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Perioperative Management and Analgesia for Patients Taking Buprenorphine and Other Forms of Medication-Assisted Treatment for Substance Abuse Disorders

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Keywords

• Substance abuse • Opioid disorder • Medication-assisted treatment
• Multimodal analgesia

Key points

- Substance abuse disorders represent a worsening public health catastrophe and a significant burden to the health care system.
- Medication-assisted treatment has emerged as an option to decrease the incidence of opioid abuse/relapse and risk of significant opioid-related harm.
- Perioperative management can be complex and requires a thoughtful, multidisciplinary, multimodal approach to pain management incorporating medical providers from a broad range of specialties.
- The perioperative surgical home approach offers significant potential advantages when applied to the perioperative management of patients with substance abuse disorders.
- Optimal perioperative management of buprenorphine has not been well-established; therefore, patient-related factors and buprenorphine prescriber involvement can help to maximize outcomes and minimize the risk of adverse outcomes.

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INTRODUCTION

The origin story of the opioid epidemic cataclysm is one of greed, misunderstanding, and unintended consequences [1]. This story of opioid abuse is also one that is well-known not just within the medical community, but also to our patients. Driving this awareness of the opioid abuse pandemic is an interplay between the current political climate, editor proxy, global events, advertiser's influence, social media, and personal events. We are perpetually inundated on the evening news or on social media regarding rising opioid deaths and there is increasing focus on legislation at the state and federal levels to put an end to the opioid crisis.

In 2017, more than 47,000 people in the United States died after an opioid overdose. This works out to 1 person dying every 11 minutes from a preventable and catastrophic death. In that same year, 1.7 million United States citizens suffered from a substance abuse disorder related to prescription opioids and 652,000 abused heroin [2,3]. According to data from the Centers for Disease Control and Prevention, drug overdose death rates in the United States have experienced a 4-fold increase between 1999 and 2017 with the greatest increase occurring in males and those between the ages of 25 and 65 years [4]. The impact of the large number of premature deaths related to opioid administration is one of the primary factors related to the decrease in overall life expectancy reported in 2017 [5]. Although there are no opioids that are entirely without blame, synthetic opioids and heroin are largely responsible for the increase in observed age-adjusted drug overdose death rates secondary to opioids [4].

If one examines only the economic burden of opioid-related abuse, the estimates of annual costs from calendar year 2013 in the United States are $78.5 billion. These costs were related to the provision of health care, lost productivity, addiction treatment, and the criminal justice system [6]. Given the growth of this problem, it is likely that annual costs will continue to increase and, without intervention, might very well overwhelm our health care system.

Behind all the staggering numerical data, there are patients longing for treatment of both their chronic disease and for acute pain management after surgical procedures in the setting of either opioid tolerance or opioid antagonists. These patients may be challenging to treat and may suffer from several comorbid psychiatric and medical conditions. Compounding the problem for patients with a history of chronic pain is that they may experience marginalization at the hands of health care providers and may subsequently harbor sentiments that make them less likely to trust health care providers in the future [7,8].

Patients with chronic pain or those who go on to develop persistent postsurgical pain may also be at increased risk for the development of postoperative complications or increased costs related to treatment of a variety of potential complications or prolonged hospital admissions [9,10]. However, a thorough and compassionate strategy that avoids marginalization of patient concerns is the best approach to improve patient satisfaction while simultaneously maximizing outcomes. We have progressed a long way since the outdated mantra

of stamping out pain and overemphasizing pain as the fifth vital sign. However, we need to recognize that the medical community contributed to the rate of opioid use and abuse disorders and that we need to have a systematic approach to management that emphasizes quality, cost-effective, and compassionate care. Patients undergoing treatment for opioid use or abuse disorders may be difficult to manage in the perioperative setting and therefore consideration should be given to evidence-based, multidisciplinary care to maximize success. The focus of this article is an overview of the medications currently approved for medication-assisted therapy (MAT) to help patients manage substance abuse disorder and the perioperative analgesic approach for these patients.

BUPRENORPHINE

Available since the 1970s, buprenorphine has been used as both an alternative to methadone in the treatment of opioid dependence and as an adjunct in chronic pain management. Buprenorphine is a partial agonist of the mu opioid receptor and an antagonist of the kappa opioid receptor. With activation of the mu opioid receptor, buprenorphine provides analgesia similar to full mu opioid receptor agonists. However, secondary to partial agonist activity at these receptors, the dose–response curve plateaus such that respiratory depression is unlikely [11]. This ceiling effect at higher doses makes buprenorphine an ideal agent for chronic pain management in opioid-dependent or -tolerant patients [12,13]. Buprenorphine has the highest affinity for the mu receptor of all opioids and will therefore displace and prevent binding of the mu receptor by concurrently administered full opioid agonists. It is metabolized hepatically via the cytochrome P-450 CYP3A4 system and has an active metabolite, norbuprenorphine, which has one-fifth the activity of buprenorphine [14]. In addition, the dissociation rate of buprenorphine from the mu receptor is approximately 166 minutes and the half-life is between 25 and 48 hours; thus, it takes 2 to 3 days for this agent to be eliminated from the body [15]. This long elimination half-life has implications for those patients treated with buprenorphine formulations who present for surgery expected to result in significant perioperative pain.

Buprenorphine is available in multiple formulations including sublingual, buccal, transdermal, and implantable or injectable formulations either alone or in combination with naloxone (Table 1). The addition of naloxone to buprenorphine formulations further decreases the abuse potential of this agent because naloxone blocks the euphoric effects of opioids if injected parenterally.

With increasing rates of opioid use disorders in the United States, the number of patients treated with buprenorphine and the number of prescribers providing buprenorphine are experiencing tremendous growth. Under the Drug Addiction Treatment Act of 2000, prescribers are required to undergo an 8-hour class to be eligible to prescribe buprenorphine and can apply for waivers to increase the number of patients that can be treated by each provider. There are more than 14,000 prescribers under Medicare Part D. Claims made by these prescribers for buprenorphine containing medications have increased

Table 1
Available formulations of buprenorphine, methadone, and naltrexone

Brand name	Generic name	Formulation
Belbuca	Buprenorphine	Transbuccal
Buprenex	Buprenorphine	IV or IM injection
Butrans	Buprenorphine	Transdermal patch
Probuphine	Buprenorphine	Implant
Subutex	Buprenorphine	Sublingual
Suboxone	Buprenorphine with naloxone	Sublingual
Zubsolv	Buprenorphine with naloxone	Sublingual
Dolophine, Methadose	Methadone	PO
Methadone HCl Intensol	Methadone	PO solution
(No brand name)	Methadone	IV
ReVia	Naltrexone	PO
Vivitrol	Naltrexone	Intramuscular

Abbreviations: IM, intramuscular; IV, intravenous; PO, orally.
Data from Lexicomp Online (Lexi-Drugs, UW Health Formulary), Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; April 15, 2013.

from 26,400 in 2011 to 90,900 in 2015 [16]. Hence, there is an increasing likelihood that anesthesia providers will encounter patients chronically consuming buprenorphine for either chronic pain or abuse disorders. Therefore, it is imperative that anesthesia providers understand the mechanism of action for buprenorphine and have developed a plan for the perioperative management of these patients.

PERIOPERATIVE MANAGEMENT

There is no consensus on the perioperative management of patients treated with buprenorphine and most published recommendations are derived from expert opinion or individual case reports. Perioperative management strategies should not be developed or implemented in a vacuum or anesthesia-dominated silo. Continuous involvement of patients and their buprenorphine prescribers is essential to minimize the risk of opioid relapse or overdose and improve the likelihood of providing perioperative analgesia.

One strategy is simply the continuation of perioperative buprenorphine and encouraging patients to administer their usual morning dose before any planned surgical procedure. Support for this approach was provided by several recently published meta-analyses. These studies have demonstrated a detrimental analgesic effect related to discontinuing buprenorphine therapy in the perioperative period, especially when patients are maintained on lower doses (ie, <16 mg/d) [17,18]. It is important to recall that buprenorphine possesses significant agonist activity. Therefore, if patients discontinue their buprenorphine therapy preoperatively, they have been found to suffer through increased pain and require significantly more opioids in the first 24 hours after surgery than those who are continued on their buprenorphine preoperatively [19].

Should buprenorphine therapy be continued, different dosing strategies may result in reasonable postoperative outcomes. In select patients, maintenance of home dosing regimens, supplemented with multimodal and opioid analgesics, may be appropriate. In other patients, the analgesic impact of buprenorphine therapy can be exploited to provide postoperative analgesia and increases in buprenorphine may be beneficial [18]. Any changes in buprenorphine therapy need to be done in concert with the patient's primary buprenorphine provider.

An alternative strategy would be to decrease the preoperative dose of buprenorphine with the hope that a decreased buprenorphine dose may increase opioid receptor availability for full opioid agonists [20]. Other, less used, strategies include converting the patient's buprenorphine needs to a short-acting full agonist opioid or methadone therapy. These changes would need to be done with the full participation of the patient's primary buprenorphine prescriber and variabilities in opioid conversions and cross-tolerance would need to be considered. Patients receiving injectable or implantable buprenorphine therapy will need to be treated similarly to those patients whose oral buprenorphine therapy has been continued throughout the perioperative process.

Protocols have been developed that have attempted to make a distinction between the acuity of surgery, the expected postoperative analgesic requirements, and the daily dose of buprenorphine. The first well-established protocol for these patients was developed at the University of Michigan and was intended to address the analgesic needs for those patients consuming buprenorphine in the setting of chronic pain management. In this protocol, patients undergoing surgical procedures expected to result in minimal postoperative pain are treated with continuation of buprenorphine therapy. For elective surgical procedures expected to result in moderate to severe postoperative pain, the protocol suggests transitioning buprenorphine therapy to a short-acting full opioid agonist. When patients consuming buprenorphine present for emergent surgery, the buprenorphine should be discontinued after surgery, and a multimodal regimen should be implemented [21].

With this protocol in mind, if the perioperative analgesic plan calls for buprenorphine therapy to be paused, the significant elimination time of this medication requires stopping the medication 48 to 72 hours before surgery [22]. This protocol also recommends that the duration of buprenorphine cessation before surgery be based on the patient's dose of buprenorphine; those on a low dose of 0 to 4 mg/d should pause therapy for 24 hours, whereas those on a moderate or high dose of greater than 8 mg/d should hold for 72 hours. In patients with implantable formulations, removing the implanted drug may not be realistic, and these patients will likely present difficulties with opioid-based postoperative analgesic regimens [21].

The decision to continue or stop buprenorphine therapy in the perioperative period is not one to be taken lightly. Reasons for this are numerous, but chief among them is that there is an increase in mortality in the first 4 weeks after cessation of buprenorphine treatment [23]. In patients with a history of depression, anxiety, or substance abuse, the decision to discontinue buprenorphine is

not without risk. In all patients on buprenorphine, not specifically limited to those in the perioperative period, discontinuing buprenorphine led to at least a 50% relapse in opioid use [24]. Decisions regarding changes to a patient's buprenorphine dosing must be done in conjunction with the patient, surgeon, anesthesiologist, and primary prescriber. See Fig. 1 for a potential algorithm to help initiate the development of a preliminary perioperative plan.

Overall, maximizing perioperative multimodal analgesia and regional anesthesia techniques may offer perioperative benefits. In addition, using a collaborative acute pain management consult service that involves representatives from anesthesiology, pharmacy, physical therapy, addiction medicine, and psychiatry may offer contributions to perioperative pain management.

Finally, after surgery and discharge from the hospital, a concrete plan needs to be in place to ensure a smooth transition back to buprenorphine therapy. Restarting buprenorphine in the setting of high doses of full opioid agonists could precipitate acute withdrawal. Buprenorphine should be restarted 12 to 24 hours after a dose of a short-acting opioid such as oxycodone and 24 to 48 hours after a dose of a long-acting opioid such as morphine [11]. Consideration should be given to restarting buprenorphine at a low dose of 1 to 2 mg/d and up titrating back to the preoperative dose over 1 to 2 days while closely observing for signs of withdrawal [11].

METHADONE

Methadone is approved by the US Food and Drug Administration for maintenance therapy in the setting of opioid use disorder and in the treatment of moderate to severe chronic pain. Methadone is also gaining popularity for acute

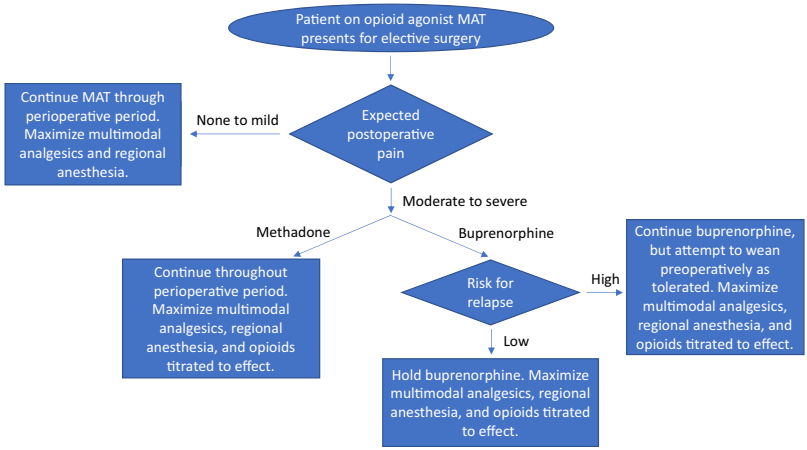

Fig. 1. Potential algorithm to help initiate the development of a perioperative pain management plan for patients on opioid agonist MAT (buprenorphine or methadone).

pain management in the perioperative setting for patients expected to experience significant postoperative pain [25,26]. Ambulatory dosing strategies are based on the indication as the analgesic effects of methadone are related to the alpha-elimination phase whereas the withdrawal suppression is related to the beta-elimination phase [27]. As such, methadone is usually administered multiple times per day if being prescribed for chronic pain and only once daily when prescribed for MAT [27,28]. Providers who prescribe methadone must have a separate Drug Enforcement Administration registration as an opioid treatment program, which also needs to be certified by Substance Abuse and Mental Health Services Administration.

Methadone is a diphenylpropylamine opioid that is a racemic mixture of 2 enantiomers. The R-methadone enantiomer is a full mu opioid receptor agonist. The S-methadone enantiomer has N-methyl-D-aspartate (NMDA) antagonist and serotonin and norepinephrine reuptake blocking properties [27,28]. Methadone is metabolized by the hepatic cytochrome P450 system. The main metabolite formed is inactive, but there are 2 minor metabolites (methadol and normethadol) that behave similarly to methadone [28]. The half-life of methadone ranges from 8 to 59 hours, but in patients with impaired hepatic function, methadone may accumulate, and exaggerated or prolonged effects may be encountered. Methadone is ultimately excreted via the fecal and renal routes, where renal excretion of unchanged drug typically accounts for less than 10% of elimination. Notably, methadone is not dialyzable [29].

Methadone is available in tablet, soluble tablet, solution, and injectable formulations (see Table 1). As a tablet or oral solution, it has up to 95% bioavailability. The duration of action is anywhere from 4 to 8 hours after a single dose to 22 to 48 hours after multiple doses [29].

There are multiple important factors to consider when initiating methadone owing to its unique pharmacologic profile. Before initiation, it is recommended to wean down or off other opioids, if possible, because initiating methadone therapy in the setting of other opioids increases the risk of adverse side effects. Methadone has a long and variable half-life, so multiple days are required to reach a steady-state concentration. Thus, care should be taken with initiation and up-titration of methadone. There is interpatient variability in absorption, duration of action, and elimination. This may be partly because methadone can accumulate in multiple tissues after multiple doses and subsequently be slowly released, thus, variably prolonging the duration of action [29,30].

Methadone has a higher binding affinity for the mu opioid receptor than morphine [31]. Therefore, when patients maintained on chronic methadone abuse heroin, which is metabolized to morphine, the euphoric effects are attenuated. There continues to be an increased risk for respiratory depression when methadone is combined with heroin as methadone does not occupy 100% of the mu opioid receptors at the typical doses given for treatment of substance abuse disorder [28]. Similar interactions occur when methadone is administered alongside short-acting opioids in the setting of acute postoperative pain.

PERIOPERATIVE MANAGEMENT

Because methadone is a full mu opioid agonist, it possesses significant analgesic properties. These patients should be instructed to take their normally prescribed methadone dose the day of their surgical procedure. A reasonable perioperative pain management plan includes continuing methadone and supplementing with immediate-release opioids as needed. Formulating an opioid agreement preoperatively may be helpful because it establishes expectations for the postoperative analgesic course including a plan for discontinuing any short-acting opioids. However, additional opioids should not be the first-line option for these patients. A multimodal approach with nonopioid and nonpharmacologic adjuncts as well as regional anesthesia should be implemented for these patients. In formulating the anesthesia and perioperative pain plan, a recent urine drug screen may be helpful to ensure that methadone has been taken as directed and that other drugs of abuse are not present [28].

Methadone can prolong a patient's QTc, so a recent electrocardiogram should be available before surgery. The QTc should be closely monitored in the perioperative period, especially if additional QTc prolonging medications (eg, droperidol) are administered. It may also be prudent to monitor serum electrolytes, because patients with prolonged QTc are at an increased risk of arrhythmias such as Torsades de pointes, and this risk may be exacerbated by electrolyte abnormalities, especially abnormalities in serum potassium and magnesium levels [28].

Methadone metabolism can be significantly altered by the co-administration of other medications that can impact the CYP450 system. Medications that enhance the hepatic CYP450 system, such as carbamazepine and phenytoin, may decrease plasma levels of methadone. Alternatively, medications that inhibit the CYP450 system, such as fluconazole and ciprofloxacin, could increase the amount of methadone available and cause over-narcotization, especially if given in combination with other opioids in the postoperative setting. Certain commonly prescribed antibiotics, antidepressant, antiepileptic, and antiretroviral medications fall into these categories, so the initiation and discontinuation of these medications should be considered carefully. Although these interactions are possible, they may not necessarily lead to clinically significant effects in every patient. After any medication changes, patients should be monitored, and appropriate adjustments should be made to their methadone dosage [32].

If methadone is discontinued abruptly and not replaced with another opioid during the perioperative period, patients may experience opioid withdrawal. Depending on the indication for methadone, these patients may also be at risk for relapse, so abrupt discontinuation is not recommended.

The perioperative analgesic management of these patients should then be similar to what might be planned for any patient with chronic opioid requirements. Preoperative consultation should focus on the establishment of realistic analgesic goals and treatment options. Analgesic therapy should consist of aggressive efforts to provide multimodal analgesia and continuous regional

anesthesia techniques. Methadone therapy should be continued and any changes to the analgesic regimen should be coordinated with the patient's primary opioid prescriber. See Fig. 1 for a potential algorithm to help initiate the development of a preliminary perioperative plan.

NALTREXONE

Naltrexone is approved by the US Food and Drug Administration for MAT of opioid use disorder. This agent differs from methadone and buprenorphine in that it is an opioid antagonist. Therefore, it is recommended that patients are abstinent from opioids for at least 7 to 10 days before initiation of naltrexone therapy to avoid the elicitation of withdrawal symptoms [33]. This pause in opioid administration can be difficult to achieve in this patient population and has been shown to be a barrier to naltrexone initiation, especially in the outpatient setting [34]. However, after overcoming this hurdle, extended-release naltrexone has been shown to be noninferior to buprenorphine in total number of opioid-negative urine tests, days of heroin and other illicit opioid use [35], and relative hazard of relapse [36]. Patients taking extended-release naltrexone also reported a higher percentage of opioid-free weeks and decreased opioid craving when compared with placebo [37]. Treatment with naltrexone may be necessary for patients who have a professional responsibility to avoid opioid agonists (physicians, air traffic controllers, etc). This agent may be slightly easier to obtain because any health care provider who is legally able to prescribe medications can write prescriptions for naltrexone.

Naltrexone is also approved by the US Food and Drug Administration to treat alcohol use disorder. Possibly because of this, alcohol use disorder was 3 times as prevalent among patients who were prescribed naltrexone than those who were prescribed buprenorphine for MAT [38]. Naltrexone is additionally being used in an off-label fashion to lessen the symptoms of fibromyalgia and chronic pain [39,40]. These topics are beyond the scope of this article, but they certainly highlight the diverse patient populations that may present for surgical interventions on naltrexone therapy.

Naltrexone is a cyclopropyl derivative of oxymorphone that acts as a competitive opioid antagonist, especially at the mu opioid receptor. Naltrexone is hepatically metabolized by noncytochrome-mediated dehydrogenase into 6-beta-naexol, an active metabolite, and minor metabolites. A small portion of naltrexone and its metabolites can also undergo glucuronidation. These metabolites and a small portion of unmetabolized naltrexone are primarily excreted in the urine. Oral naltrexone has a half-life of 4 hours and its active metabolite has a half-life of 13 to 14 hours, much longer than naloxone's half-life. Injectable extended-release naltrexone has a half-life of 5 to 10 days [41].

Naltrexone is currently available as an oral tablet and an intramuscular injection (see Table 1). Each tablet is 50 mg and is taken once a day in doses ranging from 50 mg to 150 mg. There is a linear relationship between oral naltrexone dosage and duration of action where each 50 mg lasts for 24 hours [41].

Intramuscular extended-release naltrexone injections contain 380 mg and are released slowly over 4 weeks. Patients receive this injection once a month without any variability in dosing. Although there are 3 brands available, Vivitrol is the only intramuscular formulation approved in the United States [41].

Although oral naltrexone was approved for MAT decades before extended-release naltrexone, a meta-analysis showed oral naltrexone was no more effective than placebo at treating opioid use disorder [42]. Despite this, oral naltrexone was prescribed more frequently than extended-release naltrexone in subsequent years [38]. Thus, patients may continue to be on either oral or injectable naltrexone.

Implantable forms of naltrexone are available but are not commonly prescribed.

As an antagonist, naltrexone blocks the euphoric, analgesic, and sedative effects of opioids, but it can also precipitate withdrawal in patients who have not fully detoxified from opioids. It is not addictive and no physiologic dependence forms. However, after discontinuation of naltrexone, patients may be more sensitive to opioids. Overdose is possible at previously tolerated doses of opioids and therefore close observation is required to ensure that patients do not experience significant respiratory depression [27,43].

PERIOPERATIVE MANAGEMENT

For surgical procedures expected to result in moderate or severe postoperative pain, naltrexone administration should be discontinued in an effort to improve analgesic management. Oral formulations should be held for at least 2 to 3 days and the last dose of the injectable extended release formulation should be 30 days preoperatively [27]. For patients at significant risk for relapse, it is important to coordinate preoperative planning with the patient's naltrexone prescriber. In addition, the patient should be involved in developing the perioperative analgesia plan and should be aware of their increased risk for relapse and difficulties with analgesic management. After discontinuation of naltrexone, patients may experience increased sensitivity to opioids and therefore close monitoring is required to detect respiratory depression [27,43]. Consideration should be given to initiating therapy with lower doses of opioids and titrating to effect once the analgesic, sedative, and respiratory depressant effects have been evaluated. These patients should also have a multimodal analgesic plan, including nonopioid analgesics, nonpharmacologic adjuncts, and continuous regional anesthesia techniques, if appropriate. In the postoperative period, naltrexone should continue to be held until the patient has been opioid free for at least 7 to 10 days to decrease the risk of withdrawal symptoms with the re-initiation of naltrexone [33].

To avoid the risks associated with these periods of time when patients are not taking naltrexone, it may be reasonable to continue this agent for procedures in which little to no pain is expected or where the risk of relapse and overdose is substantially increased. In this situation, it is extremely important that the anesthesia providers and surgical team are aware that the patient will react

differently to opioid medications, and they should rely heavily on a multimodal approach to analgesia. It is therefore vital that the surgical team, anesthesia team, and prescribing provider work together to formulate a plan for these patients well before the day of surgery. See Fig. 2 for a potential algorithm to help develop a preliminary perioperative plan for these patients.

If a patient taking naltrexone presents for emergent surgery, it may not be practical to wait until naltrexone has been sufficiently metabolized to allow for opioids to provide effective analgesia. In these scenarios, providers should rely on nonopioid analgesics, nonpharmacologic adjuncts, and continuous regional anesthesia techniques as the foundation of their postoperative pain plan. This is especially true for patients receiving intramuscular naltrexone therapy, because the duration of effect from this route of administration is approximately 4 weeks. If the patient had been taking oral naltrexone, opioid medications could be considered 48 to 72 hours after their last naltrexone dose if pain control remains inadequate. Additionally, naltrexone therapy should continue to be held in the postoperative period until the patient has been opioid free for at least 7 days [33]. Again, multidisciplinary pain management teams can be profoundly helpful in the perioperative management of these patients, especially during the required detoxification period before re-initiation of naltrexone.

THE PERIOPERATIVE SURGICAL HOME

The perioperative surgical home (PSH) emphasizes the benefits that might be realized with a collaborative, interdisciplinary, comprehensive, protocolized, and innovative model of care. PSHs are involved in managing patient care

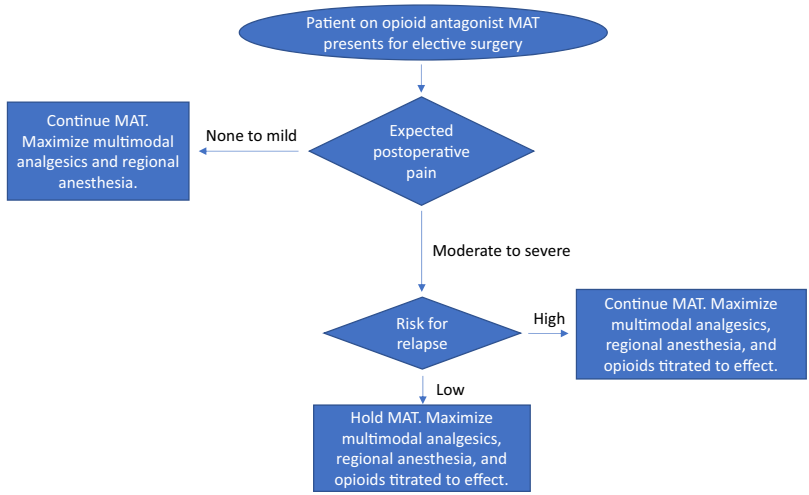

Fig. 2. Potential algorithm to help initiate the development of a perioperative pain management plan for patients on opioid antagonist MAT (naltrexone).

from the time that the decision is made to operate and help to establish the optimal timing of any surgical procedure. The PSH would then coordinate management of all necessary preoperative testing and consults, would ensure that patients are appropriately routed through perioperative pathways (eg, enhanced recovery) and that patients receive evidence-based perioperative management.

With regard to perioperative analgesia, an anesthesia-led PSH and comprehensive perioperative pain service would then be involved in determining a perioperative analgesic plan that would include multimodal preoperative analgesics, regional and neuraxial analgesic techniques, analgesic infusions, and other opioid sparing techniques [44]. This preoperative management may include a preoperative reduction in baseline opioid administration, cessation of opioid antagonists or transitioning from a partial opioid receptor agonist to a full agonist [45]. This model would decrease variability in care, create seamless transitions in patient care, integrate various medical providers, and foster enhanced patient–clinician shared decision making [46]. Broad pain-related management concepts that can be addressed by a well-functioning PSH include emphasizing continuity, coordination, integration, patient-centered and shared decision making, and variability reduction while focusing on improving quality and reducing costs [44].

In the setting of opioid tolerance or history of abuse, the PSH presents an opportunity to deliver patient-centered pain management throughout the perioperative period. These patients need to be identified and met by members of the pain management team before surgery. These visits will help to establish care with the pain management team and allow for the formulation of a perioperative pain management plan. During this initial visit, the patient's history of painful symptoms and medication management (prescriber, medication, dose, frequency, duration, and route) can be discussed. This visit determines if opioid maintenance therapy is prescribed for MAT or analgesic purposes because this information impacts the decision to continue or pause buprenorphine or other opioid antagonist therapies. During this visit, these patients will also have an opportunity to create and take ownership of a personalized perioperative pain management plan. Available multimodal and complementary therapies should be discussed with patients during the preoperative visit. There should also be a discussion about expected postoperative pain levels, how pain exacerbations will be managed, and what the patient's anticipated pain management regimen will be at the time of discharge. Psychological factors that might impact pain management should be addressed, and patients should be allowed an opportunity to discuss relevant fears and anxiety [47].

After the surgery, daily visits by a multidisciplinary pain service will help to provide pain assessments, reinforce and encourage adherence to the predetermined pain regimen, and provide necessary adjustments (Box 1). Members of this multidisciplinary team should include anesthesia pain specialists, but could also include members of the pharmacy, spiritual services, addiction medicine, health psychology, psychiatry, physical medicine and rehabilitation, and

Box 1: A multidisciplinary approach to pain management and patient care is required

Multidisciplinary components required for patients on MAT

- Medication-assisted treatment prescriber
- Anesthesia providers
  - Preoperative clinic
  - Intraoperative anesthesia provider
  - Acute pain service
  - Chronic pain service/opioid transition clinic
- Surgical team
- Pharmacy
- Spiritual services
- Addiction medicine specialists
- Health psychology
- Physical medicine and rehabilitation
- Physical/occupational therapy
- Complementary medicine

Coordination with other services will facilitate long-term success.

physical and occupational therapy. Providers of integrative medicine (acupuncture, massage, hypnosis, etc) may also supply complementary therapies that aid in pain management [45].

The specifics of analgesic management prescribed by this inpatient team will vary depending on the patient, their personal history of pain symptoms and treatment modalities, and the surgical procedure. However, there are a number of treatment strategies that deserve general consideration. Multimodal analgesic approaches should be considered to decrease opioid administration and opioid-related side effects and to provide analgesia in patients for whom opioids are unlikely to be effective (Fig. 3) [48]. Nonpharmacologic efforts at pain management should also be encouraged as low-risk alternatives to opioid dose escalation (Box 2). These strategies might include distraction, meditation, mirror therapy, heat or ice, or transcutaneous electrical nerve stimulation devices. Finally, efforts to provide regional anesthesia should be maximized.

NONOPIOID PHARMACOLOGIC MECHANISMS TO TREAT PAIN

Regional anesthesia

Patients with a history of poorly controlled pain or opioid abuse may benefit from regional anesthetic procedures. Neuraxial and peripheral nerve blocks can block the transmission of painful stimuli and decrease the intensity of pain symptoms and opioid requirements for a variety of surgical

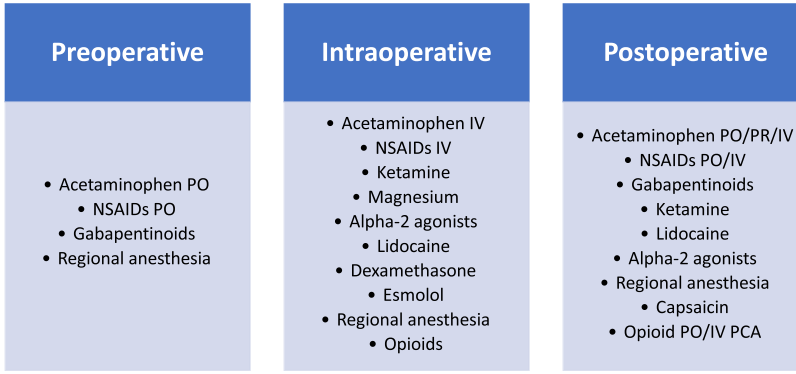

Fig. 3. Pharmacologic approaches to perioperative management of the patient with medication-assisted treatment for substance abuse disorders. IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally; PR, per rectum.

procedures [49]. Decreases in acute postoperative pain may also result in a decreased frequency and severity of chronic pain symptoms. The introduction and adoption of fascial plane blocks, including erector spinae, retrolaminar, quadratous lumborum, pectoralis, and serratus anterior plane blocks, have allowed for an increase in the application of regional anesthesia procedures beyond what was traditionally available. Ultrasound guidance may improve

Box 2: Nonpharmacologic approaches to perioperative management of the patient with medication-assisted treatment for substance abuse disorders

Nonpharmacologic analgesic adjuncts for opioid tolerant patients

- Transcutaneous electrical nerve stimulation
- Heat/cold
- Acupuncture
- Massage
- Distraction
- Mindfulness/meditation
- Breathing exercises
- Mirror therapy
- Pastoral services
- Aromatherapy
- Hypnosis
- Music therapy
- Physical therapy

the safety and efficacy of regional anesthesia procedures and allow for even more widespread application [50]. Local anesthetic adjuncts (eg, clonidine and dexamethasone), liposomal formulations, or continuous catheter techniques should be considered to both prolong the duration of analgesia and decrease the incidence or severity of rebound pain. Surgical colleagues should be encouraged to provide surgical site administration of local anesthetic via either infiltration or continuous infusion techniques if a peripheral nerve block is contraindicated.

Intravenous lidocaine

The intravenous administration of lidocaine provides analgesia without the need for an invasive procedure. Intravenous infusions of lidocaine are proposed to be beneficial via sodium channel blockade-related analgesic and anti-inflammatory mechanisms that are yet to be well-defined [51]. Lidocaine may also directly act on the dorsal horn of the spinal cord to inhibit glutamate release [52], which may be why it is especially effective in treating neuropathic pain [53]. Although the literature is mixed with regard to efficacy, lidocaine infusions have demonstrated significant pain management benefits when used for select abdominal or thoracic procedures [54]. Other studies have demonstrated that perioperative lidocaine infusions are also associated with decreased hospital length of stay and earlier return of bowel function [55]. Patients with intravenous lidocaine infusions require close monitoring for the development of severe adverse neurologic or cardiac reactions and oftentimes infusions are discontinued at the time of discharge from the postanesthesia care unit secondary to limited monitoring capabilities on surgical floors [56]. Caution should be exercised in patients with a history of seizures, hepatic disease, or cardiac conduction abnormalities. Dosing should also be cautiously done in those with obesity or low muscle mass. See Table 2 for a potential dosing strategy.

Acetaminophen

Acetaminophen is a centrally acting analgesic that possesses weak anti-inflammatory properties. Preoperative oral acetaminophen administration represents an inexpensive mechanism to enhance perioperative analgesia. Rectal and intravenous routes of administration are also available, but suffer from either decreased provider–patient enthusiasm for route of administration or increased cost without significant benefits relative to oral administration [57]. In fact, a recent analysis has demonstrated that although both intravenous and oral acetaminophen decrease opioid consumption on postoperative day 1, oral acetaminophen decreases opioid consumption more effectively [58].

Ketamine

Perioperative ketamine use can decrease postoperative opioid requirements while simultaneously decreasing the development of opioid induced hyperalgesia via its NMDA receptor antagonism. Dextromethorphan and amantadine have also been administered to provide NMDA receptor antagonism, but are much less frequently used in a clinical setting [59]. In 1 study of

Table 2
Potential dosing strategies for various analgesics that can be used as part of a multimodal approach

Medication	Potential dosing strategy	Route of administration
Acetaminophen	1000 mg before surgery QID dosing postoperatively	PO, PR, IV
Lidocaine	1–2 mg/kg bolus at induction 1–2 mg/kg/h infusion	IV
Ketamine	0.25–0.5 mg/kg IV bolus at induction 2–10 μg/kg/min intraoperatively 10–12 mg/h postoperatively	IV
Gabapentin	600 mg before surgery 600 mg TID postoperatively	PO
NSAIDs	Ketorolac: 15–30 mg QID Celecoxib: 200 mg QD	Ketorolac: IV Celecoxib: PO
Alpha-2 agonists	Dexmedetomidine: 1 μg/kg load over 10 min with 0.2–1.4 μg/kg/h infusion Clonidine: 200 μg/d	Dexmedetomidine: IV Clonidine: PO or TD
Magnesium	250 mg bolus at induction 500 mg/h infusion	IV
Esmolol	0.5–1 mg/kg at induction 5–50 μg/kg/min infusion	IV
Dexamethasone	0.1 mg/kg at induction	IV

Abbreviations: IM, intramuscular; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally; PR, per rectum; QD, daily; QID, 4 times per day; TD, transdermal; TID, 3 times per day.

opioid-tolerant patients undergoing spine surgery, intraoperative ketamine administration demonstrated long-lasting pain management and opioid sparing effects that were sustained at 6 weeks after surgery [60]. Other studies have demonstrated that decreases in sedation and pain scores after ketamine administration persisted at 6 months after surgical procedures [61]. Ketamine therapy is well-tolerated, but rare hallucinations, liver function test elevations, sympathetic stimulation, or increases in intracranial pressure may limit the ability to safely prescribe this agent in select patients [62]. Ketamine infusion therapy is commonly safely administered on a general care floor, but local institutional policies may dictate a higher level of care and monitoring. See Table 2 for a potential dosing strategy.

Dexamethasone

Dexamethasone at doses of 0.1 to 0.2 mg/kg are effective at decreasing postoperative pain and opioid administration [63,64]. Perineural administration of dexamethasone may also provide prolongation of regional anesthesia techniques [65]. See Table 2 for a potential dosing strategy.

Esmolol

Recent evidence suggests that intraoperative esmolol infusions can decrease intraoperative opioid administration, postanesthesia care unit pain, and postanesthesia care unit opioid requirements. The mechanism of pain reduction

associated with esmolol infusions is unclear but may be related to diminishing the impact of opioid induced hyperalgesia by limiting intraoperative opioid administration [66]. See Table 2 for a potential dosing strategy.

Gabapentin

Gabapentinoids (gabapentin and pregabalin) bind to an auxiliary subunit of voltage-dependent calcium channels, which in turn inhibit the release of excitatory neurotransmitters. The gabapentinoids have been successfully used to decrease both acute postsurgical and chronic postoperative pain [67,68]. Other studies have also demonstrated diminished postoperative opioid requirements with perioperative gabapentin [69]. The ideal dosing regimen has not yet been well-established, but reductions in dosing should generally be considered in the elderly and those with significant renal impairment. Dosing may be limited by the development of significant nausea or sedation. In the setting of acute pain, doses of gabapentinoids can generally be discontinued after 2 weeks of therapy [70]. See Table 2 for a potential dosing strategy.

Alpha-2 agonists

In the realm of pain management, alpha-2 agonists (clonidine and dexmedetomidine) act at the dorsal horn of the spinal cord to dampen the transmission of painful impulses. Use may be limited by the development of side effects, including sedation, bradycardia, and hypotension. Parenteral forms are available for both clonidine and dexmedetomidine, but clonidine is also available as a tablet, patch, or transdermal cream. This may increase the applicability and tolerance of this agent. Finally, perineural alpha-2 agonists have also been used to provide prolongation of regional anesthesia techniques [71]. See Table 2 for a potential dosing strategy.

Magnesium

Magnesium exerts its analgesic effect via antagonism at NMDA and calcium channel receptors. A 2013 meta-analysis demonstrated decreased pain and opioid requirements for 24 hours after surgery [72]. Dosing reductions or omission should be considered in patients with significant renal failure because accumulations may occur. In addition, neuromuscular blockade should be monitored closely for prolongation in the setting of magnesium supplementation. See Table 2 for a potential dosing strategy.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs represent an additional inexpensive analgesic modality that is, available for administration via either the oral or intravenous route. Nonsteroidal anti-inflammatory drugs function via inhibition of the cyclooxygenase enzyme. Concern over the potential for nonsteroidal anti-inflammatory drugs to inhibit platelet aggregation or impact renal function may limit the ability to administer these agents in the perioperative setting. However, the risk of increased surgical or gastrointestinal bleeding is not significantly affected with the postoperative administration of ketorolac, an intravenous cyclooxygenase-1 inhibitor [73,74]. Ketorolac dosing should be limited to

5 days over concerns related to adverse gastrointestinal or renal effects. Cyclooxygenase-2 inhibitors, such as celecoxib, may be less likely to result in clinically significant postsurgical bleeding and may therefore be better tolerated in certain clinical scenarios. However, patients with significant cardiac abnormalities (heart failure or revascularization) may not be appropriate candidates for nonsteroidal anti-inflammatory drug therapy because they may have an increased risk of thrombotic events, including myocardial infarction and stroke. See Table 2 for a potential dosing strategy.

Opioids

For patients with a history of opioid dependency or currently prescribed maintenance therapy with agents intended to curb opioid abuse, an opioid-free anesthetic, if possible, may be the preferred analgesic technique. To accomplish this goal, patients must be a motivated component of the decision-making process and regional and multimodal analgesic administration must be maximized. If opioid therapy cannot be avoided, consideration should be given to using multimodal intraoperative analgesic regimens that avoid rapid-acting or ever-escalating doses of intraoperative opioids that can result in acute tolerance and increased postoperative dosing requirements [75]. Baseline opioid therapy, partial opioid agonists, or opioid antagonists may make postoperative opioid dosing requirements quite high. These patients may therefore be at increased risk for postoperative respiratory depression and should be closely monitored [76]. Alternatively, loading patients with methadone intraoperatively has been shown to decrease the need for postoperative opioids, decrease patient-reported pain scores, and improve overall patient satisfaction [25]. Opioid rotations may be beneficial to some patients, but this practice should be closely directed by an inpatient pain service. Finally, in patients with a history of substance abuse, consideration should be given to prescribing an appropriate discharge analgesic regimen that decreases the likelihood of abuse. For example, newer formulations of extended-release oxycodone (eg, Xtampza ER and REMOXY ER) may decrease the risk of abuse or diversion by lessening the impact of drug crushing and injection [77,78]. Any changes to the home-going analgesic regimen should be closely communicated to the patient's outpatient opioid prescriber and consideration should be given to coordinating care with an opioid transition clinic. Opioid prescriptions for these patients should be for a limited time period, be limited in dose, and refills should not be allowed without reevaluation.

SUMMARY

There are many patients in treatment for opioid abuse disorders and this number will likely continue to increase. Appropriately treating these patients in the perioperative period requires a thoughtful and multidisciplinary approach that considers the patient's individual pain management history, history of opioid-related use or abuse, and history of effective analgesic management therapies. Management of these patients begins well before the day of surgery and not

simply in the postoperative period. Although the management of these patients may be associated with significant difficulties, the opportunity to provide effective and compassionate pain management will be deeply appreciated by the patient, their family, and your surgical colleagues. Ultimately, the management of these complex patients represents a phenomenal opportunity for anesthesiologists to distinguish themselves as experts in pain management and essential components of the entire arc of the perioperative process.

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