Perioperative Considerations for Medications for Opioid Use Disorder

Buprenorphine, Methadone, or Naltrexone

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KEYWORDS

- Buprenorphine • Methadone • Naltrexone • Perioperative
- Multimodal pain management • Opioid use disorder • Addiction relapse
- Initiation of MOUD

KEY POINTS

- Buprenorphine and methadone for the treatment of opioid use disorder should be continued in the perioperative period.
- Oral naltrexone should be discontinued 2 to 3 days and extended-release injectable naltrexone should be discontinued 28 days before surgery and resumed 7 to 10 days after the last opioid dose.
- Multimodal pain management is critical for any patient on chronic opioid therapy including medications for opioid use disorder.
- Patients with opioid use disorder who are not currently on medications to treat opioid use disorder (MOUD) should be offered and started on MOUD even in the perioperative period.

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Abbreviations	
AAG	alpha-1-acid glycoprotein
FDA	Food and Drug Administration
IV	Intravenous
MOUD	medications for OUD
MWGOUD	Multi Society Working Group on Opioid Use Disorder
NMDA	N-methyl-D-aspartate
OUD	opioid use disorder

INTRODUCTION

The United States continues to struggle with an epidemic of opioid misuse. In 2022 there were over 80,000 opioid involved overdose deaths and it is estimated that 3.7% of the US adult population needs treatment of opioid use disorder (OUD) with only a quarter receiving medications for opioid use disorder (MOUD).[1] It is estimated that up to 11% of hospitalized patients have an OUD.[2] Patients receiving methadone or buprenorphine for OUD treatment is associated with substantial reductions in all-cause mortality.[3] With the lifesaving effects of MOUD and the increasing frequency of patients with OUD presenting for surgery a thorough understanding of the perioperative considerations for patients receiving medications for opioid use disorder is needed for anyone caring for these patients. This article will discuss the perioperative considerations of MOUD.

MEDICATIONS FOR OPIOID USE DISORDER

The Food and Drug Administration (FDA) has approved 3 medications to treat opioid use disorder/addiction: (1) methadone, (2) buprenorphine alone (sublingual tablets or long-acting injectable—weekly and monthly) or combined with naloxone (sublingual tablets or films), and (3) naltrexone (oral or long-acting injectable form).[4]

Methadone

Pharmacology

Methadone is considered a full mu-opioid receptor agonist with additional N-methyl-D-aspartate (NMDA) antagonist activity. When methadone is taken orally it has 70% to 80% bioavailability and peak plasma levels are reached in approximately 3 hours (range 1–5 hours).[5] Methadone is highly bound to plasma proteins primarily alpha-1-acid glycoprotein (AAG). Methadone is metabolized in the liver and renally eliminated with a small amount in the fecal route. Although methadone is a very long-acting opioid, it does undergo a biphasic pattern of elimination. The alpha elimination (8–12 hours) is associated with analgesic properties of methadone and the beta (30–60 hours) with the withdrawal suppression aspect. Since the cytochrome P450 system is the major contributor in methadone metabolism, any coadministered medications that induce or inhibit the P450 system can dramatically alter the metabolism, resulting in lower or higher systemic levels for the same dose of methadone. In addition, acute phase proteins including AAG can dramatically increase during surgical stress and inflammation and may reduce the effectiveness of a prior stable dose of methadone. Methadone binds approximately 30% of the mu receptors allowing for additional activity from both endogenous and exogenous mu-opioid agonists.[6–9]

Sedation, respiratory depression, and death can occur with methadone administration especially after dose increases even after being on a stable dose for several days. The toxic dose can be difficult to predict secondary to the long half-life, changes in patient's health status, changes in metabolism, and variable tolerance profile at higher

doses. Higher doses are associated with improved abstinence from nonprescribed opioids with 60 to 100 mg/d outperforming moderate (40–60 mg/d) and low dose (<40 mg/d).[10] Methadone has been associated with prolongation of the QT interval and increases to greater than 500 milliseconds are associated with arrhythmias including Torsade de Pointes and sudden cardiac death.[11]

Perioperative use

Patients should be instructed to take their usual dose of methadone on the day of surgery. If the patient did not take their usual dose, you should administer the dose orally before surgery and they should be maintained on their home dose throughout the perioperative period. Since the alpha elimination (8 hours) is associated with the analgesic component of methadone, dosing the patient's daily dose in 3 divided doses might improve pain control.[12] If possible, confirm the patient's maintenance dose with their methadone prescriber and document the contact information for postoperative discharge planning. If there is any concern about the correct dose, you can divide their reported daily dose into 3 times a day dosing and monitor for sedation or respiratory depression. Intravenous (IV) dosing should be reserved for patients who cannot take their dose orally, and the IV dose should be reduced by up to two-thirds and given with appropriate monitoring for respiratory depression. As with any patient on high doses of opioids, the patient will likely need additional opioids but up-titration of the methadone is not advised. If any adjustments in the methadone dose are done, it should be communicated to the methadone provider upon discharge so they can continue the higher or lower dose as an outpatient. If there is a significant delay (>5 days) in restarting the methadone for any reason, it should be restarted slowly and likely at a reduced dose with ongoing monitoring of respiratory depression or sedation.[6]

Buprenorphine

Pharmacology

Buprenorphine, which is a synthetic analog of the opium poppy constituent thebaine, was first used as an acute pain medication in the parental form in Europe in 1978 and then in the United States in 1981. In 2002, the sublingual formulation was approved for the treatment of opioid use disorder.[13] In 2010, buprenorphine was approved for chronic pain as a transdermal patch and in 2015, as a buccal film.[14] Buprenorphine has multiple different formulations, including parenteral, sublingual tablet, sublingual. film, transdermal patch, mucoadhesive film, and a weekly and monthly depot for subcutaneous injection.[15] Although sublingual buprenorphine (2−24 mg) is not currently FDA-approved for chronic pain, it is often used in chronic pain patients with risk factors for developing opioid use disorder or as a safer opioid with less risk of respiratory depression and overdose.[16]

When buprenorphine was first approved in 2002 to treat OUD, additional training and registration above the usual Drug Enforcement Administration (DEA) license was required to prescribe (DEA X-waiver). This requirement was removed in 2023. Following the removal of the DEA X-waiver requirements, the number of prescribers of buprenorphine has significantly increased but the number of patients being treated with buprenorphine for OUD has not.[17]

Buprenorphine like other opioids retains an abuse liability although lower than other opioids. Buprenorphine is a schedule III-controlled substance as compared to other opioids, which are schedule II. Since it is a schedule III medication, buprenorphine can be ordered with multiple refills unlike other opioids. The range of buprenorphine doses is more than 2 orders of magnitude, with the lowest dose of the mucoadhesive form (Belbuca) at 0.075 mg (75 mcg) and the highest dose of the sublingual film

(Suboxone) at 12 mg (12,000 mcg). The high-dose forms of buprenorphine are available as a monoproduct containing only buprenorphine or combined with naloxone in a 4:1 ratio. The addition of naloxone helps prevent misuse because it induces withdrawal symptoms when injected IV.

Buprenorphine acts as both an agonist and antagonist at different opioid receptors. Buprenorphine has a high binding affinity at the mu-opioid receptor but only partially activates it compared with other opioids. Despite partial activation, buprenorphine still provides analgesia but has a ceiling effect on respiratory depression, conferring significantly less risk of respiratory compromise and overdose compared with opioids, such as morphine and fentanyl.[18] Buprenorphine when compared to other opioids shows lower risk of respiratory depression, lower immunosuppressive effects, less suppression of the gonadal axis and may reduce the incidence of constipation. Buprenorphine shows antagonism at the κappa-opioid receptor, which may reduce the incidence of hyperalgesia and tolerance.[19,20]

There are no oral forms of buprenorphine secondary to extensive first past metabolism with the resultant poor bioavailability, thus buprenorphine must be delivered parentally, sublingually, transdermally, buccally, or subcutaneously.

Respiratory depression can occur when buprenorphine is used along with central nervous system sedating agents, including alcohol, sedative-hypnotics, and neuroleptic drugs, especially in fragile, very young, or elderly populations.[21]

Buprenorphine is primarily metabolized in the liver to norbuprenorphine. Buprenorphine and norbuprenorphine are primarily eliminated through bile and feces. Only a small amount of buprenorphine metabolites is excreted in the kidney. Buprenorphine can be safely used in patients with both renal and hepatic insufficiency with only dose reductions needed for severe hepatic dysfunction.[22]

Perioperative use

Buprenorphine's ability to tightly bind to the mu-opioid receptor and potentially block additional opioids from binding has created a concern that additional opioids are potentially less effective in the presence of buprenorphine, thus reducing the analgesic efficacy resulting in conflicting guidelines on stopping or lowering the buprenorphine dose perioperatively.

It has now been established by multiple expert panels, most recently by the Multi Society Working Group on Opioid Use Disorder (MWGOUD) in 2021, that "To decrease the risk of OUD recurrence, buprenorphine should not be routinely discontinued in the perioperative setting."[23] It is our experience that patients can be maintained on their home dose without dose reduction independent of the total daily dose. The decision to lower the perioperative dose to 16 mg if on higher daily dosing, which has been advocated by some pathways, should only be considered if it is done in consultation with providers with expertise in addiction medicine and acute pain and it warrants a thorough discussion with both the patient and the primary buprenorphine prescriber regarding the associated risks and benefits, including the increased cravings or OUD recurrence during and after the hospitalization. For further discussion on this topic, it is advisable to review the buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel.[23] The MWGOUD was created by the boards of directors of the American Society of Regional Anesthesia and Pain Medicine, the American Society of Anesthesiologists, the American Academy of Pain Medicine, the American Society of Addiction Medicine, and the American Society of Health System Pharmacists. Although the expert panel reached this recommendation with 100% consensus, it was not based on prospective or randomized trials but based on 34 case reports/series, reviews,

and published guidelines on the management of buprenorphine in the perioperative period published between 2004 and 2021.[23]

Although many publications during this period have recommended prospective studies to clarify this issue, only one study has been proposed in the literature as a study protocol, and this was limited to the question of whether the dose of buprenorphine should be reduced or not preoperatively.[24] Two studies of "unknown status" pertaining to this issue are currently listed on ClinicalTrials.gov (NCT 03266445 and NCT 04091009) but have not been updated since 2018 and 2019, respectively.

When buprenorphine became available for the treatment of OUD in the United States in 2002, it had already been introduced in France for OUD 7 years earlier and had been available as a parenteral injection and tablet form for pain in the United Kingdom since 1978. As early as 1990, observations in patients with cancer established that IV morphine was effective when given sequentially after IV buprenorphine.[25] Greenwald and colleagues[26] established in 2003 mu-opioid receptor availability for full agonists even at high doses of sublingual buprenorphine in heroin users.

Nevertheless, without reference to the basic science or early clinical literature or referencing clinical use in other countries or even proposing new research, the US Substance Abuse and Mental Health Services Administration issued guidance in 2004 recommending discontinuation of buprenorphine for several days prior to anticipated pain that would call for the use of a full agonist opioid. As experience developed, particularly at academic centers, in managing patients on buprenorphine with OUD, it became clear that this conjecture was incorrect. These issues were described in detail in 2010[27] and also summarized in the previous review on this subject in this journal in 2018.[6]

Since the publication of the multisociety MWGOUD article, additional case reports and retrospective cohort studies have been published focusing on trauma,[28] orthopedic surgery,[29,30] cardiac surgery,[31] obstetrics/cesarean section,[32] and painful procedures,[33] with ongoing support for the recommendation to continue buprenorphine perioperatively. A retrospective case series of surgical patients on buprenorphine reported that if buprenorphine was held during the hospitalization over half of the patients were not discharged on buprenorphine greatly increasing their risk of relapse, overdose, and death.[34] Although a population-based retrospective cohort study from the province of Ontario, Canada, verified the continuation of buprenorphine in a significant majority of cases,[35] a National Provider Survey in the United States found that "The majority of institutions surveyed do not have an established protocol for perioperative buprenorphine management."[36]

A narrative review and case series (n = 4) on the perioperative management of extended-release buprenorphine suggests that when possible, in elective situations that surgery be planned during the trough serum levels before the next monthly injection, but the recommendations reflect only the authors expert option and is not based on data and does not address the concerns of lowering or holding buprenorphine in the perioperative period.[37,38] If extended-release buprenorphine is held, it should be replaced with an adequate dose of sublingual buprenorphine to prevent possible relapse. Aligning with the Multisociety Working Group on Opioid Use Disorder guidelines,[23] it is reasonable to assume that the extended-release formulation of buprenorphine can be treated in the same manner as other formulations.

Additional opioids likely will be required in the perioperative period. Although it has not be thoroughly studied, it is reasonable to select opioids that have higher μ-opioid receptor affinity, such fentanyl, hydromorphone, and oxycodone. Increasing the

buprenorphine as the primary opioid analgesic has also been advocated by some investigators as well as dividing the daily dose into 3 times-daily dosing.[39,40]

Postoperative weaning of additional opioids should be accomplished as soon as postoperative pain is adequately controlled. Utilizing a transitional pain service/clinic greatly facilitates the weaning of postoperative opioids and provides a safety net for the patient helping to address ongoing pain issues and reduces the risk of opioid-related complications.[41]

Naltrexone

Naltrexone is a semisynthetic opioid antagonist, derived from oxymorphone, which has a broad pharmacodynamic profile, best known for its competitive antagonism at mu-opioid receptors. In addition, it also functions as a partial agonist at kappa receptors and has minimal activity at delta receptors.[42] Naltrexone works by blocking opioid receptors, reducing the euphoric effects of alcohol and opioids short-term, while long-term use diminishes cravings and prevents relapse by modulating reward pathways in the brain. Unlike naloxone, which has minimal oral bioavailability due to extensive first-pass metabolism, naltrexone is orally bioavailable due to rapid absorption and its primary metabolite, 6-β-naltrexol, produced largely from first-pass metabolism, is also active.[43] Orally, naltrexone is typically dosed once a day and due to activity of both the parent molecule and the metabolite, its half-life is approximately 10 hours in the setting of normal renal excretion.[44] Oral formulations are approved for alcohol-use and opioid-use disorder but are widely used off-label in psychiatry for several conditions, including impulse-control disorders and eating disorders. Naltrexone is also available in a combination product with bupropion for chronic weight management. Low-dose formulations are being increasingly used off-label for chronic pain, fibromyalgia, and autoimmune disorders. An extended-release intramuscular injectable formulation is available for 28 day continuous opioid antagonism for alcohol-use and opioid-use disorder.

Perioperative use

Given the increasing growth of use of naltrexone, there is increasing interest in how to manage patients on naltrexone in the perioperative period. A scoping review done by the Perioperative Pain and Addiction Interdisciplinary Network published in 2024 reported current lack of high-quality evidence in this area necessitates individualized management based on patient history, naltrexone formulation, and the anticipated need for opioid analgesia.[45] Guiding principles can be considered from naltrexone's pharmacokinetics; given a 10 hour half-life, after 2 days (48 hours), approximately 3% of the original serum concentration will remain, as such, it would seem reasonable to ask patients to discontinue oral naltrexone 2 to 3 days prior to surgery. For extended-release naltrexone, there is less guidance, and a balanced risk–benefit decision should be made including the ability to proceed with surgery using opioid-free analgesic methods (eg, regional anesthesia and neuraxial anesthesia). From case reports, successful pain management with opioids has been reported in the fourth week of treatment with extended-release naltrexone as well as a complete lack analgesic response to opioids in the first 2 weeks.[46,47] A point of caution is that, in patients treated with long-term naltrexone as in the case of extended-release formulations, variable responses have been seen to opioids after cessation including the need for higher dose opioids as well as paradoxically enhanced responses.[48–50] There is little guidance of when to restart naltrexone therapy; most sources, including FDA-approved prescribing information, advise avoiding opioids for 7 to 10 days prior to restarting naltrexone.[45,51]

INITIATION OF MEDICATIONS FOR OPIOID USE DISORDER IN THE PERIOPERATIVE PERIOD

Initiation of MOUD is a lifesaving intervention.[3] Patients hospitalized with or for opioid use disorder who are not currently on MOUD should be offered treatment.[52] Naltrexone is not a viable choice for many hospitalized patients especially in the perioperative period, so the decision is most often between methadone or buprenorphine. The MOUD chosen will be based on several factors including postdischarge prescribing provider, patient preference, and comorbidities. Buprenorphine affords more flexibility but may require a longer period to start in hospitalized patients requiring opioids who may need a microdose or low-dose induction plan to cross taper off their other opioids. Although methadone may be viewed as more favorable by acute care providers since they may be more comfortable with the dosing, there are more restrictions in postdischarge prescribing of methadone for opioid use disorder versus buprenorphine. Methadone for opioid use disorder can only be prescribed as an outpatient by a federally registered opioid treatment clinic often referred to as a methadone clinic. Primary care or pain providers cannot prescribe methadone for OUD like they can for pain. Additional challenges with methadone maintenance include the requirement that patients attend in person methadone clinic daily to receive their methadone dose. There has been increased flexibly with the ability to obtain take home doses early in treatment, but this is based on stability determined by the methadone prescriber. The expectation should be that the patient will have to attend in person methadone clinic appointments daily to receive care with the goal of but not guarantee of take-home dosing in the future.[53,54] Another complicating factor of methadone induction for OUD is that patients discharged from an inpatient setting to a skilled nursing facility need to establish care with a methadone clinic to continue to receive methadone for OUD. Fortunately, methadone clinics are now allowed to conduct intake evaluations of patients using tele health, but this still may pose a barrier to continued MOUD if using methadone and transferring to a skilled nursing facility.[55] Finally, the appropriate starting dose of methadone for OUD is limited in an outpatient setting to 40 mg, so if the dose that was started during the hospitalization is higher, there may be issues with transferring the higher dose to the methadone clinic. Communication with the new provider in the methadone clinic prior to discharge is vital to support ongoing MOUD and prevent loss to follow-up, which can be lethal in patients with OUD.[56,57] The initial methadone induction period should be considered a high-risk period with all-cause mortality and drug-related mortality being higher for methadone versus buprenorphine. This risk is reduced if patient is transitioned from buprenorphine to methadone or once the patient has been on methadone for greater than 4 weeks.[58]

Buprenorphine, on the other hand, can be prescribed by any DEA licensed provider like all other opioid medications for either pain or OUD. The DEA X-waiver has been removed, which was a barrier to buprenorphine prescribing in the past. Buprenorphine can be dispensed as a monthly prescription, and since it is a schedule III medication, there can be multiple refills providing increased flexibility when compared to

Table 1
Multimodal pain management options

Regional Anesthesia	Lidocaine Infusion	Ketamine
Magnesium	Acetaminophen	Gabapentinoids
Dexamethasone	Dexmedetomidine	Psychological interventions
Nonsteroidal anti-inflammatory drugs	—	—

Table 2
Perioperative plan for medications for opioid use disorder dosing

Drug	Preoperative	Day of Surgery	Postoperative
Buprenorphine	Continue daily dose Document buprenorphine provider's contact information for postoperative follow-up	Patient should receive usual daily dose Plan for multimodal pain management	Continue daily dose but consider switching to tid dosing Consider increasing buprenorphine to target pain Continue multimodal pain management Arrange for follow-up with buprenorphine provider early in the postoperative period Discharge with the lowest dose and shortest duration of additional opioids as possible
Methadone	Continue daily dose Document methadone dose and methadone provider's contact information for postoperative follow-up	Patient should receive usual daily dose. If unable to take PO, give IV (reduce dose by one-half to two-thirds and split into tid dosing) Plan for multimodal pain management	Continue daily dose but consider switching to tid dosing Continue multimodal pain management Arrange for follow-up with methadone provider early in the postoperative period If daily dosing patient may need to go to methadone clinic postoperatively Discharge with the lowest dose and shortest duration of additional opioids as possible
Naltrexone	Oral—discontinue >48 h preoperatively XR-NXT—discontinue 30 d preoperatively	Confirm last dose >48 h for oral and >30 d for implanted XR-NXT Plan for multimodal pain management	Continue multimodal pain management Patient may be more sensitive or less sensitive to opioids Resume after patient has been off opioids for 7 d

methadone. There is also not a maximum starting dose of buprenorphine as compared to methadone. The classic approach to starting buprenorphine is to have the patient off all opioids for an amount of time that they are in mild opioid withdrawal and then the buprenorphine is dosed to relieve the withdrawal and suppress cravings. The reason for this approach is that buprenorphine binds more avidly to the mu-opioid receptor. The binding affinity is known as Ki and the Ki of buprenorphine is 0.21 nM, versus fentanyl Ki = 1.346 nM, methadone Ki = 3.378, or oxycodone Ki = 25.87.[59] This higher binding affinity can displace other opioids and in conjunction with the partial agonist affects can result in a temporary reduction in mu opioid receptor (MOR) output causing a temporary withdrawal effect in some highly dependent individuals. This phenomenon is known as precipitated withdrawal and can be uncomfortable and distressing. The postsurgical patient presents a challenge with the classic induction strategy since most postoperative patients may need ongoing opioids and may not be able to stop opioids prior to the induction. The low-dose or microdose induction pathway that was originally created for patients who were at risk of precipitated withdrawal from prior fentanyl use can be utilized in the perioperative setting. The low-dose/microdose induction pathway starts with dosing the buprenorphine in the microgram range with a patch and then slowly increasing the dose over the next few days until reaching the dose that will be adequate to stop all additional opioids while still achieving adequate pain control, withdrawal relief and craving suppression.[60] IV buprenorphine has also been used in conjunction with additional full mu agonist for patients in pain for a microdose/low-dose strategy with good results. In a small study, patients who were receiving full mu agonist were started on 0.15 mg IV buprenorphine q 6 to 12 hours for the first day and then increased to 0.3 mg q 6 to 12 hours and then on day 3, they were transitioned to sublingual once on an adequate dose of buprenorphine the full mu agonist were discontinued.[61] An injectable extended release (7 day) formulation of buprenorphine has been used as an alternative to the standard induction for patients presenting to the ED with mild withdrawal including patients using illicit fentanyl. Since the plasma levels rise more slowly than with sublingual, it may provide a smoother transition to maintenance doses of buprenorphine. Currently, it has not been studied in the inpatient setting or in the perioperative period, but further study is warranted.[62] Which ever induction strategy is selected based on patient and clinical factors, most patients are able to be safely and successfully started on buprenorphine even while experiencing acutely painful conditions such a surgery.[63]

MULTIMODAL ANALGESIA

The approach to perioperative analgesia should be no different in the patient on MOUD than for any patient on long-term opioid therapy. All patients receiving long-term opioid therapy will require at a minimum their routine daily dose of opioids and often require higher doses of opioids perioperatively. In addition to opioids, nonopioid-based pain management strategies should be utilized including regional anesthesia, NMDA receptor antagonist-ketamine, alpha 2 adrenoceptor agonist-dexmedetomidine, glucocorticoids-dexamethasone, lidocaine infusion, gabapentinoids-gabapentin/pregabalin, nonsteroidal anti-inflammatory drugs, acetaminophen, and psychological approaches like cognitive behavior therapy and mindfulness to lower pain and anxiety.[6,64,65]

SUMMARY

Opioid use disorder is a highly lethal disease but with a highly effective treatment—MOUD. Having a thorough understanding of the medications used to treat opioid

use disorder is vital in the care of patients with OUD in the perioperative period (Tables 1 and 2).

CLINICS CARE POINTS

- Buprenorphine is an effective analgesic and should be continued in the perioperative period but additional opioids may be required.
- Methadone should not be routinely increased in the perioperative period.
- Naltrexone should be avoided in the perioperative period.
- Buprenorphine offers more flexibility when starting MOUD in the perioperative period compared to Methadone.

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DISCLOSURE

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