been correlated with infection are Neisseria meningitidis [20, 21], oral candidiasis [22, 23] and sexually transmitted disease [24]. As well, marijuana users with chronic hepatitis C may be at greater risk of developing steatosis and fibrosis in the liver [25, 26].

Opioids
Use of opioids is often associated with risky behavior, thus increasing the likelihood of being infected by human immunodeficiency virus (HIV), hepatitis B and C, and other sexually transmitted pathogens. Intravenous use of opioids can increase the risk of cellulitis and endocarditis.

Cancers

Cocaine
There appears to be an increased risk of developing non-Hodgkin’s lymphoma in frequent users of cocaine compared to those who used amphetamines, lysergic acid diethylamide (LSD) or methaqualone [27].

Marijuana
There appears to be a link between marijuana use and some cancers in long-term users. However, many studies are hampered by selection bias, small sample size, lack of adjustment for concurrent tobacco use and other problems. Marijuana use has been linked to bladder cancer [28], cancer of the head and neck [29, 30], and lung cancer [31–33]. Marijuana use has also been associated with testicular germ cell tumors [34–36]. Smoked marijuana tar contains carcinogens similar to those found in cigarettes [37], and while studies are still inconclusive, it is reasonable to suspect that marijuana smoking may contribute to other cancers as well, including oral and pharyngeal cancer.

Hematopoietic Disorders

Cocaine
Cocaine has a role in coagulopathy. Recent research has found that use of cocaine increases von Willebrand factor release from the endothelium [38]. An increase in plasma von Willebrand factor can enhance platelet aggregation and thrombus formation, leading to increased risk for systemic thrombi in large and small vessels. Cocaine use is associated with thrombi formation in coronary stents [39] and atherosclerotic lesions and total thrombus occlusion in the main coronary arteries in long-term cocaine users [40].

Marijuana
A determination has yet to be made regarding whether cannabis arteritis is a distinct and separate disease from the thromboangiitis obliterans seen in cigarette smokers. Over 50 cases of cannabis arteritis have been reported since 1960 in marijuana users who did not smoke tobacco [41],

and cases of arteritis have been described in regular marijuana users who were moderate users of tobacco [42]. Cannabis arteritis may contribute to juvenile peripheral obstructive arterial disease [41]. In addition, arteriographic studies have found distal abnormalities similar to thromboangiitis obliterans, with changes in the architecture of the vasa nervorum [42].

**Cardiovascular Disease**

**Cocaine**

The surge of catecholamines in the plasma soon after use of cocaine can cause significant diffuse and focal coronary vasospasm. Additionally, the increase in heart contractility and heart rate and resultant high blood pressure can cause cardiac ischemia, vasospasm and infarction. Cocaine-related endothelin-1 release from the endothelium and alterations in platelet aggregation and formation of vessel thrombi can contribute to the increased risk of acute myocardial infarction in cocaine users. Young cocaine users may experience chest pain, ischemia, arrhythmias and acute myocardial infarction. Atherosclerotic lesions are not primarily associated with cocaine-related infarcts [43]. However, myonecrosis and coronary stenosis is often found in cocaine users with previous infarctions. Asymptomatic cocaine users may have significant cardiac disease (myocardial dysfunction, tissue edema or fibrosis) [44] and cocaine-users may have a higher risk than nonusers in developing silent acute myocardial infarction. The young age of cocaine users may be a survival benefit for those who experience a resuscitated cardiac arrest [45]. Compared to noncocaine users, cocaine users often survive the arrest without neurological sequelae. However, the likelihood of young cocaine users experiencing a nonfatal acute myocardial infarction was higher than those who were not cocaine users. Twenty-five percent of nonfatal acute myocardial infarction in 18- to 45-year-olds has been attributed to cocaine use. Cocaine users may also be more susceptible to developing coronary artery aneurysm [46]. Compared to a control group of individuals with similar cardiovascular risk, 30.4% of cocaine users (mean age 44 years) had coronary artery aneurysms, compared to only 7.6% in a control group. Although rare, postpartum coronary artery dissection has been reported in a 25-year-old woman who had been using cocaine [47]. Arrhythmias, in addition to tachycardia, may occur in cocaine users and have been attributed to ischemia and electrolyte imbalance. However, cocaine sequestration in myocytes may interfere with calcium storage and release and normal excitation and contraction, thus predisposing the heart to lethal arrhythmias [48]. Oxidative stress and direct myocardial toxicity has been suggested as another reason for the myocardial cell death associated with ischemia and acute myocardial infarction in cocaine users [49]. Cardiac oxidative stress occurs soon after cocaine enters the vascular system, leading to myocyte dysfunction and an increase in the number of inflammatory cells in the heart.

**Marijuana**

Marijuana use has already been associated with some clinical cardiovascular issues, specifically heart palpitations, orthostatic hypotension and acute increase in heart rate [50, 51]. Long-term users may experience an increase in heart rate, potentially resulting in cardiac ischemia and the arrhythmic effects of the catecholamines [52]. These users may delay pursuing medical help in response to the pain normally associated with ischemia because of marijuana’s effect as an analgesic and dissociative agent, further exacerbating damage over time. There are competing data regarding marijuana and mortality risk with acute myocardial infarction. While marijuana has been shown to increase the risk of acute myocardial infarction within an hour of use when compared to nonsmokers [53], a longitudinal study taken over the course of 15 years did not find an increased
risk of acute myocardial infarction in users [54]. Furthermore, no statistically significant association has yet been found between marijuana use and general mortality [55]. It should be noted that marijuana users often have other cardiovascular risk factors, such as higher alcohol and overall caloric intake, which increase postmyocardial infarction mortality in those individuals with coronary heart disease [56].

**Opioids**

Cardiovascular effects of opioids include some risk of infective endocarditis (associated with intravenous opiate use) and cardiac arrhythmias, especially long QT syndrome and torsades de pointes. Long QT syndrome is a condition associated with an abnormal gene coding for a protein component of myocardial cell potassium-voltage gated channels that is important in repolarization, resulting in a lengthening of the depolarization/repolarization cycle [57]. Other risks for long QT syndrome include hypokalemia. Long QT syndrome can lead to the development of torsades de pointes, a potentially lethal ventricular arrhythmia. In a randomized trial comparing the rate-adjusted QT length (QTc) in opioid-dependent subjects, the QTc increased in those subjects treated with the opioids levomethadyl (21%) and methadone (12%), but not in those treated with buprenorphine [58]. Significant risk factors for the development of a prolonged QTc in individuals on methadone maintenance therapy include the presence of congestive heart failure and other cardiac disease, elevated HbA1c and use of cocaine [59]. Congestive heart failure and poor glycemic control increase the risk for mortality.

**Oral, Ear, Nose and Throat Disorders**

**Cocaine**

Midline nasal and oral destructive lesions are significant complications of insufflation of cocaine [60]. Lesions can include ischemic and necrotic changes to the mucosa, perichondrium, nasal septum (including perforation), hard and soft palate, and sinuses. Lacrimal duct obstruction and destruction of the nasal turbinates may also be seen. Because similar lesions may be seen in patients with granulomatosis, sarcoidosis and lymphoma, diagnosis can be difficult, particularly since antineutrophil cytoplasmic antibody tests may be positive in all of these conditions. Sniffling, nasal crusts, nosebleeds and sinus problems are common problems in cocaine users who may also have burns to their upper airway. Depressed hearing and diminished sense of smell have also been reported.

**Marijuana**

Similar to tobacco, marijuana smoking increases the risk of a number of oral diseases and disorders, including xerostomia, tooth decay, periodontitis, severe gingivitis and mucosal abnormalities [23], as well as leukoedema and traumatic ulcers of the mouth [61]. It should be noted that it is not yet clear whether the higher incidence of caries and periodontal disease in marijuana smokers is a direct effect of use or a byproduct of attendant poor hygiene [62].

**Opioids**

A recent article suggests that nasal mucosal necrosis found in a small number of patients is related to heroin snorting [63].

**Respiratory Disease**

**Cocaine**

Bronchial and lung dysfunction in cocaine users include cough, black sputum, hemoptysis and chest pain [9]. Some studies have reported an exacerbation of asthma symptoms in those who smoke crack cocaine [64] and a higher incidence of out-of-hospital asthma deaths [65].
Although crack cocaine users are less likely to have hemoptysis, respiratory distress and abnormal pulmonary function tests than those participants who use tobacco [66], cocaine users are more likely to have an increase in alveolar macrophages and endothelin-1 (a potent vasoconstrictor) in bronchial alveolar lavage samples, suggesting that microvascular injury is associated with heavy crack cocaine smoking.

Marijuana
Studies suggest that marijuana users are at an elevated risk of experiencing increased mucus production as well as symptoms of chronic bronchitis [67–70]. Cannabis may also be an allergen for some [71]. A recent report found that forensic laboratory workers handling hashish or marijuana for 16–25 years developed marijuana hypersensitivity [72]. Others may be at risk for developing an allergy to the drug.

Opioids
Respiratory depression is a major adverse effect of many of the opioids and can cause death in users. As many as 58% of the deaths related to drug abuse in Ontario, Canada, between 2006 and 2008 were related to opioid use, with over one third of these associated with oxycodone use [73]. Respiratory depression and death may also occur with opioid use in neonates, the elderly and obese, and those with cardiopulmonary disease. Opioid respiratory depression has also been reported in noncancer patients using methadone or transdermal fentanyl for chronic pain [74]. Other opioid-related respiratory conditions have also been reported. Use of methadone was found to be associated with sleep apnea in a study of 392 patients using the opioid for chronic pain [75, 76]. Exacerbation of asthma symptoms can occur in heroin users [77, 78], possibly associated with histamine release by the opioid. Aspiration pneumonia is also associated with opiate use. Chest wall rigidity in adults [79] and infants [80] can occur with fentanyl use in procedural events, but can also occur with illegitimate use of the drug.

Gastrointestinal Disorders

Cocaine
Cocaine use has been implicated in ischemic disease of the digestive system, with ischemia and/or infarction being reported in the mesentery vessels [81], and occlusive disease of the small and large bowel [82]. Frequently, the onset of abdominal pain is in temporal proximity to use of either crack or intravenous cocaine. The mortality rate associated with ischemic colitis has been found to be higher in cocaine users than noncocaine users [83].

Marijuana
A number of articles, including a case series [84], have been published on cases of chronic marijuana users who were diagnosed with cannabinoid hyperemesis, characterized by cyclical, chronic vomiting and severe abdominal pain, and often accompanied by a compulsion to take hot baths or showers. The authors report that discontinuing marijuana use causes symptoms to dissipate and further assert that the illness is often underdiagnosed and underreported.

Hepatobiliary Disease

Cocaine
Hepatotoxicity in cocaine users is likely the result of direct toxicity mediated by oxidative stress and mitochondrial dysfunction occurring during metabolism of cocaine [85]. It is likely that cocaine-induced oxidative cell stress leads to cell damage, fibrosis and abnormal liver function. This mechanism also occurs in the kidney and many body systems, including the cardiovascular, central nervous, immune and reproductive systems [86].
**Metabolic, Nutritional and Endocrine Disorders**

**Marijuana**
Although some research has shown that overactivity of cannabinoid receptors may lead to abdominal obesity, dyslipidemia and hyperglycemia [87], there is little clinical evidence that marijuana use is associated with development of diabetes mellitus or hyperlipidemia.

**Cocaine**
While cocaine use has not been found to have an effect on the development of diabetes mellitus, cocaine use has been shown to increase the risk of diabetic ketoacidosis and for hospitalization of recurrent diabetic ketoacidosis [88]. Noncompliance with the therapeutic regimen is thought to be a contributing factor in diabetic ketoacidosis.

**Renal and Male Urogenital Disorders**

**Cocaine**
The risk for rhabdomyolysis and acute renal failure is significant for those who use cocaine. Cocaine has direct toxic effects on skeletal muscle and, along with severe vasoconstriction, can cause muscle ischemia and release of myoglobin and other cell contents from damaged cells [89]. Myoglobin is freely filterable in glomeruli, but accumulates in the distal tubules, resulting in obstruction. The effect of vasoconstriction on the renal vessels by cocaine, and a possible direct toxic effect of cocaine and myoglobin on renal tissue, contributes to the development of acute renal failure. However, with aggressive therapy, almost 80% of the individuals survive and most recover adequate renal function.

Genital ulcer disease found in male cocaine users is generally related to unprotected sex and contact with partners with sexually transmitted diseases and immune dysfunction associated with cocaine use.

**Marijuana**
Glomerular, interstitial and renal vascular disease may all be associated with marijuana use [90], though that link is not definite [91]. Marijuana may contribute to male infertility [92], decrease spermatogenesis and circulating testosterone levels [93], and has been linked to inhibited orgasm and painful sex [94].

**Opioids**
A recent study found that morphine use can accelerate chronic kidney disease [95]. Glomerular podocytes appear to be affected by morphine-induced oxidative stress, leading to albuminuria and renal dysfunction.

**Female Reproductive System**

**Cocaine**
Genital ulcer disease and pelvic inflammatory disease have been reported in women who use cocaine. Both conditions are likely due to sexually transmitted diseases associated with risky behavior and unprotected sex, as well as immune dysfunction.

**Marijuana**
There is a potential link between female infertility and marijuana, either as a lone agent or in concert with other illicit substances [96]. A case control study found that women who used marijuana within 1 year of attempting to conceive were not likely to become pregnant [97]. Additionally, marijuana users are six times more likely to develop Trichomonas vaginalis infections than nonusers [98].

**Pregnancy**

**Cocaine**
A comparison of 18 studies describing pregnancy complications found increased risk for preterm labor, placenta abruptio, fetal death, placenta previa and spontaneous abortion [9]. Infants of co-
Cocaine-using mothers are more at risk for decreased weight and length than infants of noncaine users. Infants of cocaine-using mothers were also found to be more at risk for transient atrial and ventricular arrhythmias than infants of noncocaine-using mothers [99]. At birth, neonates may experience some autonomic dysregulation, but withdrawal symptoms are generally minimal [100]. Cocaine is not likely to be a direct fetal teratogen, although some evidence exists for alteration of cerebral development [101].

**Marijuana**

Young women using marijuana during pregnancy may often have infants with low birth weight and decreased length. However, a direct link to these consequences as a result of marijuana use is unclear. Often lack of prenatal care, social problems or poor economic conditions may be associated with these infant outcomes.

**Opioids**

As seen with other drugs of abuse, use of opioids during pregnancy can have detrimental effects on newborns, including low birth weight and length. Often, infants are exposed in utero to a number of drugs, including cocaine, heroin, cannabinoids and benzodiazepines, and their related side effects. Newborns of opioid-using mothers are particularly at risk for neonatal abstinence syndrome, which typically occurs within the first 3 days of life [102]. Methadone and buprenorphine have both been used to manage opioid dependence in pregnant women. In the newborn, buprenorphine appears to be less likely to alter cardiac function and produces fewer severe side effects than methadone [103].

**Dermatologic Disorders**

**Cocaine**

Cutaneous vasculopathy is a dermatologic condition seen in cocaine users, especially in women [104]. Retiform rashes with purpuric plaques are found predominantly on the lower extremities, but can also develop on the face and ears. Leukopenia and neutropenia may be seen, and laboratory tests for antineutrophil cytoplasmic antibodies can be positive, suggesting an immune reaction. Thrombotic vasculopathy and small-vessel vasculitis may be found on skin biopsies. Levamisole contamination in cocaine often contributes to the development of these skin lesions.

**Neurological Disorders**

**Cocaine**

The major harms associated with cocaine abuse of the nervous system are related to cerebrovascular disease. Cocaine users are at risk for development of subarachnoid hemorrhage associated with ruptured aneurysms, ischemic stroke and hemorrhagic stroke [105]. Compared to nonusers, cocaine users are more likely to experience an aneurysm rupture and less likely to survive subarachnoid hemorrhage than nonusers. Ischemic strokes are also seen in cocaine users and may be associated with hypertension, vasospasm, arteritis and increased platelet aggregation [106]. Cocaine users with ischemic stroke are often younger than nonusers and are more likely to smoke tobacco. Morbidity and mortality are similar in both cocaine users and nonusers. Seizures may also occur after cocaine use, especially in women, when high doses are used, with chronic use of cocaine, and in users previously experiencing seizures [107].

**Marijuana**

Use of marijuana has been associated with vascular disease in the central nervous system, with several cases of ischemic strokes documented in recent literature [108–110], including a study finding increased risk of stroke in marijuana users [111]. Marijuana use may increase the risk of the movement disorder tardive dyskinesia [112]. In a study of the incidence of tardive dyskinesia in
a group of people with chronic schizophrenia, women and older patients who smoked marijuana while taking antipsychotic drugs were more likely to develop repetitive and involuntary movements than other patients. Links between marijuana and transient amnesia [113], ataxia [114], propriospinal myoclonus [115] and spasticity [116] have yet to be fully explored.

Opioids
Opioids are often abused because of their stimulatory effects on the nervous system. However, in large doses, opioids can have a detrimental effect on the central nervous system and can lead to delirium and coma. Hydromorphone, on the other hand, can cause neuroexcitation, as reported in a study of 156 hospice patients receiving the drug while in an inpatient setting [117]. An increased risk of hydromorphone-induced neuroexcitation was associated with large doses and longer duration of drug use, increased age of the patient, and increased serum creatinine. Symptoms often associated with hydromorphone-induced neuroexcitation include tremor, myoclonus and agitation. Cognitive dysfunction is also commonly seen [118]. Spongiform leukoencephalopathy is a rare sequela of inhalation of heated heroin smoke. In one study, postmortem findings in 4 patients with spongiform leukoencephalopathy showed significantly higher numbers of apoptotic cells in both the cerebellum and corpus callosum [119]. Cerebral vacuolar degeneration was also found, particularly around microvessels. Sequelae include hydrocephalus and cerebellar swelling [120]. Although rare or possibly underreported, seizures can occur with opioid use, including generalized tonic-clonic seizures and status epilepticus [121].

Musculoskeletal Disease

Cocaine
As previously mentioned, two musculoskeletal conditions, rhabdomyolysis with acute renal failure and midline destructive lesions of the face and oral cavity, are strongly associated with cocaine use. Although no other significant musculoskeletal disorders have been reported with cocaine use, the inclusion of levamisole in cocaine has the potential of leading to untoward rheumatic consequences [122].

Conclusion
In this review, we relate the recent literature regarding the physical health associations of the use of three drugs of abuse (cocaine, marijuana and opioids) and a variety of physical illnesses (table 1). The use of cocaine, marijuana and opioids has been shown to impart a plethora of physical illnesses, many with purported and examined pathophysiological mechanisms. While associations of these conditions are known, the causative rationales for these conditions are less known. More research is certainly needed to examine causation of these drugs with physical illness. It may be that when more people use certain drugs (e.g. legalization of marijuana and increase in opioid prescription drug misuse), their related physical health conditions will become more readily apparent.

For the clinician, our findings that use of illicit substances, namely cocaine, marijuana and opioids, have some evidence in the peer-reviewed literature of physical health consequences may not be a surprise. Clinicians often treat patients who use illicit substances and often appreciate the deleterious social and environmental harms associated with this use. Often, patients who use illicit substances have co-occurring mental health conditions and these are readily appreciated by clinicians. However, what may be less known are the physical health conditions that may be directly attributable to use of illicit substances. Certainly, we found that significant evidence exists of a myriad of physical health conditions that may be directly attributable to illicit substance use.
### Table 1. Conditions clinicians are likely to see with use of three commonly abused substances

<table>
<thead>
<tr>
<th>System</th>
<th>Cocaine</th>
<th>Marijuana</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system</td>
<td>altered cytokine release leading to increased risk of infections; leukopenia, agranulocytosis, vasculitis associated with additive levamisole</td>
<td>no association with altered immunity, inflammation</td>
<td>altered cytokine function; increased risk of altered cellular, humoral immune response</td>
</tr>
<tr>
<td>Infection</td>
<td>increased due to risky behavior, unhealthy living conditions, malnutrition</td>
<td>higher risk for <em>Neisseria, Candida</em>, sexually transmitted diseases, chronic hepatitis C with liver steatosis, fibrosis</td>
<td>increased risky behavior associated with HIV, hepatitis B and C, other sexually transmitted disease; intravenous use and increased cellulitis, endocarditis</td>
</tr>
<tr>
<td>Cancer</td>
<td>increased risk of non-Hodgkin's lymphoma</td>
<td>increase risk of bladder cancer, cancer of head and neck, lung; testicular germ cell cancer; oral and pharyngeal cancer</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic disorders</td>
<td>increased risk of coagulopathy (VWF), thrombus formation; atherosclerotic lesions, thrombi in systemic, main coronary arteries</td>
<td>cannabis arteritis (thromboangiitis obliterans); peripheral obstructive arterial disease</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>high blood pressure, cardiac ischemia, vasospasm, infarction; increased systemic vessel thrombi, AMI, silent infarct; arrhythmias; coronary aneurysms</td>
<td>cardiac palpitations, orthostatic hypotension, tachycardia; increased risk of silent AMI and infarct soon after use; coexisting cardiac risk factors</td>
<td>respiratory depression and death (oxycodone), particularly in neonates, elderly, obese, those with cardiopulmonary disease; increased sleep apnea; exacerbation of asthma symptoms (heroin); aspiration pneumonia; chest wall rigidity</td>
</tr>
<tr>
<td>Oral, ear, nose, throat disorders</td>
<td>midline nasal, oral destructive lesions with insufflation, positive ANCA test; sinus disease; upper airway burns</td>
<td>xerostomia, periodontitis, gingivitis, mucosal lesions, ulcers</td>
<td>mucosal necrosis in heroin snorters</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>bronchial, lung dysfunction, cough, hemoptysis, chest pain; exacerbation of asthma symptoms; increased microvascular injury</td>
<td>increased mucus production, signs and symptoms of chronic bronchitis; increased risk for marijuana allergy</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>mesenteric ischemia, infarction, occlusive disease of small and large bowel; increased risk of death from ischemic colitis</td>
<td>cannabinoid hyperemesis, often associated with compulsion for hot bath or shower</td>
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<tr>
<td>Hepatobiliary disease</td>
<td>liver fibrosis, abnormal liver function secondary to oxidative stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic, nutritional, endocrine disorders</td>
<td>increased risk of diabetic ketoacidosis secondary to noncompliance to treatment regime</td>
<td>possible abdominal obesity, dyslipidemia, hyperglycemia</td>
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</tbody>
</table>
Clinicians, particularly general practitioners or primary care providers, should screen and assess for illicit substances among their patients. If they identify a patient who uses an illicit substance, our review of literature relates that they should consider evaluating for physical health conditions associated with that use. Even mental health providers should consider assessing for these physical health conditions, as patients with illicit substances may not seek care with a general practitioner or primary care provider. A proactive approach for assessing and treating these physical health conditions associated with illicit use may be valuable, as patients who use illicit substances may not seek medical care, and certainly may not establish longitudinal healthcare services, such as a general practitioner or primary care provider. In addition, attention in healthcare professional schools and training programs regarding the association of illicit substances and physical health may be warranted. In sum, physical health conditions associated with use of illicit

<table>
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<tbody>
<tr>
<td>Renal, male urogenital disorders</td>
<td>increased risk of rhabdomyolysis, acute renal failure; genital ulcer disease secondary to unprotected sex</td>
<td>glomerular, interstitial, renal vascular disease; possible infertility with decreased spermatogenesis and testosterone; erectile dysfunction</td>
<td>acceleration of chronic renal disease associated with oxidative stress</td>
</tr>
<tr>
<td>Female reproductive system</td>
<td>genital ulcer disease, pelvic inflammatory disease</td>
<td>infertility; increased risk of <em>Trichomonas</em> infection</td>
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<tr>
<td>Pregnancy</td>
<td>increased risk of preterm labor, placenta abruption, fetal death, placenta previa, spontaneous abortion; transient atrial and ventricular arrhythmias; decreased birth length and weight</td>
<td>decreased birth length and weight</td>
<td>decreased birth length and weight; high risk for neonatal abstinence syndrome</td>
</tr>
<tr>
<td>Dermatologic disorders</td>
<td>cutaneous vasculopathy (retiform rash, purpuric plagues); leukopenia, neutropenia; small vessel disease; positive ANCA test; thrombic vasculopathy</td>
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<tr>
<td>Neurological disease</td>
<td>cerebrovascular disease (ischemic, hemorrhagic stroke); aneurysm rupture, subarachnoid hemorrhage; seizures</td>
<td>cerebrovascular disease (ischemic stroke); increased risk for tardive dyskinesia; transient amnesia; ataxia; propriospinal myoclonus, spasticity</td>
<td>delirium, coma; neuro-excitation (hydromorphone); cognitive dysfunction; spongiform leukoencephalopathy (heated heroin smoke); seizures</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>rhabdomyolysis with acute renal failure; midline destructive lesions (face, oral cavity); rheumatoid findings with levamisole</td>
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</tbody>
</table>

AMI = Acute myocardial infarction; ANCA = antineutrophil cytoplasmic antibody; VWF = von Willebrand factor.
drugs is a significant concern for all patients who use illicit substances and should be a concern for their healthcare providers as well as healthcare provider educators.

This review has significant limitations related to our approach which should temper over-reaching or generalizing our findings. We reviewed only the recent (over the last 2 decades) peer-reviewed literature, and only that which was published in English. It may be that some published studies remained undiscovered in the process of our electronic review. We did not cover other illicit drugs of abuse, but much of the literature on amphetamines is similar to the literature on cocaine and much of the literature on hallucinogens is similar to the literature on marijuana. We did not examine the behavioral, mental health, social and environmental problems that afflict persons who use substances of abuse, and we did not concentrate this review on the associations made through the route of drug administration (e.g. increase in hepatitis C and HIV through injections of illicit drugs) as these were not direct drug associations to physical illness, but due to the route of exposure. While we critically examined the literature, much of the literature examines associations rather than causations, or exists in the form of case reports, case series or descriptive studies. Conclusions regarding the specificity and strength of the association with drugs of abuse and physical illness should be tempered unless there is evidence of biological mechanisms to support the association.

Despite these limitations, drugs of abuse unquestionably cause physical health effects. Some of the diseases connected to cocaine, marijuana and opioid use possess strong evidence of disease association. These diseases are often serious, resulting in a significant burden on healthcare systems to finance, treat or support long-term management of these conditions. All healthcare providers should be aware of these associations and discuss these associations with patients who use these substances. By doing so, illicit use, as well as the physical harm and diseases associated with that use, may be diminished or even eliminated.

References


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