Systemic Complications and Radiographic Findings of Opioid Use and Misuse: An Overview for Orthopedic Surgeons

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Abstract Amid growing concern about the misuse of prescribed opioids, the rising rates of opioid use disorder, and the use of illicit opioids, clinicians in ambulatory, inpatient, and operative environments are encountering opioid-related complications in their patients. These complications can affect multiple organ systems including cardiovascular, pulmonary, gastrointestinal, and neurologic and are related to excess opioid levels in the body or contamination from non-sterile injection. It is important for the orthopedic surgeon to have a general understanding of the pathologies associated with opioid use disorder and their appearance on diagnostic imaging. This article reviews image findings of several complications, organized in a systems-based approach, for the orthopedic surgeon.

Keywords opioids · diagnostic imaging · complications of opioid use · infective endocarditis · arterial/mycotic pseudoaneurysm · noncardiogenic pulmonary edema

Introduction

Beginning in the early 2000s, when pain came to be known as the “fifth vital sign” and the number of prescribed opioids rose dramatically, visits to US emergency departments related to opioid use and misuse increased, as well. In 2014, 18,893 people died from overdose to prescription opioids, and in 2015 there were 33,091 overdoses to prescribed and illicit opioids [25]. Although the USA represents less than 5% of the global population, Americans consume 80% of the global opioid supply, 99% of the global hydrocodone supply, and about two-thirds of all illegal drugs [16]. The Centers for Disease Control and Prevention (CDC), which tracks overdose-related deaths, reported that between 2012 and 2014 the rates of fentanyl-related deaths more than doubled, and approximately 41% of heroin-related deaths involved fentanyl [11]. The rising rates of complications and deaths related to synthetic opioids stem from their higher potency (50 to 100 times more potent than morphine) and lower costs; illicit fentanyl costs about \$3500 per kilogram, compared to \$65,000 per kilogram for heroin [11].

Patients with non-fatal opioid-related conditions and complications often present to the emergency department; these complications may include cardiovascular, pulmonary, gastrointestinal, and neurologic sequelae. Often, such complications result from the effect of potent opioids on the central nervous system and/or contamination from opioid injection. Emergency department physicians and radiologists are at the forefront of diagnosing and managing comorbidities related to opioid misuse [2], but orthopedic

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Fig. 1. Echocardiogram images show tricuspid valve vegetation (arrow) in an intravenous drug-using patient. Moderate tricuspid valve regurgitation was noted.

surgeons may also treat hospitalized patients with dangerous complications of opioid use disorder. The following radiographic image findings, showing pathologies seen in orthopedic patients, are designed to benefit orthopedic surgeons who are part of multidisciplinary teams managing patients with complex conditions and possible opioid use disorder.

Cardiovascular Complications

Cardiovascular complications of opioid use disorder may include infective endocarditis and mycotic aneurysm.

Infective Endocarditis

Infective endocarditis has a reported prevalence of 37.8% of patients who are intravenous (IV) drug users and results

Fig. 2. Computed tomography of the abdomen and pelvis with intravenous contrast demonstrates a mycotic aneurysm centered in the upper abdominal aorta with a surrounding inflammatory rind (arrows). The flowing lumen had increased nearly 2 cm in 2 weeks.

Fig. 3. Chest computed tomography with intravenous contrast shows a thick pneumonia within the superior segment of the right lower lobe of the lung (arrows). This is the classic location for aspiration pneumonia.

from self-injection using non-sterile needles [12]. *Staphylococcus aureus* is the most common infecting organism leading to septicemia and eventual cardiac valve damage from bacterial vegetation. Given the flow of venous blood returning to the heart, the tricuspid valve is most commonly affected [17, 21]. Bacterial vegetation of the heart valve can be readily detected on transthoracic echocardiography (Fig. 1). Early detection can prevent complications arising from septic emboli to the lungs, systemic vasculature, and brain [9].

Fig. 4. Anteroposterior portable radiograph demonstrates a young intravenous drug user with acute respiratory distress syndrome with severe hypoxemia and the need for mechanical ventilatory support (arrow). This was the sequela of noncardiogenic pulmonary edema (NPE), defined as evidence of alveolar fluid accumulation and a normal-size cardiac silhouette (dotted arrows), suggesting the absence of hemodynamic compromise. NPE can occur following intravenous injection of cocaine and, more commonly, opioids, as in this case.

Fig. 5. Septic emboli are seen on computed tomography of the chest with contrast in a 26-year-old IV drug user, who presented with fever, pleuritic chest pain, shortness of breath, productive cough, and hemoptysis. Echocardiography demonstrated tricuspid vegetation. Multiple peripheral, broad-based, mass-like densities with central lucencies in a multilobar and peripheral distribution (arrows) are suggestive of septic emboli.

Mycotic Aneurysm

Mycotic aneurysms develop from bacterial infection in blood vessel walls. The most commonly reported cause of mycotic aneurysms is infective endocarditis [7]. Clinical suspicion of a mass on imaging in a patient who is an IV drug user should warrant diagnostic testing with a computed tomographic (CT) arteriogram (Fig. 2). Affected large vessels include the pulmonary arteries, aorta, mesenteric arteries, and intracranial arteries forming the circle of Willis [2].

Pulmonary Complications

Pulmonary complications may include respiratory depression, pneumonia, noncardiogenic pulmonary edema, septic pulmonary emboli, iatrogenic lung injury, or pulmonary fibrosis.

Respiratory Depression

Opioid-induced respiratory depression results from respiratory inhibition within the brainstem [5]. All routes of opioid ingestion (including sniffing, snorting, smoking, and injection) can cause respiratory depression. Complications can include aspiration pneumonia, noncardiogenic pulmonary edema, and death [19].

Fig. 6. **a** Coronal reformatted computed tomography (CT) of the neck demonstrates a linear foreign body (arrow), near the subclavian vein, in a 50-year-old intravenous drug user. The patient reported a history of a broken needle tip. **b** CT scan of the chest demonstrates talc (arrow) at the right lung base, initially passed as the rib. **c** Posteroanterior radiograph of the same patient demonstrates a left apical pneumothorax, with displaced pleura (arrowheads), after the patient reported an attempted subclavian vein needle puncture. **d** Magnified anteroposterior view of the left lung apex more clearly defines the pneumothorax (arrowheads).

Fig. 7. Pulmonary fibrosis. **a** Posteroanterior chest radiograph of an intravenous drug user with idiopathic pulmonary fibrosis shows diffuse, bilateral peripheral subpleural reticular opacities (arrows) and lower lung predominant distribution of the abnormalities. **b** Computed tomography of the chest without contrast demonstrates extensive basilar honeycombing (black dotted circles). These findings are consistent with pulmonary fibrosis.

Pneumonia

There is an increased prevalence of bacterial pneumonia among people who inject opioids [22], although this is not exclusive to IV drug users. A recent study reported that

elderly individuals prescribed opioids had a 38% increased risk of pneumonia compared to those who were not prescribed opioids [10]. Aspiration pneumonia can be diagnosed on radiograph or non-contrast chest CT scan (Fig. 3).

Fig. 8. Body packing. **a** Anteroposterior radiograph of the abdomen shows multiple intra-abdominal high density tubular structures (dotted circles) consistent with body packing. Dilated small bowel loops in the upper abdomen are secondary to bowel obstruction. **b** Coronal and **c** axial computed tomography re-demonstrate the packets of heroin in the small bowel with retrograde dilated small bowel loops (dotted arrow) with small obstruction and fat stranding in the mesenteric fat (arrowheads).

Fig. 9. Anteroposterior radiograph shows abundant retained stool in the large bowel (dotted arrows) and rectum (arrows) consistent with constipation.

Fig. 10. Ogilvie syndrome. Anteroposterior radiograph demonstrates colonic dilation involving the right colon (arrow) and cecum (dotted arrow) with no evidence of mechanical obstructive cause.

Noncardiogenic Pulmonary Edema

The mechanism of noncardiogenic pulmonary edema among those who misuse opioids is unknown, although one theory proposes that central nervous system depression in the mid-brain leads to neurogenic pulmonary edema. One study reported that 10% of patients with symptoms of opioid overdose had radiographic evidence of noncardiogenic pulmonary edema [21]; findings include bilateral perihilar air-space opacification (Fig. 4) without pleural effusions or enlargement of the cardiac silhouette as seen in patients with heart failure. Radiographic abnormalities of edema typically resolve within 24 to 48 h after onset of treatment. Longer-acting opioids such as methadone may have a more delayed resolution of radiographic findings [24].

Septic Pulmonary Emboli

Infective endocarditis among IV drug users raises risk for septic pulmonary emboli. Non-specific clinical symptoms such as fever may delay diagnosis; nevertheless, clinical signs of IV drug use, infective endocarditis, and pulmonary complications should raise concern for septic pulmonary emboli [2]. Diagnosis is made with cross-sectional CT imaging to reveal peripheral pulmonary nodules with cavitation (Fig. 5).

Acute Lung Injury

One method of injecting opioids is crushing oral tablets containing talc and other fillers and suspending the particles in injectable solvent. These undissolved microparticles can embolize to the lungs and develop into foreign-body granulomas, which may appear on imaging similarly as a neoplasm (Fig. 6a, b). Damaged peripheral veins, from chronic IV administration, can lead individuals to make use of the larger vessels such as the supraclavicular vein, known as a “pocket shot,” that greatly increases the risk of lung puncture and pneumothorax (Fig. 6c, d) [2].

Pulmonary Fibrosis

Chronic heroin use has been attributed to endothelial injury and embolization of the small pulmonary vessels leading to pulmonary hypertension and interstitial granulomas, increasing the risk of interstitial pulmonary fibrosis [19]. Radiographs demonstrate reticular or reticulonodular opacities at the lung bases (Fig. 7a). The best imaging modality is a high-resolution CT to determine the extent of lung disease (Fig. 7b) [13]. Patients are particularly susceptible to acute respiratory decompensation secondary to blood clots, pneumonia, aspiration, and lung collapse.

Gastrointestinal Complications

Gastrointestinal complications of opioid use may include intracorporal concealment of drugs, constipation, or pseudo-obstruction.

Fig. 11. A 57-year-old man developed acute leukoencephalopathy after “chasing the dragon”—inhaling heroin vapor. Magnetic resonance imaging (a) and (b) shows diffuse white matter hyperintensity on fluid-attenuated inversion recovery with symmetrical butterfly wing pattern of the cerebellar white matter (arrows) and sparing of adjacent gray matter structures.

Intracorporal Concealment of Drugs

Intracorporal concealment of drugs, colloquially referred to as “body packing,” involves the storage of drugs within a plastic package that can be swallowed or inserted into the vagina or rectum (Fig. 8) [2]. Rupture of the drug package exposes the

person to dangerously high levels of opioids, posing significant risk of respiratory depression and sudden death. Small bowel obstruction from the drug package can also occur.

Fig. 12. Diffuse cerebral edema related to hypoxia. Axial computed tomography of the brain shows diffuse hypodensity of the brain parenchyma with absent differentiation of corticosubcortical matter.

Fig. 13. Pseudo-subarachnoid hemorrhage in hypoxic brain. Axial non-enhanced computed tomography shows diffusely low-density supratentorial region of the brain, with complete obliteration of all sulci and subarachnoid spaces. Note how hypodense brain makes middle cerebral arteries (arrows) appear hyperdense and thus mimic subarachnoid hemorrhage.

Fig. 14. Brain abscess. **a** Axial T1-weighted magnetic resonance imaging (MRI) in a 24-year-old intravenous drug user with a 5-day history of flu-like illness and increasing headache shows a predominately hypointense mass (arrow) with a surrounding hypointense rim (dotted arrow). **b** Axial T1 post-contrast MRI demonstrates peripheral nodular enhancement of the mass. **c** Fluid-attenuated inversion recovery MRI demonstrates surrounding vasogenic edema (arrow).

Constipation

Constipation is a common complication of opioid use [4]. Chronic and severe constipation can lead to hemorrhoids, rectal pain and burning, bowel obstruction, and bowel rupture, which can lead to death [3]. Plain abdominal radiographs may demonstrate the extent of fecal impaction and of impacted stool in the sigmoid colon and rectum (Fig. 9). In a retrospective study involving 677 patients who underwent orthopedic surgery, Lee et al. found severe constipation to be an independent risk factor for post-operative ileus in patients who undergo orthopedic surgery [15]. Also, a retrospective study of 402 patients examining the relationship between adverse effects of opioid use and post-operative hospital length of stay (LOS) reported that constipation, emesis, and confusion were associated with increased LOS in patients who received opioids after orthopedic surgery [20].

Pseudo-Obstruction

Acute colonic pseudo-obstruction (Ogilvie syndrome) is a result of colon dilation without an anatomic or mechanical obstruction. Opioid-induced pseudo-obstruction results from impairment of the parasympathetic response, resulting in an atonic distal colon and functional proximal obstruction [18, 26]. Upright abdominal radiographs demonstrate a dilated colon, often from the cecum to the splenic flexure, with normal haustral markings (Fig. 10). Orthopedic surgeons must be aware of and monitor for signs of pseudo-obstruction, as an increasing colonic diameter resulting in increased tension on the colonic wall may lead to colonic ischemia and perforation [23].

Neurologic Complications

Neurologic complications of opioid use may include heroin-induced leukoencephalopathy, hypoxic ischemic brain injury, or brain abscess.

Heroin-Induced Leukoencephalopathy

Toxic leukoencephalopathies are toxin-related pathologies affecting the white matter of the brain. One such example is heroin-induced leukoencephalopathy (HIL), a rare and devastating disease with a 23% estimated mortality rate [14]. HIL has distinct pathological findings on imaging studies (Fig. 11) including extensive and symmetrical lesions in the white matter, mainly in the cerebellum, posterior limb of internal capsule, splenium of the corpus callosum, parietal lobe, and occipital lobe [27].

Hypoxic Ischemic Brain Injury

Respiratory depression from excess opioid use can lead to both short-term and long-term brain hypoxia and ischemia, exposing neurons to potentially harmful reductions of oxygen needed for homeostasis and metabolism. Cerebral edema can be seen on CT as diffuse decreased attenuation of the cerebral cortex with loss of gray–white matter distinction (Fig. 12) [8]. Additionally, CT image findings of pseudo-subarachnoid hemorrhage can occur and are caused by cerebral swelling due to acute hypoxic–anoxic encephalopathy, leading to increased attenuation in the basal cisterns and subarachnoid spaces on CT (Fig. 13). These findings can appear similar to those of acute subarachnoid hemorrhage [1].

Brain Abscess

Sepsis and hematogenous spread of bacteria, a consequence of contaminated needles in IV drug use, can reduce the number of astrocytes in the basal lamina, disrupting the blood–brain barrier, leading to cerebral infection and brain abscess [2, 6]. Brain abscess demonstrates a fairly classic pattern on CT and magnetic resonance imaging with surrounding edema and an enhancing capsule (Fig. 14).

Conclusion

The US opioid epidemic is a complex and pressing issue. Mitigation will require the combined efforts of healthcare providers and government agencies. Because orthopedic surgeons often prescribe opioids to alleviate acute post-operative pain, they share the concern over patients' potential misuse of prescribed or illicit opioids. Knowledge of the radiographic and advanced image findings associated with clinical pathologies and complications of opioid use and misuse will help orthopedic surgeons better understand non-fatal complications of opioid use disorder, which also may result in a different approach to treating orthopedic patients.

Compliance with Ethical Standards

Conflict of Interest: Harry G. Greditzer IV, MD, Dustin H. Massel, MD, Carlos M. Barrera, BS, Nisreen Ezuddin, BS, Christopher P. Emerson, MS, and Jean Jose, DO, MS, declare that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Informed Consent: Informed consent was waived from all patients for being included in this review.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Agha A, Al-Hakami M. A case report of pseudo-subarachnoid hemorrhage. *Maedica (Buchar)*. 2011;6(3):210–212.
2. Bates DDB, et al. Acute radiologic manifestations of America's opioid epidemic. *Radiographics*. 2018;38(1):109–123.
3. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2 Suppl):S105–120.
4. Boland JW, Boland EG. Pharmacological therapies for opioid induced constipation in adults with cancer. *BMJ*. 2017;358:j3313.
5. Boom M, Niesters M, Sarton E, Aarts L, Smith TW, Dahan A. Non-analgesic effects of opioids: opioid-induced respiratory depression. *Curr Pharm Des*. 2012;18(37):5994–6004.
6. Buttner A, Weis S. Neuropathological alterations in drug abusers: the involvement of neurons, glial, and vascular systems, *Forensic Sci Med Pathol*. 2006;2(2):115–126.
7. Carmelli G, Surles T, Brown A. Endophthalmitis and mycotic aneurysm: the only clues to underlying endocarditis. *Clin Pract Cases Emerg Med*. 2018;2(1):16–20.
8. Chaudhry AA GM, Baker KS, Gould ES. Radiologic manifestations of recreational drug abuse. *Contemp Diagn Radiol*. 2016;39(4):1–8.
9. Chou DW, Wu SL, Chung KM, Han SC, Cheung BM. Septic pulmonary embolism requiring critical care: clinicoradiological spectrum, causative pathogens and outcomes, *Clinics (Sao Paulo)*. 2016;71(10):562–569.
10. Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc*. 2011;59(10):1899–1907.
11. Frank RG, Pollack HA. Addressing the fentanyl threat to public health. *N Engl J Med*. 2017;376(7):605–607.
12. Hartman L, Barnes E, Bachmann L, Schafer K, Lovato J, Files DC. Opiate injection-associated infective endocarditis in the Southeastern United States. *Am J Med Sci*. 2016;352(6):603–608.
13. Hidalgo A, Franquet T, Gimenez A, Bordes R, Pineda R, Madrid M. Smoking-related interstitial lung diseases: radiologic-pathologic correlation. *Eur Radiol*. 2006;16(11):2463–2470.
14. Hill MD, Cooper PW, Perry JR. Chasing the dragon—neurological toxicity associated with inhalation of heroin vapour: case report. *CMAJ*. 2000;162(2):236–238.
15. Lee TH, Lee JS, Hong SJ, et al. Risk factors for postoperative ileus following orthopedic surgery: the role of chronic constipation. *J Neurogastroenterol Motil*. 2015;21(1):121–125.
16. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids, *Pain Physician*. 2008;11(2 Suppl):S63–S88.
17. Moreillon P, Que YA, Bayer AS. Pathogenesis of streptococcal and staphylococcal endocarditis. *Infect Dis Clin North Am*. 2002;16(2):297–318.
18. Ogilvie WH. William Heneage Ogilvie 1887–1971. Large-intestine colic due to sympathetic deprivation. A new clinical syndrome. *Dis Colon Rectum*. 1987;30(12):984–987.
19. Peroš-Golubičić T, Sharma O. Drug addict's lung. *Clinical Atlas of Interstitial Lung Disease*. London: Springer; 2006.
20. Pizzi LT, Toner R, Foley K, et al. Relationship between potential opioid-related adverse effects and hospital length of stay in patients receiving opioids after orthopedic surgery. *Pharmacotherapy*. 2012;32(6):502–514.
21. Radke JB, Owen KP, Sutter ME, Ford JB, Albertson TE. The effects of opioids on the lung. *Clin Rev Allergy Immunol*. 2014;46(1):54–64.
22. Roy S, Ninkovic J, Banerjee S, et al. Opioid drug abuse and modulation of immune function: consequences in the susceptibility to opportunistic infections. *J Neuroimmune Pharmacol*. 2011;6(4):442–465.
23. Saunders MD. Acute colonic pseudoobstruction. *Curr Gastroenterol Rep*. 2004;6(5):410–416.
24. Schaaf JT, Spivack ML, Rath GS, Snider GL. Pulmonary edema and adult respiratory distress syndrome following methadone abuse. *Am Rev Respir Dis*. 1973;107(6):1047–1051.
25. Soelberg CD, et al. The US opioid crisis: current federal and state legal issues. *Anesth Analg*. 2017;125(5):1675–1681.
26. Vanek VW, Al-Salti M. Acute pseudo-obstruction of the colon (Ogilvie's syndrome). An analysis of 400 cases. *Dis Colon Rectum*. 1986;29(3):203–210.
27. Yin R, Lu C, Chen Q, Fan J, Lu J. Microvascular damage is involved in the pathogenesis of heroin induced spongiform leukoencephalopathy. *Int J Med Sci*. 2013;10(3):299–306.