Chronic Drug Use and Abdominal Pain

Alexis L. Cates, DO[a,*], Brenna Farmer, MD, MBA, MS[b,1]

KEYWORDS

• Alcohol use disorder • Opioid use disorder • Gastrointestinal emergencies
• Hepatotoxicity • Chronic drug use

KEY POINTS

- Alcohol use disorder contributes to emergent pathology throughout the gastrointestinal tract and liver.
- Chronic opioid use contributes to often unrelenting constipation.
- Building a rapport with patients who have substance use disorders is important to gain the history and insight needed to guide your diagnostic differential.

INTRODUCTION

It is well known that abdominal pain and related complaints are among the top reasons for Emergency Department (ED) visits. The National Hospital Ambulatory Medical Care Survey (NHAMCS) in 2017 noted that injury and poisonings also make up a significant percentage, 18.9%, of the primary diagnoses for ED visits. Alcohol use disorder and substance use disorder are associated with 3.1% and 5.8% of all ED visits, respectively.[1] There is overlap in these diagnoses, and it is not surprising patients present with a combination of these diagnoses. In this article, we discuss a general approach to abdominal pain in patients with chronic drug and alcohol use disorders with an emphasis on an expanded diagnostic differential. Several substance-specific diagnoses and therapeutic options for the management of chronic abdominal pain in patients with substance use disorders are highlighted.

APPROACH

The general approach to abdominal pain in a patient with chronic drug use includes a detailed history, review of systems, medications, allergies, and an in-depth discussion

[a] Division of Medical Toxicology, Department of Emergency Medicine, Einstein Healthcare Network, Korman B-14, 5501 Old York Road, Philadelphia, PA 19141, USA; [b] Quality and Patient Safety, Department of Emergency Medicine, Weill Cornell Medicine, New York Presbyterian/Lower Manhattan Hospital Emergency Department
[1] Present address: Department of Emergency Medicine, 525 E 68th St., New York, NY 10065, USA.
* Corresponding author.
E-mail address: catesale@einstein.edu

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of social history and substance use. The substance use history should include types of substances used and frequency of use, routes of exposure, methods in which the patient obtains the substance, and any recent changes to use patterns. A detailed physical examination as guided by the history should follow.

A broad list of differential diagnoses should be developed based on the history and physical examination. Certain substance use may add a specific diagnosis to the differential. Testing can then be tailored to the clinician's suspicions.

General laboratory testing in patients with substance use concerns may include complete metabolic panel, complete blood count, serum acetaminophen and salicylate levels (as common coingestants), ethanol level, serum osmolality, urinalysis, and pregnancy testing. Occasionally, if the patient's presentation lends concern for specific organ dysfunction, labs such as amylase and/or lipase, troponin, urine and blood cultures, viral hepatitis panels and testing for commonly transmitted infections may be considered.

A urine drug screen may be useful to determine previous exposure to a particular drug of abuse such as cocaine, tetrahydrocannabinol (THC), or opioids. It is not helpful for diagnosing acute intoxication or withdrawal, nor is it inclusive of all drug exposures. Urine immunoassays may only include opiates or the compounds that include or metabolize to morphine or codeine. Therefore, there is limited utility in a patient that may have been exposed to a semisynthetic or synthetic opioid such as methadone, oxycodone, or fentanyl. Some laboratories may have the ability to screen for specific opioids such as fentanyl, 6-monoacetylmorphine (the metabolite of heroin), tramadol, methadone, and buprenorphine or obtain more specific testing via gas chromatography and mass spectrometry.[2]

In addition to laboratory testing, imaging studies can greatly increase diagnostic accuracy. Plain radiographs, ultrasonography, computed tomography (CT), and or MRI may be helpful depending on the differential diagnosis and is discussed below with specific substances.

CLINICAL RELEVANCE

There are numerous gastrointestinal manifestations of chronic alcohol and drug use. Although the NHAMCS survey was limited and diagnoses potentially underreported, alcohol-related disorders accounted for 0.8% and opioid-related disorders reported for 0.1% of all diagnoses made in the ED setting.[1] The use of both substances likely accounts for abdominal pain due to disorders of the gastrointestinal tract, as well as abdominal pain due to disorders of the cardiovascular and genitourinary systems. The focus of this article will be on frequently encountered substances of abuse and associated common gastrointestinal pathologies, as well as emergent evaluation and pertinent diagnostics. The most detailed discussion will occur with ethanol and opioids, given the evidence supporting abdominal complaints with chronic use.

ETHANOL

Ethanol, more commonly called "alcohol," is one of the most used substances in the world. Excessive alcohol use and subsequent damage to the gastrointestinal tract are vast. As the site of alcohol absorption, the gastrointestinal tract can be negatively affected by numerous metabolic and functional changes and has been extensively researched.[3] The pathology can vary widely, from simple gastritis to esophageal varices and from oral lesions to numerous cancers.

Esophagus and Stomach

Chronic alcohol use may lead to a variety of disorders in the esophagus and stomach. In the acute period following alcohol consumption, there may be an increase in symptoms of gastroesophageal reflux (GERD). GERD symptoms can lead to vomiting and potentially Mallory-Weiss syndrome.[4] Esophageal bleeding may also be indicative of esophageal varices, as a complication of portal venous hypertension in patients with cirrhosis. Persistent vomiting and increased pressure in the portal venous system could lead to variceal rupture, a potentially fatal complication producing significant upper gastrointestinal hemorrhage.[5] Obtaining complete blood counts, hepatic panels, and coagulation studies are critical in defining severity of disease. In addition, type and screen with crossmatching of blood is necessary to allow for blood product replacement during resuscitation. Advanced diagnostic and therapeutic interventions such as esophagogastroduodenoscopy are often indicated while resuscitative efforts continue.

Boerhaave's syndrome, a tear in the esophageal mucosa leading to complete spontaneous rupture, can be associated with chronic alcohol use. It occurs following a sudden increase in intra-esophageal pressure due to persistent vomiting. Vomiting, chest pain, and subcutaneous emphysema are classic findings.[6] Chest x-rays cannot be used to exclude the diagnosis but may identify abnormalities such as subcutaneous or mediastinal emphysema, mediastinal widening, or associated pleural effusion concerning for this diagnosis. Advanced imaging such as a contrast-enhanced CT scan of the chest, abdomen, and pelvis are more specific. Significant complications requiring surgical intervention may occur, so early surgical consultation is recommended.

Inflammation along the stomach lining, or gastritis, may also cause hemorrhage due to ulceration. There is a known association between alcohol use and the development of active *Helicobacter pylori* infection, as well, which can contribute to ongoing discomfort.[7] Peptic ulcer disease may be multifactorial and is not likely to be directly associated with an increase in alcohol consumption.[8]

Pancreas

Pancreatic disease is commonly associated with morbidity and mortality due to chronic alcohol use. Gallstones and excessive alcohol use are most commonly associated with acute pancreatitis in Western societies, although the amount to which either contributes varies among geographic regions and alcohol consumption patterns.[4] Two explanations of the mechanism involved include the premature activation of pancreatic enzymes within the acinar cell (auto-digestion) and organelle dysfunction leading to abnormal secretion of digestive enzymes.[4,9]

Patients may present with reported prior acute pancreatitis and a history of significant alcohol use. Mild symptoms of abdominal discomfort with nausea and vomiting can occur, whereas severe cases may develop multi-organ dysfunction, infection, and complications such as abscesses, pseudocysts, or necrosis. There is often abdominal tenderness, particularly in the upper abdomen and epigastric region. Diagnosis of acute pancreatitis is made by the presence of at least two of the following: significant upper abdominal pain typically radiating to the back, serum lipase or amylase levels that are at least three times the upper limit of normal, or findings on advanced imaging such as contrast-enhanced CT of the abdomen.[9,10] Other causes of acute pancreatitis should be excluded by history, physical examination, laboratory results, advanced imaging, and procedures such as endoscopic retrograde cholangiopancreatography as indicated.[4]

Chronic pancreatitis is characterized by often irreversible fibrosis and inflammation, atrophy, calcifications, dysplasia, exocrine or endocrine insufficiency, and chronic abdominal pain. Although there are multiple potential causes for chronic pancreatitis (eg, hypertriglyceridemia and hyperparathyroidism), the diagnosis is most commonly associated with excessive alcohol use in 75% of cases.[4,11] A linear dose–response relationship with increasing daily alcohol intake is associated with development of chronic pancreatitis.[12] Other risk factors include concomitant use of smoking tobacco and certain genetic factors.[4] Patients often present with severe upper abdominal pain that radiates to the back, increasing with meals and subsequently leading to decreased appetite. Patients may also present with steatorrhea, new-onset diabetes, and significant weight loss.

Chronic pancreatitis is primarily a clinical diagnosis; however, owing to complications such as pseudocyst formations, biliary obstructions, pseudoaneurysms, and cancer, imaging such as contrast-enhanced CT or MRI is often obtained. Amylase and lipase levels may be normal as the disease progresses and more fibrotic tissue replaces pancreatic parenchyma.[13]

Liver

Alcoholic liver disease (ALD) is one of the major causes of chronic liver disease in the United States. The term covers a spectrum of hepatic disorders, from steatosis and hepatitis to irreversible alcoholic cirrhosis. Several factors may play a role in the development of ALD, including gender, obesity, and metabolic, genetic, environmental, and immunologic factors. However, the largest risk factor is the quantity and duration of alcohol use, with an increase of either correlating with disease development.[14] ALD and continued use may synergistically impair hepatic function with the presence of other hepatotoxins such as acetaminophen, infections such as hepatitis C and human immunodeficiency virus, and nutritional impairments.[15,16]

Alcohol itself is a hepatotoxin. The end products of alcohol metabolism, such as acetaldehyde, damage the liver by triggering inflammation and fibrogenesis.[16] A spectrum of clinical syndromes can occur, ranging from asymptomatic illness to end-stage liver disease. A patient with hepatic steatosis may present with right upper quadrant discomfort, nausea, vomiting, and anorexia.[15] The liver may be normal or enlarged in size. A patient with alcoholic hepatitis may present with jaundice, anorexia, right upper quadrant pain, fever, ascites, and enlarged liver. These symptoms may be more insidious when compared with a viral or toxin-mediated hepatitis. More severe cases of alcoholic cirrhosis may feature hepatic encephalopathy and synthetic liver dysfunction, reflecting impending hepatic failure.[15]

Alcoholic cirrhosis may lead to hepatorenal syndrome, of which the complicated pathophysiology is beyond the scope of this article. However, this syndrome may be identified on recognition of a patient in extremis with oliguria and an insidious increase in serum creatinine, thought to be related to renal vasoconstriction and associated fulminant liver failure.[17] Despite adequate resuscitation and removal of any potentially nephrotoxic or hepatotoxic xenobiotics to explain the clinical presentation, patients with this syndrome have a poor prognosis and may ultimately require liver transplantation.[17]

Although a history of excessive alcohol use may indicate ALD and related complications, other causes of hepatobiliary disease and liver failure should be considered. Diagnostic imaging dedicated to the hepatobiliary system may be beneficial in this delineation, including but not limited to abdominal ultrasonography. Laboratory abnormalities seen with ALD may include thrombocytopenia, anemia, elevated liver transaminases (often a greater increase in aspartate aminotransferase),

hypoalbuminemia, hyperbilirubinemia, elevated gamma-glutamyl transpeptidase (GGTP), elevated prothrombin time, and international normalized ratio (INR) and possible renal dysfunction or electrolyte abnormalities.[14] A viral hepatitis panel may also be beneficial in ruling out concomitant acute or chronic viral etiologies.

Small Intestine, Large Intestine, and Rectum

Chronic alcohol use can lead to diarrhea due to impaired gut motility, permeability, nutritional disorders, and impaired absorption of critical vitamins and nutrients.[4] Associated folate deficiency due to reduced intake and impaired liver function can further malabsorption.[18] Although alcohol is not likely to directly transit through the gut to the large intestine, there may be indirect mucosal damage from significant inflammatory responses resulting in the loss of mucosal integrity and contributing to impaired permeability.[16] Toxic metabolites of alcohol such as acetaldehyde can contribute to carcinogenesis.[16] Lastly, colonic varices due to portal hypertension can occur, and bleeding from hemorrhoids may be increased.[4]

Miscellaneous Effects

Chronic use of alcohol can contribute to a variety of other pathologies not mentioned here, due to the limitations of this article. This does not imply a lack of importance, however. Many of these other pathologies may involve abdominal pain as one of the presenting symptoms.

Alcoholic ketoacidosis (AKA) can be seen in patients with chronic ethanol use due to the cessation of adequate nutrition during a "binge" drinking episode or due to nausea, vomiting, and abdominal pain from related gastritis, hepatitis, pancreatitis, or other illness.[19] Findings will include significant dehydration, nausea, vomiting, abdominal discomfort, tachycardia, tachypnea, and presence of ketoacids, mainly in the form of beta-hydroxybutyrate.[20] Alcohol withdrawal following an abrupt cessation or significant decline in use may also present with gastrointestinal and central nervous system complaints and may contribute to AKA.

Additionally, alcohol is a cocarcinogen, increasing cancer risk of those patients exposed to another carcinogen. In a compilation of meta-analyses, chronic alcohol use is associated with increased risk of gastrointestinal carcinogenesis, including cancers of the tongue, mouth, pharynx, esophagus, stomach, pancreas, colon, and liver.[21]

Therapeutic Options

Initial resuscitation would include usual care of airway management, placement of intravenous lines, volume resuscitation, glucose administration, and vitamin and electrolyte supplementation as needed. Blood products would be indicated in massive gastrointestinal hemorrhage. Pain control in the form of parenteral opioids or other non-opioid analgesics may be warranted, depending on the suspected diagnosis. Monitoring patients for alcohol withdrawal and treating as needed can mitigate in-hospital comorbid conditions. Controlled cessation of alcohol use and therapeutic options therein should be discussed. Molecular Adsorbent Recirculating System (MARS), essentially a liver replacement therapy, has been used in patients with liver failure.[22]

OPIOIDS

Opioid agonists have been used as pharmacotherapy for acute or chronic pain for centuries.[23] Unfortunately, the addicting effects of opioids have led to abuse of

both prescription and illicit opioids with an increasing group of patients meeting criteria for opioid use disorder (OUD).[a]

In 2016, there were 1.9 million American adults with OUD with approximately 360,000 persons enrolled in a federally licensed treatment program.[24] It is not uncommon for the gastrointestinal effects associated with opioids to lead patients to seek medical care.

Opioids commonly decrease gastrointestinal motility with symptoms manifesting as constipation, bloating, early satiety, and pain leading to bowel dysfunction with blockade of peristalsis and an overall decrease in intestinal fluids.[4] In contrast, opioid withdrawal results in nausea, vomiting, diarrhea, and abdominal cramping. The following is a discussion of common gastrointestinal complaints related to opioid use.

Narcotic Bowel Syndrome

Narcotic bowel syndrome describes the progressive increase of colicky abdominal pain with continued or increased use of opioids.[b]

One of the perpetuating factors is likely related to the hyperalgesia effects of opioids, although exact molecular mechanisms are poorly understood.[25] Increasing doses of opioids in response to pain enhance adverse effects on pain sensation and ultimately delays gastrointestinal motility.[4] Ideal treatment includes a biopsychosocial approach of appropriate opioid weaning, prevention or reduction of opioid withdrawal symptoms, aggressive bowel regimen, alternative therapies for pain control, and behavioral health intervention.

If obtaining an abdominal plain film, be mindful that, in instances of presumed narcotic bowel syndrome, there may be evidence of a partial intestinal obstruction, which is more likely due to adynamic ileus or a pseudo-obstruction.[26] There may also be a large amount of retained fecal matter. In instances where more advanced imaging would be needed, a contrast-enhanced CT of the abdomen and pelvis may be beneficial.

Motility Disorders

Motility disorders such as opioid-induced constipation (OIC) and esophageal motility disorders occur from chronic opioid use.

OIC may present immediately or gradually over time. Opioid-replacement therapies such as methadone and buprenorphine have also been associated with OIC.[27] Norbuprenorphine, the active metabolite of buprenorphine, may play more of a role as the opioid receptor agonist while buprenorphine itself has a higher risk of OIC.[28]

OIC is due to inhibition of gastric emptying or inhibition of peristalsis resulting in delayed absorption of medications and increased absorption of fluid, hardening of stool, and ultimately constipation.[29] Other gastrointestinal symptoms may develop such as nausea, vomiting, and bloating.

The effects of opioids on esophageal motility have been evaluated in small studies with variable results.[30] Chronic use of opioids may lead to dysphagia or GERD due to impairment at lower esophageal sphincter and potentially esophagogastric junction outflow obstruction.[31] A large retrospective study of chronic opioid users noted

[a] Opioid Use Disorder (OUD): Defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress.

[b] Although the term "narcotic" is not favored when describing opioids, this term has been widely recognized in the literature in the setting of "narcotic bowel syndrome," and so it is used in this article.

esophageal dysmotility with increased esophagogastric junction outflow obstruction and esophageal spasticity within 24 hours of use.[30]

Hepatic Disease Related to Opioid Use

Currently, there are no evidence-based studies demonstrating hepatotoxicity from pure opioid agonists. One case report from 2008 identified suspected cholestatic hepatitis, diagnosed via liver biopsy, thought to be related to oxycodone use.[32]

Patients who chronically use or misuse opioids may expose themselves to opioid combination products, such as oxycodone with acetaminophen. Unfortunately, the combination with acetaminophen has been linked to acute liver failure, mostly from unintentional overdose with acetaminophen.[33] Many patients may not be aware of the acetaminophen coproduct and could potentially take more than is prescribed or use the product illicitly. Some may take additional acetaminophen or other hepatotoxic medications.

Hepatic disease such as hepatitis B and C related to injection opioid use could be a cause of nausea, vomiting, abdominal pain, and jaundice. In particular, the number of hepatitis C infections has risen dramatically since 2009 correlating with injection opioid use patterns.[34] Unsafe injecting practices contribute substantially to these rising infections.[35] Although specific treatment is not likely to be initiated in the emergency setting, diagnosis and arranging outpatient follow-up is important. If left untreated, continued transmission to others is possible and places further strain on the health care system.

Opioid Withdrawal

Depending on the opioid, a patient can experience symptoms of opioid withdrawal with variation in onset after a sudden reduction in use or abstinence. It may also occur when a partial agonist or antagonist is introduced in the presence of agonists bound to the mu opioid receptors. Opioid withdrawal symptoms are complex and beyond the scope of this article, except for mention of gastrointestinal symptoms such as nausea, vomiting, abdominal cramping, and diarrhea. These symptoms are due to the presence of opioid receptors in the gastrointestinal tract. Although opioid withdrawal is not likely to result in severe morbidity or mortality directly, it can cause significant discomfort and be temporarily disabling. Persistent vomiting or diarrhea can lead to fluid and electrolyte derangements with acute kidney injury. Poorly treated opioid withdrawal may result in decreased tolerance over time, such that if the patient seeks opioid agonist use again, a significant overdose may occur and indirectly increase morbidity and mortality.

Treatment of the gastrointestinal symptoms of opioid withdrawal is often guided by supportive care. Fluid resuscitation, electrolyte replacement, and antiemetics may be needed. Initiation of medication-assisted treatment (MAT) with medications such as buprenorphine, methadone, or naltrexone will also likely provide relief of these symptoms. A clinical opioid withdrawal scale can assess for severity of opioid withdrawal symptoms and assist in determination of appropriate intervention with MAT in combination with symptomatic management.

Therapeutic Options

The approach for patients with OUD can begin with an evaluation for potential weaning of opioid use as much as possible. If this is not feasible, a variety of other therapeutics may be employed, depending on the symptoms.

Conservative measures to relieve opioid-induced bowel dysfunction may be attempted with increased fluid intake, dietary fiber supplementation, and osmotic

laxatives.[36] For more complicated cases or those that do not respond to conservative measures, numerous pharmaceutical interventions can be considered.

Patients who use opioids for pain control long-term may find some benefit in oral preparations of opioid agonists with naloxone for improved bowel function and analgesia without the effects of opioid withdrawal.[37–39] Preparations such as the long-acting mu opioid antagonist methylnaltrexone and naloxegol do not penetrate the blood brain barrier, but rather exhibit their activity peripherally to counteract full opioid agonists' effect on the gut.[40] OIC relief is often slow and full resolution is difficult. A summary of common pharmaceutical treatments are found in **Table 1**.

In patients with illicit use, MAT would be ideal, leading them away from opioid misuse to a regulated and supervised treatment program. This treatment involves a combination of biopsychosocial approaches plus office-based pharmacotherapy, such as buprenorphine, buprenorphine/naloxone combination products, methadone or naltrexone (**Table 2**). Unfortunately, there is still a high prevalence of OIC in patients treated with MAT, in particular methadone and buprenorphine.[41] In these patients, the preferred treatment is a supportive bowel regimen with increased fluid, fiber intake, and osmotic laxatives as needed.

Patients with acute opioid withdrawal will also present to the ED with gastrointestinal distress; treatment should include symptomatic and supportive care (**Table 3**). Opioid replacement therapy can also be initiated depending on the circumstances, as shown in **Table 2**. Maintenance therapy is represented by one of the following: gradual cessation of an opioid agonist, use of a partial mu-opioid agonist, or use of an opioid antagonist as maintenance.[42] The more uncomfortable symptomatology that patients experience are the gastrointestinal symptoms and may lead the patient to further misuse opioid agonists to treat their symptoms.[24] Occasionally, patients with OUD and concomitant painful medical or surgical pathology will require short-acting opioid agonists for pain control and withdrawal symptoms. Appropriate tapering to abstinence or MAT is worth consideration following resolution of said pathology.

AMPHETAMINES

Although there are select derivatives approved for medicinal use, amphetamines are also commonly drugs of abuse. Users seek the central stimulatory effects and effects caused by an increase in neurotransmission of dopamine, norepinephrine, and serotonin.[43] Amphetamines are addicting, and long-term effects are still under evaluation.[44] In relation to the gastrointestinal tract, certain amphetamines have been associated with gut ischemia, hepatotoxicity, and liver failure.

Numerous case reports describe significant intra-abdominal pathology secondary to poor organ perfusion in sympathomimetic and vasoconstrictive states due to amphetamine use. The accumulation of norepinephrine postsynaptically contributes to systemic hypertension, tachycardia, and local vasospasm or vasoconstriction leading to organ ischemia. Chronic use may exacerbate this effect, and fatalities have been reported.[45] Ischemic colitis, small bowel ischemia, gangrenous cholecystitis, ulcerations of the intestines, and perforated viscus are all reported.[45–50] Surgical consultation should be considered.

Significant hepatotoxicity, though rare, has been identified as a complication of the use of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) and synthetic cathinones (bath salts), another sympathomimetic drug of abuse. Although hepatitis may result from the use of contaminated needles with viral hepatitis, there are also reports of direct hepatotoxicity.[51] Patients present with abdominal pain, systemic toxicity, and accompanying fulminant liver failure, or they with jaundice present days to weeks

Table 1
Opioid-induced constipation (OIC) treatment options

Medication/Mechanism of Action	Dosing/Routes/frequency	Indication	Caution
Docusate sodium (Surfactant laxative, stool softener)	50 mg - 300 mg daily or divided doses	Adults with constipation	Avoid with intestinal obstruction or risk for perforation Avoid concomitant use with mineral oil Avoid use >7 d
Methylnaltrexone (peripherally acting mu opioid antagonist)	12 mg SC daily OR 450 mg PO daily in AM	Adults with OIC and chronic non-cancer pain	Avoid with intestinal obstruction or risk for perforation Needs renal/hepatic adjustments
Naloxegol (peripherally acting mu opioid antagonist)	12.5 mg to 25 mg PO per day in the AM (1 h AC or 2 h PC)	Adults with OIC and chronic non-cancer pain	Do not administer with CYP3A4 inducers or inhibitors Avoid with intestinal obstruction or risk for perforation
Oxycodone-Naloxone (Combination mu opioid agonist and antagonist)	Initial dose 10 mg/5 mg tablet PO up to twice daily Not to exceed daily dose of 80 mg/40 mg (or 40 mg/20 mg twice daily)	Adults with chronic severe pain and OIC	Avoid with other opioid agonists Needs renal/hepatic adjustments
Polyethylene glycol (osmotic laxative)	17 g packet or large spoonful of oral powder in 4–8 oz of beverage (water) daily	Adults with constipation	Avoid with intestinal obstruction or risk for perforation Avoid with intestinal infection Avoid with concomitant use of stimulant laxatives Monitor electrolytes Avoid use >7 d Caution in renal impairment
Senna (intestinal irritant and stimulant)	15 mg PO once daily Not to exceed daily dose of 70–100 mg	Adults with constipation	Avoid with intestinal obstruction or risk for perforation Avoid use >7 d

[a]Options may include usual symptomatic and supportive care as with other similar conditions, or specific products to target mu opioid receptors of the gastrointestinal tract.

Table 2
Medication-assisted therapy for opioid use disorder (OUD)

Medication/Mechanism of Action	Dosing/Routes/Frequency	Indication	Caution
Buprenorphine *(Partial agonist at mu opioid receptor*)	*Dosing/Frequency:* varies depending on patient response. Typical initial dosing: 4 mg - 8 mg but can be as high as 16 mg - 32 mg. hen, 4 mg - 24 mg daily, divided into daily, twice daily or three times daily dosing *Routes:* sublingual (disintegrating tab)	Maintenance in OUD. Monoproduct is therapy of choice for pregnant patients.	Precipitated withdrawal possible in presence of full mu opioid agonists. Has some value on illicit markets as monoproduct.
Buprenorphine/Naloxone *(partial agonist at mu opioid receptor with poorly bioavailable antagonist at mu opioid receptor when administered sublingually)*	*Dosing/Frequency:* varies depending on patient response. Typical initial dosing: 4 mg - 8 mg but can be as high as 16 mg - 32 mg. Then, 4 mg - 24 mg daily, divided into daily, twice daily or three times daily dosing *Routes:* sublingual (disintegrating strip)	Maintenance in OUD.	Precipitated withdrawal possible in presence of full mu opioid agonists. Not indicated for pregnant patients due to potential for naloxone to cause withdrawal in fetus.
Methadone *(long-acting full agonist at mu opioid receptor)*	*Dosing/Frequency:* Varies depending on patient response. Initial daily dosing 30mg-40 mg. *Routes:* oral	Maintenance in OUD.	Strict rules on credentialing of distributing pharmacies; usually associated with a daily clinic Caution with QTc prolongation and escalating doses.
Naltrexone *(long-acting antagonist at mu opioid receptor)*	*Dosing/Frequency:* Initial dose 25 mg then upwards to 50 mg daily in oral form. 380 mg every 4 wk in injection form. *Routes:* oral tab, intra-muscular	Maintenance in OUD.	May have loss of tolerance to opioids during a relapse period.

[a]Currently, buprenorphine prescriptions greater than 3 days (72 h) must be written by those with a waiver to their Drug Enforcement Administration (DEA) license. This is subject to change.

Table 3
Common medications[a] used for treatment of opioid withdrawal

Medication	Dosing/Route/ Frequency	Indication	Caution
Acetaminophen	650 mg PO every 4–6 h, maximum 4 g/d	Abdominal pain, myalgias	May contribute to hepatotoxicity
Clonidine	0.1 mg PO every 6–8 h, maximum 1.2 mg/d	Anxiety, CNS hyperexcitation	May cause bradycardia and hypotension
Dicyclomine	20 mg IM or PO every 6 h	Abdominal cramping	
Ibuprofen	600 mg PO every 4–6 h	Abdominal pain, myalgias	May cause gastritis
Loperamide	2–4 mg PO every every 6 h, maximum 16 mg/d	Diarrhea	May be misused, and in high doses may cause prolonged QTc interval
Metoclopramide	10 mg IV or PO every 6 h	Nausea, vomiting	
Ondansetron	4–8 mg IV or SL every 8 h	Nausea, vomiting	May cause prolonged QTc interval
Prochlorperazine	2.5 mg - 10 mg IV every 4 h, maximum 40 mg/d	Nausea, vomiting	

[a] These commonly used substances may be considered in the absence of other contraindications and in conjunction with opioid replacement therapy.

following the exposure potentially progressing to fulminant liver failure.[15] Patient history is key to differentiate from other causes. This disease process may be multifactorial, particularly when the patient may also suffer from hepatic dysfunction due to hyperthermia, hypovolemia resulting in poor organ perfusion, and rhabdomyolysis.[15] Treatment is largely supportive but may also include infusions such as N-acetylcysteine when drug-induced liver injury is suspected. Some cases may be fatal or lead to liver transplantation.[15]

CANNABINOIDS

Cannabinoids extracted from the plant *Cannabis sativa* have long been used for proposed medicinal properties in addition to euphoric effects. Although policy in the United States regarding its recreational and medicinal use is constantly evolving, cannabis remains one of the most used substances. THC has the most psychoactive effect of the cannabinoids and plays a role in the potency. Recent findings suggest high THC content in recreational cannabis, in conjunction with prolonged frequent use and dysregulation of the endocannabinoid system plus other factors, contribute to the development of cannabinoid hyperemesis syndrome (CHS).[52]

CHS represents a clinical syndrome of cyclical nausea, vomiting, and abdominal cramping in the setting of chronic cannabis use, typically relieved by taking a hot shower.[53] Patients often seek emergency medical treatment when hot showers no longer provide relief. Although the exact pathophysiology remains uncertain, two

main theories exist: chronic overstimulation of the endocannabinoid receptors leading to derangements in intrinsic control of nausea and vomiting from central and peripheral sources and inactivation of the transient receptor potential vanilloid 1 nociceptor system in the peripheral nervous system.[53] CHS might respond to supportive care and usual anti-emetics. Some evidence supports capsaicin cream and haloperidol.[52,54] Cessation of cannabis use usually results in full recovery.[52]

There have been several case reports of cannabinoid-associated pancreatitis, the pathophysiology of which seems to be poorly understood.[55–57] Endocannabinoid receptors are found on the islet of Langerhans cells in the pancreas, and agonism at those receptors from exogenous cannabinoids likely plays a role.[58]

COCAINE

Cocaine is extracted from *Erythroxylum coca.* Cocaine is highly addictive, and its users may experience euphoria, sympathomimetic effects, CNS stimulation, vasoconstriction, vasospasm, and thrombus formation. Abdominal pain overall seems to be relatively infrequent in the cocaine user and are most likely to be associated with vascular pathologies.

Intestinal ischemia secondary to cocaine use has been reported and can cause significant morbidity and mortality.[59,60] The exact pathogenesis of organ ischemia remains unclear, but the theoretic etiology is profound mesenteric vasoconstriction.[61] Deep ulcerations of the gut may also occur and result in significant gastrointestinal bleeding or perforation of a viscus.[61–63] Patients with viscus perforation typically present with sudden, sharp epigastric pain with occasional referred shoulder pain.[61] Less commonly, they present with nausea, vomiting, and diarrhea with vague abdominal discomfort. The pathogenesis has yet to be fully elucidated, but consideration is given to focal ischemia secondary to vasoconstriction.[64]

Hepatic necrosis resembling ischemic hepatitis may occur following cocaine use, although there is some speculation that toxic cocaine metabolites may directly contribute.[15,65] Patients may have evidence of hepatotoxicity following an acute overdose.[65] Reported cases include elevated liver transaminases, elevated lactate dehydrogenase, elevated INR, and potential progression to fulminant liver failure or death.[66–68] One case noted an associated thrombotic microangiopathy with cocaine-induced acute hepatitis.[68] Hepatic injury in a patient with a cocaine use history may be multifactorial including damage from common hepatotoxins such as acetaminophen, other substances of abuse, adulterants or concomitant development of viral hepatitis from injection drug use.[69,70]

Lastly, there are rare reports of cocaine-associated pancreatitis, although this is quite difficult to isolate. Pathophysiology is multifactorial. It is thought to be the result of vasoconstriction and thrombotic microangiopathy of the mesenteric vessels, presynaptic nerve endings with elevated amounts of norepinephrine or indirectly related to levamisole-adulterated cocaine leading to an associated vasculitis.[59,70,71] Patients may present with typical signs and symptoms of pancreatitis as previously denoted. Other etiologies of pancreatitis must be considered before making this diagnosis.

Appropriate control, benzodiazepines as needed, avoidance of beta-adrenergic antagonists, and surgical consultation should be highly considered in the aforementioned cases.

KETAMINE AND PHENCYCLIDINE

Chronic ketamine use has been associated with abdominal and pelvic pain, usually from a urologic cause and potentially manifesting as hemorrhagic cystitis.[72] Less

commonly, gastrointestinal pathology such as cholestasis, biliary dyskinesia, and upper abdominal pain with symptoms of gastritis has been described.[72] Elevated transaminases may signify hepatobiliary dysfunction from ketamine.[73] Abstinence from ketamine use should lead to recovery.

Phencyclidine is a similar xenobiotic with mostly CNS manifestations in acute toxicity and is not known to be directly toxic to the gastrointestinal tract. However, hyperthermia, hypovolemia and hypoxia may occur and lead to ischemic hepatitis.[74] Treatment is largely supportive.

RECOMMENDATIONS

As with any patient with abdominal pain, the approach to diagnosis and management needs to remain broad until a thorough history, physical examination, and testing can exclude emergent conditions, narrow the focus and management to the determined diagnosis. Patients with substance use disorders need to be approached in such a way that the physician or provider can establish good rapport, and the patient does not feel the stigma that can arise with a substance use disorder. Consultation and or referral to an addiction specialist to aid in management of the substance use disorder will be helpful to address and try to prevent any recurrence of disease.

SUMMARY

Patients with substance use disorders present commonly to the ED for illnesses related to their substance use. Often these illnesses include abdominal and gastrointestinal complaints. Alcohol use disorder and patients with OUD can have a wide range of diagnoses leading to ED visits such as gastritis, hepatitis, motility dysfunction, and pancreatitis. These patients should have complete history, physical examination, laboratory, and imaging studies to evaluate gastrointestinal emergencies based on their chief complaints. Treatment should focus on symptom relief or control and management of the underlying etiology of their illness. Patients should be assessed for motivation to seek aid for their substance use disorders as both a treatment and prevention of future episodes of illness.

CLINICS CARE POINTS

- Alcoholic liver disease exists on a spectrum with minimal gastrointestinal symptoms to near-death from upper gastrointestinal hemorrhage
- In the absence of other risk factors or obvious causes, use of cocaine and amphetamine derivatives may be implicated in hepatic ischemia, bowel ischemia, and viscus perforation
- Cannabinoids and cocaine have rarely been associated with pancreatitis
- With significant hepatotoxicity or hepatic failure of unclear etiology, consideration should be given to hepatitis or chronic use of hepatotoxins such as ethanol, MDMA, cocaine, amphetamines, or acetaminophen-containing compounds
- Hyperalgesia resulting from chronic opioid use can be associated with narcotic bowel syndrome and opioid withdrawal
- Aggressive bowel regimens for patients on chronic opioids should be considered
- Symptomatic and supportive care are the mainstays of treatment in opioid withdrawal which often manifest with abdominal complaints, although consideration should be given to medication-assisted treatment in the right candidate

DISCLOSURE

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