Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy

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KEYWORDS

• Buprenorphine • Methadone • Naltrexone • Perioperative
• Multi modal pain management • Opioid use disorder • Addiction • Relapse

KEY POINTS

- Buprenorphine and methadone for the treatment of opioid use disorder (opioid addiction) should be continued in the perioperative period for most patients.
- Oral naltrexone should be discontinued 2 days before surgery and resumed once additional opioids are no longer needed.
- Extended-release injectable naltrexone is active for 28 days with peak at 7 days.
- Multimodal pain management is critical for patients on chronic opioid therapy. Regional anesthesia, ketamine, nonsteroidal anti-inflammatory drugs, acetaminophen, dexamethasone, lidocaine, magnesium, gabapentinoids, dexmedetomidine, esmolol, and mindfulness relaxation training have all been shown to reduce opioid use and decrease postoperative pain.

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INTRODUCTION

The United States is facing the worst drug crisis in US history, with more than 63,600 drug overdose deaths in 2016, almost double the deaths caused by traffic accidents or gun violence.[1] Two-thirds of drug overdose deaths are opioid related. Furthermore, overdose death is only 1 metric by which to measure the impact of the epidemic. By conservative estimates, 2.5 million people in this country are addicted to opioids (prescription and illicit), and more than 11 million people in the United States are misusing prescription opioids obtained directly or indirectly from a doctor's prescription (according to the 2016 National Survey on Drug Use and Health).[2] Prescription opioid misuse, addiction, and overdose cost the US more than $78 billion annually.

MEDICATION-ASSISTED TREATMENT OF OPIOID USE DISORDER

The Food and Drug Administration (FDA) has approved 3 medications to target opioid use disorder/addiction:

1. Methadone (generic oral and injectable forms, Dolophine, or Methadose)
2. Buprenorphine alone (generic sublingual tablets or Probuphine intradermal implant) or combined with naloxone (Suboxone, Zubsolv, Bunavail, or generic sublingual tablets)
3. Naltrexone (generic tablets, ReVia, or Vivitrol long-acting injectable form)

The first 2 fall into a category called opioid agonist treatment, because they are both long-acting opioids that are believed to decrease the physiologic cravings that drive drug-seeking behavior. The third, naltrexone, acts as a deterrent by blocking the opioid receptor, preventing other opioids from binding. It may also reset the reward pathway through an opponent process mechanism.

All 3 of these medications, methadone maintenance, buprenorphine products, and naltrexone (oral or injectable), comprise in part what is called medication-assisted treatment of opioid use disorder. Medication-assisted treatment is defined by the Substance Abuse and Mental Health Services Administration as the use of medications in combination with counseling and behavioral therapies for the treatment of substance use disorders.

Multiple placebo-controlled trials across continents and decades demonstrate the effectiveness of opioid agonist treatment (methadone and buprenorphine) in opioid use disorder.[3–5] Both methadone and buprenorphine result in significant reductions in overdose death, illicit drug use, criminal activity, and HIV and hepatitis C incidence. These treatments are also associated with improved health status and overall improved quality of life. By contrast, short-term use of opioid agonist therapy as part of a "detoxification protocol" is rarely effective.[6,7] Patients randomized to placebo withdrawal, compared with methadone or buprenorphine maintenance treatment, are 2 times to 4 times more likely to be dead at a year.[3,8]

A Cochrane meta-analysis of oral naltrexone showed no difference compared with placebo when comparing retention in treatment, use of illicit opioids, or side effects, a year after initiating treatment.[9] However, 2 recently published studies comparing injectable extended-release naltrexone (XR-NXT) to buprenorphine-naloxone found comparable rates of retention and abstinence from heroin and other illicit drugs at 12 weeks[10] and 24 weeks,[11] respectively. The latter study[11] showed that initiating patients onto injectable naltrexone was more difficult than on buprenorphine, which may have significant real-world implications, despite comparable efficacy in this study.

BUPRENORPHINE

Pharmacology

Several decades after the development of methadone, buprenorphine—a synthetic analog of the opium poppy constituent thebaine—was discovered and introduced into clinical practice in Europe in 1978 for acute and chronic pain.[12] In the United States, the FDA approved buprenorphine for (1) acute pain in 1981 as a parenteral injection; (2) opiate use disorder in 2002, as a sublingual tablet; and (3) chronic pain in 2010, as a transdermal patch. Buprenorphine is available in many different formulations, including parenteral, sublingual tablet, sublingual film, transdermal patch, mucoadhesive film, and implant.[13] In 2017, several FDA advisory committees voted to recommend approval of an additional dose form, once-monthly and once-weekly injections of a depot form of buprenorphine for the treatment of opioid use disorder.

Although prescribing buprenorphine for addiction requires special registration (Drug Enforcement Agency Prescriber identification number X), any physician with a Drug Enforcement Agency license can prescribe it for pain. Buprenorphine retains abuse liability and thus is a Schedule III controlled drug. 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 μg) and the highest dose of the sublingual film (Suboxone) at 12 mg (12,000 μg). This reflects the potency of low-dose forms of buprenorphine for pain, particularly in patients who are not opioid dependent, compared with the higher doses used for patients with opioid use disorder. The high-dose forms of buprenorphine are available as a monoproduct containing only buprenorphine but also in a form combined with naloxone in a 4:1 ratio. The addition of naloxone helps prevent misuse because it induces withdrawal symptoms when injected intravenously (IV).

Buprenorphine is unique in that it acts as both an agonist and antagonist at different opioid receptors. Buprenorphine has a high binding affinity at the mu 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.[14] Unique to buprenorphine is its antagonism of the kappa opioid receptor, which, along with its agonist action at the nociceptin opioid receptor (ORL-1), may confer several advantages over other opioids. These advantages include improved respiratory safety and attenuated euphoria and may contribute to its role in managing neuropathic pain, opioid-induced hyperalgesia, and psychiatric syndromes.[15]

As a result of its extensive first-pass metabolism, oral bioavailability is poor and buprenorphine is often given via the sublingual (or transmucosal) routes. Due to its lipophilic nature and potency, buprenorphine is remarkably well suited to transdermal delivery.

Respiratory depression can occur when buprenorphine is used along with central nervous system sedating agents, including alcohol, sedative-hypnotics, and neuroleptic drugs, or in fragile, young, or elderly populations. Reversal requires greater than the usual dose of naloxone: a 2-mg bolus is usually recommended in adults followed by 4-mg per hour infusion under close observation.[16]

Buprenorphine is primarily metabolized in the liver by phase I reactions (*N*-dealkylation) through the cytochrome P450 Cyp 3A4 enzyme to norbuprenorhpine. Both buprenorphine and norbuprenorphine are conjugated by uridine 5′ diphosphoglucuronosyltransferase (UGT), in phase II reactions to their glucuronide forms. Buprenorphine and norbuprenorphine are primarily eliminated through bile and feces. Only a small amount of the glucuronide metabolites are excreted in the kidney. These

pharmacokinetics confer relative safety compared with other opioids, when buprenorphine is used in patients with moderate to severe hepatic failure or in renal insufficiency. Due to little influence of buprenorphine on the activity of the cytochrome p450 Cyp 3A4 enzyme, drug-drug interactions are usually not a significant concern.[17]

Due to its tight binding and attenuated intrinsic activity at the mu receptor, parenteral or sublingual (but not transdermal) buprenorphine can precipitate withdrawal symptoms in patients who are dependent on other opioids. Therefore, an induction process involving early opioid withdrawal before introduction of sublingual buprenorphine is required.

Perioperative Use

Buprenorphine's ability to tightly bind to the mu receptor and potentially block additional opioids from binding has created a concern that additional opioids are less effective in the presence of buprenorphine, thus reducing the analgesic efficacy. Clinical research conducted early in the history of buprenorphine development[18] and multiple investigations and clinical practice in more recent years,[19,20] however, provide strong reassurance that standard opioids given to buprenorphine maintained patients are effective and additive to the baseline analgesia associated with the buprenorphine.

Clinical guidelines issued in 2004 by the Center for Substance Abuse Treatment,[21] despite acknowledging lack of evidence, set into motion a misconception in the United States, widely quoted, that perioperative analgesia is difficult to achieve with standard opioids in buprenorphine-maintained patients and that buprenorphine in most cases should be stopped and converted to methadone preoperatively. This misunderstanding may stem from addiction research, which did not assess analgesia but rather demonstrated that buprenorphine in higher doses blocked the euphoric and reinforcing effects of subsequently administered heroin.[22]

Case studies have been published describing difficult to control pain in postoperative buprenorphine-maintained patients.[23,24] Other cases, however, have been published describing adequate management, particularly when combined with multimodal analgesia.[22,25]

Extenuating circumstances, including intraoperative nerve injury, nonoptimal dosing of buprenorphine, and failure to use multimodal analgesia in a timely way characterize the published cases reporting difficult postoperative analgesia.[22] Furthermore, difficult postoperative analgesia is a common occurrence in patients who are preoperatively dependent on opioids of any type.

The experience in Australia established opioids were effective in hospitalized and postsurgical patients maintained on buprenorphine.[26,27] This was confirmed by US obstetricians, who did discontinue buprenorphine in pregnant patients for either vaginal deliveries or planned caesarean sections and reported adequate pain control.[28–30]

Stopping buprenorphine in stabilized opioid use disorder and/or chronic pain patients confers medical risk, discomfort, and logistical burden on patients, their prescribing clinicians, and the health system. A significant opioid debt will exist that will need to be filled with another opioid, risking over-dosing or under-dosing, and reinduction can be clinically and symptomatically problematic in the immediate postoperative period and can also prolong hospital stays.

Optimal use of buprenorphine in the perioperative setting has not be established. Whether to continue a patient's current dose or wean the dose down but not off to provide more mu receptor availability has not been studied. Nonetheless, receptor binding studies using radiolabeled carfentanil and PET scans to identify available mu receptors in buprenorphine-treated heroin-addicted persons confirm a

dose-response curve of reduced but conserved receptors available for additional analgesia, even at high sublingual doses of buprenorphine.[31] Which opioid to use for additional analgesia has not been studied, but using opioids that have higher mu receptor affinity, such as sufentanil, fentanyl, or hydromorphone, should be considered. 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 because a daily dose may not provide adequate analgesia throughout the entire 24-hour period.[32,33] Finally, patients who have stopped buprenorphine postoperatively and are still taking additional opioids potentially could be restarted on buprenorphine by using a daily microdose escalation known as the Bernese method without precipitating withdrawal. Once a sufficient dose of buprenorphine is reached, patients can discontinue their additional postoperative opioids.[34]

METHADONE

Pharmacology

Methadone is a full mu opioid receptor agonist. It is a racemic mixture with the R enantiomer responsible for the opioid effect and the R and S enantiomers having *N*-methyl-D-aspartate receptor (NMDA) antagonist activity. Oral administration has a moderate bioavailability approximately of 70% to 80% and is 90% bound to plasma proteins. Peak plasma levels are reached within 2 hours to 4 hours. Methadone undergoes a biphasic pattern of elimination—α-elimination (8–12 hours) and β-elimination (30–60 hours). The α-elimination is associated with analgesia and the β-elimination with withdrawal suppression. Methadone is metabolized in the liver and eliminated through renal and fecal routes. Hepatic metabolism is through the cytochrome P450 system, and coadministered medications that induce or inhibit the cytochrome P450 system can dramatically alter the metabolism, resulting in lower or higher systemic levels for the same dose of methadone. Methadone binds approximately 30% of the mu receptors allowing for additional activity from both endogenous and exogenous mu opioid agonists.[35,36]

Sedation, respiratory depression, and death can occur with increasing doses of methadone. The toxic dose can be difficult to predict secondary to long half-life, changes in metabolism, and variable tolerance profile at higher doses. Methadone can also increase the QT interval and has been associated with sudden cardiac death. Prolongation of the QT to greater than 500 milliseconds is associated with arrhythmias, including torsades de pointes.[37]

Perioperative Use

Patients should take their usual dose of methadone on the day of surgery. Patients are opioid tolerant; thus, additional opioids likely are needed. Patients should be continued on their home maintenance dose throughout the perioperative period. Because the α-elimination (8 hours) is associated with the analgesic component of methadone, dosing a patient's daily dose in 3 divided doses might improve pain control.[38] It is important to confirm a patient's home dose with the methadone prescriber. If there is concern about what the actual dose is, the methadone can be administered in divided doses throughout the day, monitoring for sedation and respiratory depression. Patients unable to take their oral dose should be given IV methadone. The IV dose should be reduced by one-half to two-thirds and be given in divided dose every 6 hours to 8 hours. Oral to IV conversion can be difficult, especially at higher doses, so consulting with a pharmacist or the methadone prescriber may be warranted. Up-titration of methadone in the perioperative period is not advised secondary to

the long half-life. If any up-titration occurs, it should be in consultation with a patient's methadone prescriber or expert on the use of methadone. If a patient's methadone dose has been interrupted for more than 5 days, restarting should be in consultation with a provider who is experienced in methadone maintenance induction.[39] Documenting the contact number of the methadone prescriber is important so appropriate follow-up at discharge can be arranged.

NALTREXONE

Pharmacology

Naltrexone is a semisynthetic opioid antagonist derived from oxymorphone via substitution of the *N*-methyl group with metylcyclopropyl group. It is a competitive antagonist at mu opioid receptors and partial agonist at kappa receptors and has minimal activity at delta receptors.[40] In oral formulation, it has rapid absorption, with peak concentration at 1 hour, undergoing first-pass hepatic metabolism.[41] After continuous administration for 7 days, the half-life is approximately 10 hours with renal excretion.[42] XR-NXT, a biodegradable microsphere matrix embedded with naltrexone, was introduced in 2010 as a 380-mg gluteal intramuscular injection to yield opioid antagonism for 28 days.[42] Pharmacokinetically, XR-NXT peaks at 7 days and avoids first-pass hepatic metabolism.[43] Opioid antagonist effects of XR-NXT decrease over the course of a month. Although currently there are no published data determining exactly when opioid antagonism can be overcome, case reports suggest it can be achieved during the fourth week postinjection.[44]

Perioperative Use

With a 10-hour half-life, oral naltrexone should be discontinued approximately 2–3 days before surgery in close coordination with the patient and prescribing physician, accounting for 5 half-lives. For XR-NXT, there is less guidance; however, a balanced risk-benefit decision of need for surgery and ability to use opioid-sparing techniques, including regional and neuraxial anesthetics, needs to be considered. Successful pain management has been reported starting in the fourth week of treatment, with complete lack of analgesia to opioids in the first 2 weeks of treatment.[43,44] Close monitoring may be required, however, if patients receive opioids postoperatively because variable responses have been observed, including both attenuation and enhancement; in some animal studies, levels 6 times to 20 times typical doses of opioids have been needed to achieve analgesia.[45–47] Restarting naltrexone requires patients to be free of opioids to avoid acute withdrawal. FDA-approved prescribing information advises patients to be abstinent from opioids for 7 days to 10 days prior to induction.[48]

MULTIMODAL PAIN MANAGEMENT

Multimodal pain management is important to improve efficacy and minimize side effects. Multimodal therapies are even more important for the opioid use disorder patient because these patients are opioid tolerant but often pain intolerant (**Table 1**).

Table 1
Multimodal pain management

Opioids	Acetaminophen	Gabapentinoids
Regional anesthesia	Dexamethasone (>0.1 mg/kg)	Dexmedetomidine
Ketamine	Lidocaine infusion	Esmolol
NSAIDs	Magnesium infusion	Mindfulness relaxation

Opioids

Opioids are still an important component of multimodal pain management; however, doses need to be increased in opioid-tolerant patients. The degree of tolerance can be difficult to predict and patients are still at risk for respiratory depression from increasing doses of opioids. Continuing the preoperative dose of opioids is important to prevent withdrawal. Early withdrawal is subjective and often results in increased pain, but as it progresses physical signs of withdrawal become evident (sweating, gastrointestinal upset, tremor, restlessness, anxiety, yawning, gooseflesh, and runny nose/tearing). As with all patients receiving perioperative opioids, careful monitoring for sedation and respiratory depression is critical.[49,50]

Regional Anesthesia

Regional anesthesia is vital to anesthetic management of opioid-tolerant patients. Neuraxial anesthesia or use of peripheral nerve blocks reduces both pain and opioid requirements and improves patient satisfaction.[51–53] Single-injection spinal with opioid (morphine or hydromorphone) with or without local anesthetic has been associated with lower pain and decreased systemic opioid requirements.[54] Thoracic epidural anesthesia is associated with decreased pain and reduced opioid requirements.[55] Transversus abdominis plane blocks provide superior pain control and lower opioid requirements for abdominal surgery compared with opioids alone.[56–58] Continuous peripheral nerve blockade is associated with improved pain control, lower opioid requirements, and greater patient satisfaction compared with single injection.[59]

Ketamine

Ketamine is an IV anesthetic and NMDA receptor antagonist. It has been shown to improve postoperative pain control as well as decrease opioid consumption in both opioid-naïve and opioid-tolerant patients. Several different dosing protocols have been studied but low-dose ketamine (0–1 mg/kg bolus and infusion of <1.2 mg/kg/h) is safe and effective at reducing both opioid consumption and time to first opioid request.[60,61] Ketamine administered at 0.5 mg/kg IV at induction and at an infusion of 10 μg/kg/min until skin closure decreased both reported pain scores as well as morphine consumption in opioid-tolerant patients at 48 hours and at 6 weeks.[62] One case report suggests potential for ketamine misuse and addiction when initiated as an analgesic alternative in a patient with opioid use disorder on buprenorphine.[63]

Lidocaine

Perioperative use of lidocaine has been shown to reduce pain scores and opioid use in the immediate postoperative period up to 24 hours. The analgesic effects were most apparent after laparoscopic and open abdominal surgery. It has also been shown to reduce ileus, postoperative nausea and vomiting, and hospital length of stay. Common dosing for perioperative lidocaine infusion is 1.5 mg/kg/h to 3 mg/kg/h after a bolus of 0 mg/kg IV to 1.5 mg/kg IV. It can be run in the immediate postoperative period usually at a lower dose. There are no data for use greater than 24 hours. Lidocaine has a narrow therapeutic index, with therapeutic levels occurring at 2.5 μg/mL to 3.5 μg/mL but with central nervous system toxicity occurring at 5 μg/kg and cardiovascular toxicity at 10 μg/mL. Lidocaine toxicity should be treated 20% lipid emulsion and supportive care.[64–67]

Magnesium

Magnesium is an often overlooked adjunct in acute pain management. A meta-analysis of 1200 patients showed IV magnesium reduced both early and late pain at rest and late pain with movement. Magnesium has also been shown to have a large effect on reducing perioperative opioid use. The usual dose range is 30-mg/kg to 50-mg/kg bolus followed by a 10-mg/kg infusion intraoperatively. Several studies continued the infusion for 24 hours to 48 hours at a reduced rate. Continuing the infusion may provide additional benefit compared withw intraoperative use only.[68] Magnesium may also help prevent opioid-induced hyperalgesia.[69]

Acetaminophen

Acetaminophen can be administered orally, rectally, or IV. The exact mechanism of action is unknown but it is believed to inhibit cyclooxygenase (COX) enzyme in the central nervous system.[70] A meta-analysis showed that 36% of patients receiving IV acetaminophen experienced at least a 50% reduction in pain and used 26% less opioids in the first 4 hours postoperatively.[71] Oral and IV administration seem to have similar efficacy.[72] Combining acetaminophen with nonsteroidal anti-inflammatory drugs (NSAIDs) confers additional analgesic efficacy over either drug alone.[73]

Gabapentinoids

Gabapentinoids (gabapentin and pregabalin) are a class of drug that bind to the $\alpha 2\delta$ subunit of the voltage-dependent calcium channel, thus inhibiting the opening of the calcium channel and reducing release of excitatory neurotransmitters. Gabapentin and pregabalin have been shown to reduce postoperative pain and reduce opioid consumption; however, they have been associated with an increase in sedation and dizziness.[74,75] When gabapentin was added to a methadone[76] or buprenorphine-assisted detoxification program, it reduced withdrawal symptoms.[77]

Nonsteroidal Anti-inflammatory Drugs

Nonselective NSAIDs (eg, ibuprofen, naproxen, and ketorolac) inhibit both the COX-1 and COX-2 isoforms whereas celecoxib is selective for the COX-2 isoform. COX inhibitors decrease conversion of arachidonic acid to prostaglandins and thromboxane, thus reducing pain and inflammation. NSAIDs have been shown to reduce pain and decrease opioid use postoperatively. Caution should be used in patients with cardiovascular disease, renal insufficiency, and gastrointestinal bleeding. The risk is increased with long term use however the risk of brief postoperative use is unclear.[70,78–81]

Steroids

Dexamethasone is a corticosteroid that has been shown to reduce pain and opioid use. A meta-analysis of 2500 patients showed that intermediate dose of dexamethasone (0.11–0.2 mg/kg) had opioid-sparing effects as well as reduced early and late pain at rest and movement. Low dose (less than 0.1 mg/kg) was not effective. Dexamethasone is more efficacious if it is administered preoperatively. Rapid administration of a small volume of dexamethasone can cause perineal pain. This risk can be reduced by giving the dose over 10 minutes and in a larger volume (50 mL). Wound infections or delayed wound healing did not seem associated with the intermediate dose. The risk-benefit analysis of perioperative blood glucose control versus pain control should be considered. The effects on blood glucose were not addressed in the meta-analysis.[82]

Dexmedetomidine

Dexmedetomidine is an α_2-adrenergic receptor agonist, which has sedative, anxiolytic, sympatholytic, and analgesic properties. When used intraoperatively, it can reduce the need for opioids and decreases pain intensity. The degree of opioid sparing is stronger than acetaminophen but weaker than ketamine or NSAIDs. Dexmedetomidine can cause hypotension and bradycardia.[83–85]

Esmolol

Esmolol is an ultra–short-acting β_1-receptor antagonist. It has been shown to decrease intraoperative and postoperative opioid consumption when used intraoperatively.[86]

Table 2
Medication-assisted treatment of opioid use disorder: perioperative considerations

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 1/2 to 2/3 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 to opioids. Resume after patient has been off opioids for 7 d.

Psychological

Psychological factors affecting pain include general anxiety, depression, posttraumatic stress disorder, pain-related anxiety, and pain catastrophizing.[87] A single scripted 15-minute session of mindfulness training or hypnotic suggestion delivered in a hospital setting has been shown to reduce pain intensity by up to 30% in one-third of patients who were reporting severe pain. Preoperatively addressing a patient's risk of pain catastrophizing can also help decrease postoperative pain.[88]

SUMMARY

The appropriate use of buprenorphine, methadone, and naltrexone in the perioperative period, for patients with opioid use disorder on maintenance therapy, is an increasingly important part of modern medical treatment (**Table 2**). Buprenorphine and methadone should be continued in the perioperative period for most patients. Oral naltrexone should be discontinued 2 days before surgery and resumed once additional opioids are no longer needed. Multimodal pain management is critical for patients on chronic opioid therapy. Regional anesthesia, ketamine, NSAIDs, acetaminophen, dexamethasone, lidocaine, magnesium, gabapentinoids, dexmedetomidine, esmolol, and mindfulness relaxation training have all been shown to reduce opioid use and decrease postoperative pain.

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REFERENCES

1. Hedegaard H, Warner M, Minino AM. Drug overdose deaths in the United States, 1999-2016. In: NCHS Data Brief No.294, 2017. Available at: https://www.cdc.gov/nchs/products/databriefs/db294.htm. Accessed January 8, 2018.
2. Center for Behavioral Health Statistics and Quality. 2016 national survey on drug use and health: detailed tables. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2017.
3. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ 2017;357:j1550.
4. Nielsen S, Larance B, Degenhardt L, et al. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev 2016;(5):CD011117.
5. Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014;(2):CD002207.
6. Amato L, Davoli M, Minozzi S, et al. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev 2013;(2):CD003409.
7. Dunn KE, Sigmon SC, Strain EC, et al. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. Drug Alcohol Depend 2011;119(1–2):1–9.
8. Strang J, Babor T, Caulkins J, et al. Drug policy and the public good: evidence for effective interventions. Lancet 2012;379(9810):71–83.
9. Lobmaier P, Kornor H, Kunoe N, et al. Sustained-release naltrexone for opioid dependence. Cochrane Database Syst Rev 2008;(2):CD006140.

10. Tanum L, Solli K, Latif Z, et al. The effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry 2017;74(12):1197–205.
11. Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X: BOT): a multicentre, open-label, randomized controlled trial. Lancet 2018; 391(10118):309–18.
12. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. J Pain Symptom Manage 2005;29:297–326.
13. Center for Drug Evaluation and Research (U.S.). Orange book: approved drug products with therapeutic equivalence evaluations. 37th edition. Rockville (MD): U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs; 2017.
14. Raffa RB, Haidery M, Huang HM, et al. The clinical analgesic efficacy of buprenorphine. J Clin Pharm Ther 2014;39(6):577–83.
15. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol 2012;10:209–19.
16. Dahan A. New insights into buprenorphine's respiratory effects. In: Budd K, Raffa RB, editors. Buprenorphine- the unique opioid analgesic. New York: Thieme; 2005. p. 22–32.
17. Walsh SL, Middleton LS. Buprenorphine pharmacodynamics and pharmacokinetics. In: Cruciani RA, Knotkova H, editors. Handbook of methadone prescribing and buprenorphine therapy. New York: Springer; 2013. p. 163–81.
18. Atkinson RE, Schofield P, Mellor P. The efficacy in sequential use of buprenorphine and morphine in advanced cancer pain. In: Doyle D, editor. Opioids in the treatment of cancer pain: proceedings of a symposium sponsored by Reckitt & Colman Pharmaceuticals and held at the Royal College of Surgeons, London. International congress and symposium series, 146. London: Royal Society of Medicine Services Limited; 1990. p. 81–7.
19. Mercadante S, Villari P, Ferrera P, et al. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. J Pain Symptom Manage 2006;32:175–9.
20. Van Niel JCG, Schneider J, Tzschentke TM. Efficacy of full μ-opioid receptor agonists is not impaired by concomitant buprenorphine or mixed opioid agonists/antagonists–preclinical and clinical evidence. Drug Res (Stuttg) 2016;66(11): 562–70.
21. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04–3939. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2004.
22. Silvia MJ, Rubinstein A. Continuous perioperative sublingual buprenorphine. J Pain Palliat Care Pharmacother 2016;30(4):289–93.
23. Huang A, Katznelson R, de Perrot M, et al. Perioperative management of a patient undergoing Clagett window closure stabilized on suboxone for chronic pain: a case report. Can J Anaesth 2014;61:826–31.
24. McCormick Z, Chu SK, Chang-Chien GC, et al. Acute pain control challenges with buprenorphine/naloxone therapy in a patient with compartment syndrome secondary to McArdle's disease: a case report and review. Pain Med 2013;14: 1187–91.

25. Kornfeld H, Manfredi L. Effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery: a case series. Am J Ther 2010;17:523–8.
26. Roberts DM, Meyer-Witting M. High-dose buprenorphine: perioperative precautions and management strategies. Anaesth Intensive Care 2005;33:17–25.
27. Macintyre PE, Russell RA, Usher KAN, et al. Pain relief and opioid requirements in the first 24 h after surgery in patients taking buprenorphine and methadone opioid substitution therapy. Anaesth Intensive Care 2013;41:222–30.
28. Meyer M, Paranya G, Norris AK, et al. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. Eur J Pain 2010;14(9):939–43.
29. Vilkins AL, Bagley SM, Hahn KA, et al. Comparison of post-cesarean section opioid analgesic requirements in women with opioid use disorder treated with methadone or buprenorphine. J Addict Med 2017;11(5):397–401.
30. Leighton BL, Crock LW. Case series of successful postoperative pain management in buprenorphine maintenance therapy patients. Anesth Analg 2017;125(5):1779–83.
31. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 2003;28:2000–9.
32. Anderson TA, Quaye ANA, Ward N, et al. To stop or not, that is the question-acute pain management for the patient on chronic buprenorphine. Anesth Analg 2017;126(6):1180–6.
33. Childers JW, Arnold RM. Treatment of pain in patients taking buprenorphine for opioid addiction #221. J Palliat Med 2012;15(5):613–4.
34. Hammig R, Kemter A, Strasser J, et al. Use of microdose for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Subst Abuse Rehabil 2016;7:99–105.
35. Kling MA, Carson RE, Borg L, et al. Opioid receptor imaging with positron emission tomography and [(18)F]cyclofoxy in long-term, methadone-treated former heroin addicts. J Pharmacol Exp Ther 2000;295:1070–6.
36. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict 2010;19:4–16.
37. Martin JA, Campbell A, Killip T, et al. QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel. J Addict Dis 2011;30(4):283–306.
38. Peng PWH, Tumber PS, Gourlay D. Perioperative pain management of patients on methadone therapy. Can J Anaesth 2005;52:513.
39. Methadone maintenance treatment program standards and clinical guidelines. 2011. Available at: http://www.cpso.on.ca/uploadedFiles/members/MMT-Guidelines.pdf. Accessed December 18, 2017.
40. Wentland MP, Lou R, Lu Q, et al. Syntheses of novel high affinity ligands for opioid receptors. Bioorg Med Chem Lett 2009;19(8):2289–94.
41. Wall ME, Brine DR, Perez-Reyes M. The metabolismof naltrexone in man. NIDA Res Monogr 1981;28:105–31.
42. Sudakin D. Naltrexone: not just for opioids anymore. J Med Toxicol 2016;12:71–5.
43. Dunbar JL, Turncliff RZ, Dong Q, et al. Single- and multiple-dose pharmacokinetics of long acting injectable naltrexone. Alcohol Clin Exp Res 2006;30(3):480–90.

44. Curatolo C, Trinh M. Challenges in the perioperative management of the patient receiving extended-release naltrexone. A A Case Rep 2014;3:142–4.
45. Dean RL, Todtenkopf MS, Deaver DR, et al. Overriding the blockade of antinociceptive actions of opioids in rats treated with extended-release naltrexone. Pharmacol Biochem Behav 2008;89:515–22.
46. Díaz A, Pazos A, Flórez J, et al. Regulation of mu-opioid receptors, G-protein-coupled receptor kinases and beta-arrestin 2 in the rat brain after chronic opioid receptor antagonism. Neuroscience 2002;112:345–53.
47. Tempel A, Gardner EL, Zukin RS. Neurochemical and functional correlates of naltrexone-induced opiate receptor up-regulation. J Pharmacol Exp Ther 1985; 232:439–44.
48. Sigmon SC, Bisaga A, Nunes EV, et al. Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice. Am J Drug Alcohol Abuse 2012;38(3):187–99.
49. Huxtable CA, Roberts LJ, Somogyi AA, et al. Acute pain management in opioid-tolerant patients: a growing challenge. Anaesth Intensive Care 2011;39(5): 804–23.
50. Shah S, Kapoor S, Durkin B. Analgesic management of acute pain in the opioid-tolerant patient. Curr Opin Anaesthesiol 2015;28(4):398–402.
51. Kumar K, Kirksey MA, Duong S, et al. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. Anesth Analg 2017;125(5):1749–60.
52. Richman JM, Liu SS, Courpas G, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg 2006; 102:248–57.
53. Liu SS, Strodtbeck WM, Richman JM, et al. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg 2005;101:1634–42.
54. Meylan N, Elia N, Lysakowski C, et al. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. Br J Anaesth 2009;102(2):156–67.
55. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003;290(18):2455–63.
56. Baeriswyl M, Kirkham KR, Kern C, et al. The analgesic efficacy of ultrasound-guided transversus abdominis plane block in adult patients: a meta-analysis. Anesth Analg 2015;121(6):1640–54.
57. McEvoy M, Scott MJ, Gordon DB, et al. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on optimal analgesia within an enhanced recovery pathway for colorectal surgery: part 1-from the preoperative period to PACU. Perioper Med (Lond) 2017;6:8.
58. McEvoy M, Scott MJ, Gordon DB, et al. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on optimal analgesia within an enhanced recovery pathway for colorectal surgery: part 2-from PACU to the transition home. Perioper Med 2017;6:7.
59. Bingham AE, Fu R, Horn JL, et al. Continuous peripheral nerve block compared with single-injection peripheral nerve block a systematic review and meta-analysis of randomized controlled trials. Reg Anesth Pain Med 2012;37:583–94.
60. De Oliveira GS, Benzon HT, White PF. The role of nonopioid analgesic infusions in the management of postoperative pain. In: Hadzic A, editor. Hadzic's textbook of regional anesthesia and acute pain management. 2nd edition. New York: McGraw-Hill; 2017. p. 1226–37.

61. Laskowski K, Stirling A, McKay WP, et al. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011;58(10):911–23.
62. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010;113:639–46.
63. Prekupec MP, Sussman RS, Sher Y, et al. Relapse on ketamine followed by severe and prolonged withdrawal. J Nat Sci 2017;3(10):1–4.
64. Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev 2015;(7):CD009642.
65. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. BJA Educ 2016;16(9):292–8.
66. Weibel S, Jokinen J, Pace NL, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. Br J Anaesth 2016;116(6):770–83.
67. Dunn LK, Durieux ME. Perioperative use of intravenous lidocaine. Anesthesiology 2017;126(4):729–37.
68. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, et al. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2013;119:178–90.
69. Song JW, Lee YW, Yoon KB, et al. Magnesium sulfate prevents remifentanil-induced postoperative hyperalgesia in patients undergoing thyroidectomy. Anesth Analg 2011;113(2):390–7.
70. Young AC, Buvanendran A. Multimodal analgesia: pharmacologic interventions and prevention of persistent postoperative pain. In: Hadzic A, editor. Hadzic's textbook of regional anesthesia and acute pain management. 2nd edition. New York: McGraw-Hill; 2017. p. 1219–26.
71. McNicol ED, Ferguson MC, Haroutounian S, et al. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. Cochrane Database Syst Rev 2016;(5):CD007126.
72. Jibril F, Sharaby S, Mohamed A, et al. Intravenous versus oral acetaminophen for pain: systematic review of current evidence to support clinical decision-making. Can J Hosp Pharm 2015;68(3):238–47.
73. Kaye AD, Cornett EM, Helander E, et al. An update on nonopioids intravenous or oral analgesics for perioperative pain management. Anesthesiol Clin 2017;35:55–71.
74. Hurley RW, Cohen SP, Williams KA, et al. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med 2006;31(3):237–47.
75. Arumugam S, Lau CSM, Chamberlain RS. Use of preoperative gabapentin significantly reduces postoperative opioid consumption: a meta-analysis. J Pain Res 2016;9:631–40.
76. Moghadam MS, Alavinia M. The effects of gabapentin on methadone based addiction treatment: a randomized controlled trial. Pak J Pharm Sci 2013;26(5):985–9.
77. Sanders NC, Mancino MJ, Gentry WB, et al. Randomized, placebo-controlled pilot trial of gabapentin during an outpatient, buprenorphine-assisted detoxification procedure. Exp Clin Psychopharmacol 2013;21(4):294–302.
78. Moore RA, Derry S, Aldington D, et al. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev 2015;(9):CD008659.

79. Alexander R, El-Moalem HE, Gan TJ. Comparison of the morphine- sparing effects of diclofenac sodium and ketoroiac tromethamine after major orthopedic surgery. J Clin Anesth 2002;14:187–92.
80. Straube S, Derry S, McQuay HJ, et al. Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. Acta Anaesthesiol Scand 2005;49(5):601–13.
81. De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. Anesth Analg 2012;114(2):424–33.
82. De Oliveira GS Jr, Almeida MD, Benzon HT, et al. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011;115(3):575–88.
83. Tang C, Xia Z. Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic. J Pain Res 2017;11(10):1899–904.
84. Blaudszun G, Lysakowski C, Elia N, et al. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2012; 116(6):1312–22.
85. Wenzel JT, Schwenk ES, Baratta JL, et al. Managing opioid-tolerant patients in the perioperative surgical home. Anesthesiol Clin 2016;34(2):287–301.
86. Gelineau AM, King MR, Ladha KS, et al. Intraoperative esmolol as an adjunct for perioperative opioid and postoperative pain reduction: a systematic review, meta-analysis, and meta-regression. Anesth Analg 2018;126(3):1035–49.
87. Darnall BD. Pain psychology and pain catastrophizing in the perioperative setting: a review of impacts, interventions and unmet needs. Hand Clin 2016; 32(1):33–9.
88. Garland EL, Baker AK, Larsen P, et al. Randomized controlled trial of brief mindfulness training and hypnotic suggestion for acute pain relief in the hospital setting. J Gen Intern Med 2017;32(10):1106–13.