

# A Brief History of Opioid-Use Disorder in the United States, Effect on Orthopaedics, and Current Management Options

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## ABSTRACT

Declared a public health emergency in 2017 and leading to 11 million years of life lost worldwide, the American opioid crisis has impacted millions of people, with up to 7 million experiencing opioid use disorder. In orthopaedic surgery, opioid analgesia has been associated with various complications, including infections, deep vein thrombosis, prolonged hospital stays, and overall inferior outcomes after surgical procedures. Orthopaedic surgeons commonly rely on opioids to provide postoperative analgesia and may frequently encounter patients with opioid use disorder. It is therefore essential that orthopaedic surgeons understand opioid use disorder, its effect on orthopaedic outcomes, and management of opioid use disorder in the context of surgical procedures. This review provides a background on opioid use disorder, a brief history of the American opioid epidemic, an overview of medications used to manage opioid use disorder, and recommendations on the management of these medications in the perioperative period.

**Keywords:** Buprenorphine; Methadone; Naloxone; Opioid, Opioid-Related Disorders

## INTRODUCTION

Defined as the chronic use of opioids that causes significant stress or impairment, opioid use disorder (OUD) affects 7 million people in the United States and up to 26.8 million people worldwide.<sup>1-3</sup> It impacts people of all socioeconomic, ethnic, and educational backgrounds, is associated with a 20 times greater risk of early death, and has led to a cumulative 11 million years of life lost worldwide.<sup>4</sup> The United States accounts for only 4.4% of the world's population, but 80.0% of its opioid consumption. More people in the United States have died as a result of opioid overdose than any other drug class in the nation's history, increasing six-fold between 1999 and 2021. Gomes et al<sup>5</sup> performed a cross-sectional study to evaluate opioid-related mortality before and after the COVID-19 pandemic, from 2011 to 2021. They found a 63.0% increase from 2019 to 2021, highlighting the alarming interplay between the pandemic and OUD. In 2021 alone, 107,000 people died from an opioid overdose in the United States, accounting for 75.0% of the nation's overdose deaths and leading to a decrease in national life expectancy of 0.67 years in 2022.<sup>3</sup>

Orthopaedic surgery is the third highest opioid-prescribing specialty, accounting for 7.7% of the United States' opioid prescriptions.<sup>6-9</sup> Multiple studies have demonstrated that opioids are overprescribed postoperatively following orthopaedic procedures, with patients often using less than half of their prescribed

amount.<sup>6-9</sup> Furthermore, a majority of patients report that they are unaware of how to safely dispose of their unused opioids, which can lead to increased risk of misuse.<sup>6-8</sup> Even when used within normal prescribing guidelines, preoperative and postoperative opioid use has consistently been associated with inferior postoperative outcomes after orthopaedic surgeries, including longer length of stay, higher rates of infection and deep vein thrombosis, increased long-term pain, worse functional scores, and other complications.<sup>10-13</sup> Given these associated risks, various studies have examined non-opioid multimodal pain protocols, reporting promising results.<sup>14,15</sup>

As opioids have become more commonly prescribed, and with OUD rising in prevalence, it is not infrequent that the orthopaedic surgeon will encounter patients with OUD. An increasing number of these patients may be prescribed medication for opioid use disorder (MOUD), such as buprenorphine, methadone, or Suboxone™, among others. While these medications effectively reduce mortality in OUD patients by curbing cravings, little research has explored their optimal management in the perioperative orthopaedic setting, including preoperative and postoperative care.<sup>16</sup> Therefore, there are very few established guidelines for managing pain and maintenance medications for patients with OUD who undergo either elective or nonelective orthopaedic procedures.

The purpose of this review is to provide an overview of the American opioid crisis, its impact on orthopaedic patients, and to review available guidelines for the management of patients with OUD undergoing orthopaedic surgery.

## A BRIEF HISTORY OF THE OPIOID CRISIS

Morphine, a natural opioid derived from the opium poppy, was first manufactured during the American Industrial Revolution in the 1830s and quickly became a mainstay of acute and chronic pain control.<sup>17</sup> It was not until the 1870s that the first widespread concerns were raised regarding the potential for morphine addiction. By 1898, heroin was developed and marketed as a cough suppressant and treatment for morphine addiction. After heroin, other semi-synthetic opioids including hydrocodone, methadone, and combinations with acetaminophen, were introduced. In 1971, the Food and Drug Administration (FDA) approved naloxone, a potent opioid antagonist, for treatment of opioid overdose.

In the 1990s, the American pharmaceutical market became flooded with newly formulated opioids, including OxyContin™ by Purdue Pharmaceuticals in 1995, which was heavily marketed as a safe and potent pain reliever.<sup>18</sup> Just one year after the release of OxyContin™, the American Pain Society promoted pain as the “fifth vital sign,” encouraging pain to be addressed with the same importance as basic vital signs such as heart rate, blood pressure, and temperature.<sup>19</sup> This was quickly adopted by major medical systems including the American Veterans Health Administration, the National Pharmaceutical Council, and the Joint Commission for the Accreditation of Healthcare Organizations.<sup>20</sup> These factors all contributed to a sharp rise in the prescription and sale of opioids, which quadrupled between 1999 and 2010. This was accompanied by a dramatic increase in opioid-related deaths, rising from 2.9 to 6.8 deaths per 100,000 people.<sup>18</sup> This rise in prescription-opioid deaths has since been labeled the “first wave” of the American opioid epidemic.<sup>18</sup>

In the early 2010s, the cost of heroin dropped as its production shifted from China and South America to Mexico. This resulted in decreased production costs, increased supply, and contributed to a nearly five-fold increase in heroin-related deaths between 2010 and 2018.<sup>18</sup> In this “second wave,” heroin remained the leading cause of American opioid-related deaths until 2016 when fentanyl, a fully synthetic opioid, surpassed it for the first time. Fentanyl supply increased due to advances in illicit manufacturing process; this rise in supply resulted in the “third wave,” and consequently, opioid overdoses soared from 10.4 to 21.4 deaths per 100,000 people between 2015 and 2020.<sup>18</sup> The United States government declared the opioid crisis a public health emergency in 2017, leading to a series of congressional initiatives, including dedicated funding

for harm reduction strategies, naloxone access, and MOUD.<sup>17,18</sup> These efforts have led to a decrease in overall opioid-related deaths from 2023 to 2024, reaching their lowest since 2020.<sup>21</sup> Most recently, a “fourth wave” of challenging substance-use disorders has emerged with the rise of easily derived synthetic stimulants and tranquilizers (eg, methamphetamine, xylazine) packaged in combination with synthetic opioids.<sup>22,23</sup>

## OPIOIDS IN ORTHOPAEDIC SURGERY

In recent years, there has been particular focus on the impact of opioid use on outcomes following orthopaedic procedures. This literature has consistently demonstrated that preoperative and/or prolonged postoperative opioid use is associated with greater postoperative analgesic needs, increased postoperative pain, less functional improvement from surgery, and a higher rate of complications across all orthopaedic subspecialties.<sup>10,11,24-27</sup> While not comprehensive, a summary of relevant literature can be found in Appendix 1.

## MEDICATION FOR OPIOID USE DISORDER

Many treatments, including medications, behavioral therapies, harm-reduction strategies, and symptomatic treatment of withdrawal symptoms have proven beneficial for OUD.<sup>4</sup> The optimal treatment of OUD for many patients likely encompasses multiple or all of these modalities. The focus of this review is on common medications used in the treatment of OUD, and the way that they should be managed preoperatively and postoperatively in orthopaedic surgery. It is important to note that given the scarcity of research specific to orthopaedics, most of the recommendations are derived from other surgical specialties. The primary findings of this section are summarized in Appendix 2.

### Methadone

Used in the treatment of OUD since the 1950s and proven to reduce the risk of overdose death by 59%, methadone is likely the longest-standing MOUD still routinely encountered by healthcare providers today.<sup>28</sup> As a synthetic, full opioid agonist, methadone fully activates mu-opioid receptors in the brain and functions by reducing cravings.<sup>29</sup> Methadone’s long half-life reduces withdrawal symptoms and blunts the euphoria of short-acting opioids like heroin and fentanyl. Unlike some treatments, it can be initiated without prior withdrawal, even during hospitalization. As a full agonist, missed doses can still cause withdrawal, and excessive doses may lead to respiratory depression. Methadone requires days to weeks to reach a therapeutic dose and therefore must be carefully adjusted to avoid withdrawal or overdose. Methadone can only be prescribed to patients enrolled in state and federally-certified opioid treatment programs.<sup>29</sup> However, exceptions are made for patients admitted to a hospital for other conditions.

In most situations, methadone should be continued at the patient's standard dose throughout the perioperative period when undergoing surgical procedures. If the patient is unable to tolerate oral medications, intravenous methadone can be administered at one half to two thirds of their normal maintenance dose.<sup>30</sup> Additional opioid and non-opioid analgesics can be added as needed for uncontrolled pain. It should be noted that attempting to replace methadone with other opioids based on morphine-equivalents is often inaccurate given its longer half-life compared to shorter-acting opioids.<sup>30</sup>

### **Buprenorphine-Based Therapies**

Buprenorphine was first released in the United Kingdom in 1978 as a pain reliever and was approved for treatment of OUD in the United States in 2002. This medication has a high-affinity partial agonist at the mu-opioid receptor as well as a weak kappa-receptor antagonist and delta-receptor agonist. Receptor interactions lead to reduced opioid cravings in patients who experience OUD while offering a safe treatment that has been shown to decrease overdose deaths in patients experiencing OUD by 38.0%.<sup>28</sup> Unlike methadone, it exhibits a "ceiling effect," meaning that respiratory and cardiac depression does not change with doses exceeding 24 milligrams, making it less likely to lead to overdose.<sup>31</sup> In higher doses, buprenorphine also exhibits greater antagonistic qualities, leading to a plateau effect on analgesia. However, it may still lead to respiratory depression, dependence, and other side effects related to opioids, especially when taken in high amounts for acute pain. Also in contrast to methadone, patients are required to abstain from using all long-acting opioids for at least 48 hours to 72 hours, and short-acting opioids 12 hours prior to initiating buprenorphine, as it can precipitate withdrawal.<sup>32</sup> This makes buprenorphine difficult to initiate in the inpatient setting. Buprenorphine is often prescribed as a formulation with naloxone, named Suboxone™. Because naloxone, a potent mu-opioid receptor antagonist, is inhibited when taken orally but fully active when injected, Suboxone™ may have a lower rate of misuse versus buprenorphine alone.

For patients taking buprenorphine prior to surgery, recommendations depend on the dose taken pre-operatively and the level of pain expected post-operatively. If the surgery is relatively minor and expected pain is low, it is recommended that patients continue buprenorphine at their baseline dose through the perioperative and postoperative period.<sup>33</sup> Rather than adding additional opioids, providers should use adjuncts such as anti-inflammatories, regional anesthetics, and acetaminophen if possible. If surgery is expected to cause relatively higher pain and is elective, the procedure should be postponed until the patient is weaned to 8 milligrams to 12 milligrams of buprenorphine daily. In emergent surgical cases for patients taking less than 8 milligrams to 12 milligrams

of buprenorphine daily, providers should continue the normal buprenorphine dose, but may also consider adding supplemental opioids if pain control is inadequate.<sup>30</sup> Providers should keep in mind that the patient may have a high opioid requirement to overcome the buprenorphine mu-receptor blockade. In patients taking higher doses of buprenorphine preoperatively, providers may consider lowering the postoperative dose but should not decrease to fewer than 8 milligrams to 12 milligrams per day, as this may precipitate opioid overdose by flooding receptors with stronger agonists.<sup>33</sup> Finally, some authors have recommended replacing buprenorphine with methadone in the perioperative period, due to the stronger analgesic effect of the latter.<sup>30</sup>

### **Naloxone**

Naloxone is a potent, fast-acting nonselective opioid receptor antagonist used to quickly reverse opioid overdose that has been approved by the FDA since 1971, available as a prescription since 2015, and available over the counter since 2023.<sup>34,35</sup> It is not used in maintenance treatment of OUD, but orthopaedic surgeons should still be knowledgeable of naloxone in case of need for emergent use in opioid overdose. As previously discussed, it is often combined with buprenorphine to limit misuse.

### **Naltrexone**

Naltrexone is a mu-opioid receptor antagonist as well as a weaker kappa and delta-opioid antagonist that was developed in 1963 and approved for use in the United States in 1984.<sup>36</sup> It is also commonly used in treating alcohol use disorder. It functions by creating a blockade at mu-opioid receptors, therefore preventing opioid intoxication, and comes in both standard and extended-release intramuscular injection.<sup>36,37</sup> However, as a mu-opioid receptor antagonist, it can quickly precipitate severe withdrawal symptoms. For this reason, patients must stop all short-acting opioids (ie, fentanyl, oxycodone) for at least seven days prior to beginning naltrexone, and 14 days for long-acting opioids (ie, methadone).<sup>37</sup> Patients undergoing surgery that is likely to cause significant pain should stop taking naltrexone 48 hours prior to their procedure to allow for adequate postoperative opioid analgesia.<sup>36</sup> Patients taking a long-acting intramuscular naltrexone formulation should stop it 28 days prior to surgery.<sup>36</sup> However, providers should be very cautious in dosing opioids post-operatively, as these patients are at risk for opioid overdose after the mu-opioid receptor blockade is removed.<sup>36</sup> Patients requiring emergent surgical procedures will need to discontinue naltrexone, and may need higher doses of additional opioids postoperatively during the naltrexone wash-out period.<sup>36</sup>

## **MEDICATION MANAGEMENT**

The authors want to acknowledge the difficulty patients may face with discontinuing MOUD in preparation for surgery. Naltrexone, methadone, and Suboxone™ have

been credited with offering significant support for patients who struggle with substance use and improving their quality of life. When undergoing an elective orthopaedic procedure, it is important for the prescribing physician and surgeon to work together to provide education and plan accordingly for the surgery. For example, stable patients who are on long-acting injectables of naltrexone can be switched to an oral formulation, which can be discontinued 48 hours before the procedure.

## CONCLUSION

OD is an increasingly common condition that will be encountered more frequently by orthopaedic surgeons. It is important that orthopaedic surgeons understand how opioids may affect postoperative outcomes in patients with or without opioid use disorder, and become comfortable managing MOUD in the preoperative, perioperative, and postoperative periods. This review discusses a brief history of the opioid epidemic, the effect of opioids and OD on outcomes following orthopaedic procedures, and basic recommendations for the management of MOUD in the context of orthopaedic surgery.

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**Appendix 1. Summary of Literature on Effects of Opioids on Postoperative Outcomes.**

<b>Author(s)</b>	<b>Population of Interest</b>	<b>Findings</b>
Cozowicz et al <sup>10</sup>	National Premier Perspective Database, containing over 1,000,000 lower extremity arthroplasty and 220,000 patients undergoing a spinal fusion	Patients who received the highest amounts of prescribed opioids (the top quartile) had higher rates of DVTs, postoperative infections, urinary, gastrointestinal, and respiratory complications, longer hospital stays, and increased healthcare cost
Brandner et al <sup>11</sup>	Patients undergoing total shoulder arthroplasty	Chronic opiate use led to a higher rate of hospital readmissions, revision surgeries, dislocations, bleeding, and gastrointestinal complications
Brandner et al <sup>11</sup> & Hills et al <sup>12</sup>	Patients undergoing spine surgery	Preoperative opioid use was associated with higher rates of postoperative pain, worse functional outcomes, decreased satisfaction, and increased disability
Curtis et al <sup>24</sup>	Patients undergoing orthopaedic surgery	Higher pain scores reported despite increased opiate medication use perioperatively
Johnson et al <sup>25</sup>	77,573 patients undergoing hand surgery	13.5% of previously opioid-naïve patients continued to take opioids at 90 days following hand surgery
Okoli et al <sup>26</sup>	Patients undergoing common elective orthopaedic surgery	6.0% of previously opioid-naïve patients continued to take opioids at six months postoperatively
Basilico et al <sup>27</sup>	17,961 opioid-naïve patients	The risk of prolonged opioid use after hospital discharge (defined as 90 days) was associated with the quantity of opioids included in the patients' discharge medications, highlighting the need for sparing use of these medications postoperatively

*Deep Vein Thrombosis, DVT*

**Appendix 2. Common Medications for Opioid Use Disorder and Management Recommendations.**

Medication	Mechanism	Advantages	Disadvantages	Recommendation
Methadone	Long-acting mu-opioid agonist	<ul style="list-style-type: none"> <li>• Most proven to reduce overdose deaths in OUD</li> <li>• No opioid cessation required prior to initiation</li> </ul>	<ul style="list-style-type: none"> <li>• Can still lead to respiratory depression and death in high doses</li> <li>• Certification required to prescribe</li> </ul>	Continue preoperative dose through the perioperative and postoperative period. IV methadone should be dosed at one half to two thirds the home dose in settings where patient is unable to tolerate oral medications. Control of postoperative analgesia can be achieved with the addition of opioids and non-opioids.
Buprenorphine/ Suboxone™	High-affinity partial mu-opioid agonist, weak delta-opioid, weak kappa-opioid antagonist	<ul style="list-style-type: none"> <li>• “Ceiling effect” limits respiratory and cardiac side effects</li> <li>• Suboxone™ limits misuse</li> <li>• Prescribed without additional certification</li> </ul>	<ul style="list-style-type: none"> <li>• Can still lead to respiratory depression</li> <li>• Can precipitate withdrawal symptoms in patients actively using other opioids</li> <li>• Need to cease opioid use for 12 hours to 72 hours prior to initiation</li> </ul>	For minor procedures, patients can continue their usual preoperative daily dose. For more extensive procedures, limit the dose to 8 milligrams/day to 12 milligrams/day, with gradual tapering to this level for elective surgeries when possible. In nonelective surgeries, reduce the postoperative dose to 8 milligrams/day to 12 milligrams/day. Breakthrough pain can be managed with additional opioids, non-opioid analgesics, anti-inflammatories, regional anesthetics, and acetaminophen.
Naltrexone	Strong mu-opioid antagonist, weak delta- and kappa antagonist	<ul style="list-style-type: none"> <li>• Prevents opioid intoxication</li> <li>• Not an opioid, does not cause opioid side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Can precipitate withdrawal</li> <li>• Must be off opioids for 7 days to 14 days prior to initiation</li> </ul>	Discontinue naltrexone a minimum of 48 hours before surgery. Long-acting injectables should be discontinued 28 days in advance of elective procedures. Use caution when prescribing opiates postoperatively, due to increased risk of overdose.
Naloxone	Fast-acting nonselective opioid antagonist	<ul style="list-style-type: none"> <li>• Quickly reverses opioid overdose</li> <li>• Over the counter</li> </ul>	<ul style="list-style-type: none"> <li>• Precipitates acute severe withdrawal</li> </ul>	Recommend providing educational resources and a prescription of naloxone to all patients on opiates.

*Intravenous, IV*