

Invited Review Article

Perioperative Management of Patients on Buprenorphine and Methadone: A Narrative Review

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Abstract

The opioid epidemic has been a major health and social problem over the last few decades. An increasing number of patients with Opioid Use Disorder (OUD) are presenting for perioperative management. These patients are either on buprenorphine or methadone for the maintenance and treatment of opioid addiction or chronic pain. In settings of acute pain, optimal management of patients with OUD is challenging and recovery can be jeopardized secondary to the unique pharmacology of these agents. This narrative review aims to summarize existing studies on the perioperative management of patients using buprenorphine and methadone and provide guidance to the management of patients with OUD during the perioperative period.

In 2016, an estimated 50 million adults in the United States struggled with chronic pain. (1) The chronic pain dilemma has led to a rapid increase in the use of opioid analgesics, which subsequently has resulted in greater overdose deaths due to opioid misuse. In 2018, according to the Department of Health and Human Services, 2 million people in the United States had opioid use disorder (OUD) and an estimated 130 people died each day due to opioid overdose. (2) Correspondingly, different states have promulgated regulations on safe prescribing by limiting the amount of opioid prescription and initiating online prescription monitoring programs to address opioid analgesic misuse. (3)

Medications such as long acting synthetic opioid methadone and partial opioid agonist buprenorphine have been found to be effective treatments for OUDs. These medications aim to decrease illicit opioid use and relapse and increase treatment engagement. (4, 5) It is paramount that these medications be continued at all times and not stopped prematurely. (4) Therefore, it is essential that anesthesia providers know how to care for these potential patients in the perioperative period. Though there has been several institutionalized guidelines and pain management strategies to help these patients, lack of standardization and paucity of data to guide providers in addressing perioperative care for patients still remain. In this narrative review, we will discuss pharmacologic profiles of buprenorphine and methadone in relation to OUDs and maintenance, highlight existing literature on the perioperative management of patients with OUDs, and summarize recommendations for the optimal care of this subset of patients in hopes to help guide providers in developing anesthetic regimen to optimize patient care.

Pharmacology of buprenorphine

Buprenorphine is a derivative of thebaine, which is a mixed opioid receptor modulator. It is highly lipophilic and has a large volume of distribution. (6) It has activity at multiple receptor types. It is a partial agonist at the mu-opioid receptor which has an analgesic effect. Compared to other opioids, buprenorphine has a strong binding affinity to the mu-opioid receptor with a slow dissociation from the receptor. (7) Buprenorphine is also an

antagonist at the kappa opioid receptor which has been linked in the treatment of depression. (7) Some patients who have been resistant to standard treatment modalities for depression have responded positively to buprenorphine therapy. Buprenorphine's ability to limit psychomimetic, euphoric, and induced hyperalgesia effect in comparison to other opioids has been attributed to its kappa receptor antagonism. (8) Additionally, buprenorphine is an agonist at the delta receptor, and its effect are not clearly understood. (7) Buprenorphine has low receptor-stimulating activity despite high receptor affinity and binding capacity leading to less euphoria, respiratory depression and sedation even in higher doses. (9) At a minimum, 40 to 50% of receptor occupancy is needed to abate withdrawal symptoms in opioid dependent patients thus causing concern as traditional dosing of opioids may not be effective in providing analgesia in the perioperative period. (10)

Buprenorphine's half-life is widely variable and dependent on the route of administration. It is poorly absorbed by the gastrointestinal system; hence it is administered by sublingual, dermal, and parenteral routes. Its half-life is 3 hours when administered intravenously (IV) and can be 24 to 60 hours when administered sublingually. (11) It is metabolized by the liver and the majority of it is excreted through bile. (6) Buprenorphine has a quick onset of 30-60 minutes when administered sublingually and 5 to 15 minutes with IV administration. (6) The usual dose of buprenorphine ranges from 2 to 32 milligram per day (mg/d) and the maximum effect occurs between 16 to 32 mg/d. (12) It provides effective analgesia at low to moderate doses and is 30 times more potent than morphine. An IV dose of 0.3mg of buprenorphine is equivalent to approximately 10mg of morphine. (13)

Pharmacology of methadone

Methadone is a long-acting synthetic opioid that is a full mu receptor agonist. It has been used both as an analgesic in severe pain and in the treatment of OUDs. When used for the treatment of OUD, the oral stock solution is often mixed with orange colored solution or cherry syrup to prevent aberrant use through the parenteral route. It is rapidly absorbed following oral administration; effects start between 15 to 45 minutes with a maximum plasma concentration of 2.5 to 4 hours after administration. Methadone is widely distributed in the body and it is highly protein bound leading to cumulative effect and slow elimination. (14) It has a long but variable half-life with mean estimates varying from 15 to 55 hours. (15) Methadone undergoes biotransformation rather than conjugation in the liver, and its metabolites are cleared via the fecal route. (16) Accumulation of methadone in the system may lead to sedation and respiratory depression, especially upon initiation of therapy. (17)

An effective daily dose of methadone for OUDs varies between 60 to 120 mg/d. (17) The purpose of high doses are to suppress withdrawal symptoms and eliminate cravings with minimal side effects. Patients on a higher dose may develop a prolonged QT interval, which could lead to the development of torsade de pointes, especially if co-administered with drugs that inherently prolong QT. (18) It is important to note that a daily methadone dose for treatment of OUD is inadequate to provide acute pain relief, and additional medications and strategies are often required to mitigate the pain. (19)

Summary of evidence

Current studies relating to the use of buprenorphine and methadone for OUDs presenting for surgery are mostly retrospective reviews, case reports, case series, and expert opinions. A summary of published studies are presented in Table I.

Summary of evidence for buprenorphine

Buprenorphine has several advantages over methadone for the treatment of OUDs. It was shown to have less potential for abuse, provides greater flexibility in prescribing, and can be managed as an office-based treatment option. (20) Therefore, there is increased utilization of buprenorphine for OUD treatment.

There are several strategies proposed to treat severe pain in patients on buprenorphine maintenance treatment. When planning to continue buprenorphine during the perioperative period, (especially in emergent and major surgeries), it is advised to use different types of oral opioids and/or IV opioid analgesics with the use of Patient Controlled Analgesia (PCA) titrated to adequate pain control. (21, 22) It was shown that patients on buprenorphine may often require higher doses of opioids to displace the avidly bound buprenorphine from the mu opioid receptors and pain control can be adequately achieved. (23) Alternatively, buprenorphine can be transitioned to full opioid agonists 3-5 days prior to elective procedures to avoid challenges of poorly controlled pain. (24)

A multimodal pain management approach with the use of dexmedetomidine, remifentanyl, and ketamine perioperatively has shown success in providing adequate pain control among patients taking buprenorphine for OUD. (25, 26) The use of regional anesthesia, though reasonable, was inconsistent in terms of decreasing the amount of opioid used in the perioperative period in one case series. (25) In patients who are on low dose buprenorphine, i.e. 2 to 8 mg per day, buprenorphine can be continued as an analgesic by increasing the frequency of the dose to every 6-8 hours. (21) In patients who will not be able to tolerate sublingual buprenorphine, buprenorphine can be discontinued 72 hours before surgery and replaced with full mu opioid agonist for titration of

analgesia. (21) If the risk of relapse is high, buprenorphine can be replaced with methadone using a modified dosing ratio of 1:5 respectively and titrated to achieve adequate pain relief. (21)

Summary of evidence for methadone

Algorithms for managing patients on methadone presenting for elective surgery have been proposed. If the patient is able to tolerate oral medication, it is advised to continue oral methadone on the morning of surgery and through the perioperative period. (16, 21, 27) If the patient is unable to do so, methadone can be dosed parenterally at a dose half to two thirds of the maintenance dose divided into two to four equal doses a day. (21) In situations when methadone is not available, conversion of methadone to any opioid can be performed; however, the conversion calculations may not be bidirectional due to the long half-life of methadone. (21) A multimodal approach (16, 27) including perioperative infusion of ketamine, (28-30) clonidine (31), and use of regional anesthesia (32) should be considered. In a retrospective cohort done by Macintyre, et.al, methadone opioid substitution therapy was continued and showed the efficacy and safety of PCA opioids for the management of post-operative pain. (26) Nevertheless, caution needs to be taken when continuing methadone in specific surgeries such as bariatric as serum levels of methadone can increase post operatively. (33)

DISCUSSION

Perioperative management of patients with OUD is complex. These patients may have underlying medical, psychiatric, surgical conditions and psychosocial problems in conjunction with their medication treatment. Managing their pain in the acute setting following surgery can be challenging and often times their OUD is not addressed. This may result with worsening of their medical condition, readmission rates, overdose, and relapse. These patients require specific considerations and planning to prevent poor outcomes.

Preoperative considerations

The stigma associated with OUDs may foster a negative judgement of the patient. These patients can be perceived as drug-seekers if their pain is poorly controlled. In this regard, patients worry about receiving inappropriate care in terms of pain control and the possibility of relapse and withdrawal symptoms.

It is recommended that these patients be seen preoperatively to obtain a full pain history, physical examination, and assessment for other psychiatric and medical comorbidities. (34) It is imperative to take a detailed medication history that includes dose, frequency of ingestion, time of last dose, and assessment of the level of treatment stability. (16) A urine toxicology screening provides useful information regarding medication compliance as well as use of illicit drugs or medications beyond the agreement with their prescription provider. Opioid monitoring databases should be accessed to review for controlled substance prescription. It is also prudent to reach out to the patient's prescription provider to discuss the pain management strategy in the acute perioperative setting as well as arrange follow-up(s) for continuation of maintenance therapy. Consultation of an in-house addiction specialist may be considered to provide support before and after the surgery. During the preoperative period, it is important to establish goals of care with the patient, which addresses realistic goals for pain management, the challenges of acute pain management as well as the concern and risk of relapse following reinstatement of opioid therapy. It is important to educate patients and their family regarding the risk of relapse and appropriate management of anxiety, craving, and pain.

Intraoperative considerations

It is important to understand that patients receiving maintenance therapy with buprenorphine and methadone do not receive adequate analgesia from these opioids in the setting of acute pain. The analgesic and addiction profile treatment differ as well as the associated neuroplastic changes associated with long-term opioid exposure, i.e., tolerance and hyperalgesia may effectively diminish their analgesic properties. (35) For example, in patients receiving methadone as maintenance therapy, the analgesic effect of morphine did not last as long as expected due to cross-tolerance. (36) Patients also have significantly higher opioid requirements and prolonged length of stay. (23, 37) This was echoed with a patient on buprenorphine therapy, who had poor pain control in the perioperative period in two different gynecological surgeries where buprenorphine was continued in the first and transitioned to full opioid agonist in the second. (38) It may be beneficial to use regional anesthesia when possible and multimodal analgesic combinations to target pain pathways at different sites to provide superior pain relief and decreased opioid consumption.

Postoperative considerations

The patient's baseline addiction treatment needs to be addressed when treating acute pain while on maintenance buprenorphine and methadone therapy. It is imperative to have a plan for aggressive pain management. (39) Undertreatment of pain predisposes patients to decreased opioid responsiveness which can lead to difficulty in controlling pain. (40) Analgesics including nonsteroidal anti-inflammatory drugs, acetaminophen, (41) and adjuvant analgesics that can enhance opioid effects such as gabapentinoids and ketamine may be used together in a multimodal approach to improve pain control. (42) (43)

If the decision is made to continue using methadone and buprenorphine, it is important to continue the patient's usual dose to avoid worsening of pain symptoms due to increased pain sensitivity associated with opioid withdrawal. (44) Adequate pain control would require administration of a higher dose of opioid analgesic that should be continuous or scheduled, instead of prescribing on an as needed basis. (39) The use of PCA is found to be helpful via increased control over analgesia and minimizing patient anxiety about pain management. (45, 46) Regarding methadone, if the patient is unable to receive oral medications, the methadone dose can be given intravenously (IV), intramuscular (IM) or subcutaneously (SC). The dosing for IV, IM and SC methadone should be given as half to two thirds of the maintenance dose divided into 2 to 4 equal doses. (47)

The high affinity of buprenorphine to the mu receptor makes pain treatment more complicated than methadone. The most effective approach comes with the clinical experience of the provider with buprenorphine. Upward titration of a short acting full opioid agonist to effect is recommended if the decision is to continue buprenorphine in the perioperative period. The buprenorphine dose can also be increased in patients who are not on a maximal dose to 24 to 32 mg daily. (20) Strategies that involve dividing daily doses of buprenorphine to every 6 to 8 hours have been discussed. A 0.4 mg dose of buprenorphine administered sublingually every 8 hours in patients who are opioid naïve may be adequate. (13) If the decision is made to discontinue buprenorphine therapy, the patient should be treated with full opioid analgesics and withdrawal should be avoided. (6) These patients should follow up with OUD provider in the postoperative period to resume maintenance therapy using an induction protocol after the resolution of acute pain. Another strategy is to convert buprenorphine to methadone to prevent acute withdrawal. (39)

Summary of recommendations

The authors' recommendation in the management of patients with OUD is outlined in Figure 1. Patients with OUD should be seen in preoperative clinic prior to elective surgery to obtain: medical and pain history, medication dosage, and to better understand the patient's support system outside of the hospital setting. In the setting of urgent or emergent surgeries, the same information and care discussion should be addressed prior to surgery if time permits. The ultimate goal is to achieve adequate pain management in patients with OUD on buprenorphine and methadone. We recommend continuing patients' buprenorphine and methadone regimen in the perioperative setting with the understanding that patient may require higher amounts of opioid agonist. Our recommendation differs from other narrative reviews, which give the option of discontinuing buprenorphine or methadone in the perioperative setting. (43) Furthermore, multimodal analgesic strategies which incorporate the use of NSAID, acetaminophen, gabapentinoid, ketamine, alpha 2 agonist, and regional anesthesia should be utilized to achieve adequate pain management. Postoperative plan should be prepared prior to discharge which incorporates written pain management regimen after discharge and follow up with their outpatient buprenorphine and methadone provider.

CONCLUSION

The increasing utilization of buprenorphine and methadone as maintenance therapy for OUDs continues to grow to combat the opioid epidemic. As a result, these patients face challenges in acute pain management during the perioperative period. These complex patients have altered neural responses of tolerance and hyperalgesia that may alter and worsen the pain experience. Management with traditional dosing of mu receptor opioid analgesics may be inadequate during the perioperative period. Patients may require higher doses of opioids with an inherent risk of precipitating patient cravings and subsequent relapse. Therefore, multimodal strategies should be employed as part of the aggressive pain management to mitigate anxiety and allow for successful treatment of pain. The author's recommendation to continue buprenorphine and methadone was based on the strength of evidence and personal experience. However, providers should be cognizant to the fact that pain is subjective and treatment needs to be individualized.

Conflict of Interest: None

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TABLE 1. Summary of studies

	Authors	Year	Study type	Key findings
Buprenorphine and Methadone	Hansen LE, Stone GL, Matson CA, et al.	2016	Prospective Matched Cohort Study	<ul style="list-style-type: none"> ❖ Dose of oral narcotics was higher at discharge in patients maintained on methadone or BUP/NAL in the perioperative period ❖ No difference in pain scores on day of surgery, post op day 1, and on post op day 2 between the study and control group

	Macintyre PE, Russell RA, Usher KAN, et al.	2013	Retrospective Cohort Study	❖ Patients who did not receive their buprenorphine the day after surgery, significantly required more PCA opioid relative to the patients that received their buprenorphine the day after surgery
Buprenorphine	Martin YN, Pearson ACS, Tranchida JR, et al.	2019	Retrospective Matched Study	❖ Patients treated with TdBUP received higher doses of intraoperative opioids than opioid naïve ❖ Postoperative opioid requirement had linear correlation with preoperative TdBUP dosing ❖ Preoperative pain scores were higher among patients on TdBUP ❖ No difference in Phase I recovery pain scores between the groups
	Martin YN, Deljou A., Weingarten TN., et al.	2019	Retrospective Observation	❖ No difference in opioid requirements during the perioperative period between combined and general anesthesia among patients maintained on SL-BUP ❖ No difference in opioid requirement between patients who continued SL-BUP on day of surgery vs stopping SL-BUP
	Silva MJ and Rubinstein A.	2016	Case Report Comparing two different outcomes for one patient undergoing two similar surgeries (knee arthroplasty)	❖ First surgery: patient was maintained on SL-BUP in the perioperative period and had adequate pain control with multimodal pain approach ❖ Second surgery: patient was not on SL-BUP and required increased pain medication in the postoperative period and required increased morphine equivalent at discharge compared to first surgery
	Huang A, Katznelson R, De Perrot M, et al.	2014	Case Report	❖ 16mg of Suboxone (BUP/NAL) twice a day was continued perioperatively ❖ Ineffective postoperative pain management ❖ Pain control was improved after tapering suboxone
	Khelemsky Y, Schauer J, and Loo N.	2015	Case Report One patient undergoing 2 similar procedure	❖ Unable to prevent intraoperative movement in patient undergoing cervical spine surgery while on Buprenorphine ❖ Prevention of intraoperative movement was achieved in the first surgery after the addition of ketamine ❖ 5 days later, after cessation of buprenorphine, during second cervical spine surgery, patient had decreased anesthetic requirement and prevention of intraoperative movement was achieved without ketamine
	McCormick Z, Chu S, Chang-Chien G, et al.	2013	Case Report	❖ Pain control was a challenge in a patient with McArldes Disease on BUP/NAL undergoing emergent bilateral fasciotomies ❖ Required increased hydromorphone PCA requirement in the perioperative period
	Chern SS, Isserman R, Chen L, et al.	2012	Case Report	❖ Poor pain control in both procedures
	Buprenorphine			

Buprenorphine			Two separate urogynecological procedure in a patient with Type I Chiari Malformation	<ul style="list-style-type: none"> ❖ In first procedure, 8mg of SL-BUP three times a day was continued up to the day of surgery with supplemental full opioids in the postoperative period ❖ In second procedure, SL-BUP was switched to full agonist 5 days prior to procedure and postoperative pain was managed with full opioid receptor agonists
	Kornfeld H and Manfredi L	2010	Case Series	<ul style="list-style-type: none"> ❖ 5 patients who underwent 7 procedures maintained on SL-BUP ❖ Majority of the patients had uninterrupted SL-BUP treatment during hospital stay ❖ All patients had good post op pain control
	Brummett C, Trivedi K, Buovoy A, et al.	2009	Case Report	<ul style="list-style-type: none"> ❖ 41 y/o male patient maintained on 16mg of SL-BUP which was continued on day of surgery, had high requirements of morphine PCA after L3-L5 spinal fusion which was not sufficient for adequate pain control. Adequate post op pain was finally achieved with Dexmedetomidine drip
Methadone	Barelli R, Sbarra GM, Sbaraglia F, et al.	2019	Case Report	<ul style="list-style-type: none"> ❖ Ketamine can reduce opioid requirements in a patient maintained on methadone
	Chan FJ, Schwartz A, Wong J, et al.	2017	Retrospective Matched	<ul style="list-style-type: none"> ❖ Patients on chronic methadone required significantly increased amount of opioid in perioperative period compared to patients not on methadone ❖ Patients on methadone had longer length of hospital stay
	Strommen M, Helland A, Kulseng B, et al.	2016	Case Report	<ul style="list-style-type: none"> ❖ Methadone was continued during bariatric surgery ❖ Caution needs to be taken on methadone dose in bariatric patient as blood concentration can increase during postoperative period
	Kaye AD, Alian AA, Vadivelu N, et al.	2014	Case Report	<ul style="list-style-type: none"> ❖ Patient on methadone for leiomyosarcoma required a multimodal approach with clonidine and ketamine for successful pain management
BUP/NAL buprenorphine/naloxone, PCA patient controlled analgesia, TdBUP transdermal buprenorphine, SL-BUP sublingual buprenorphine				

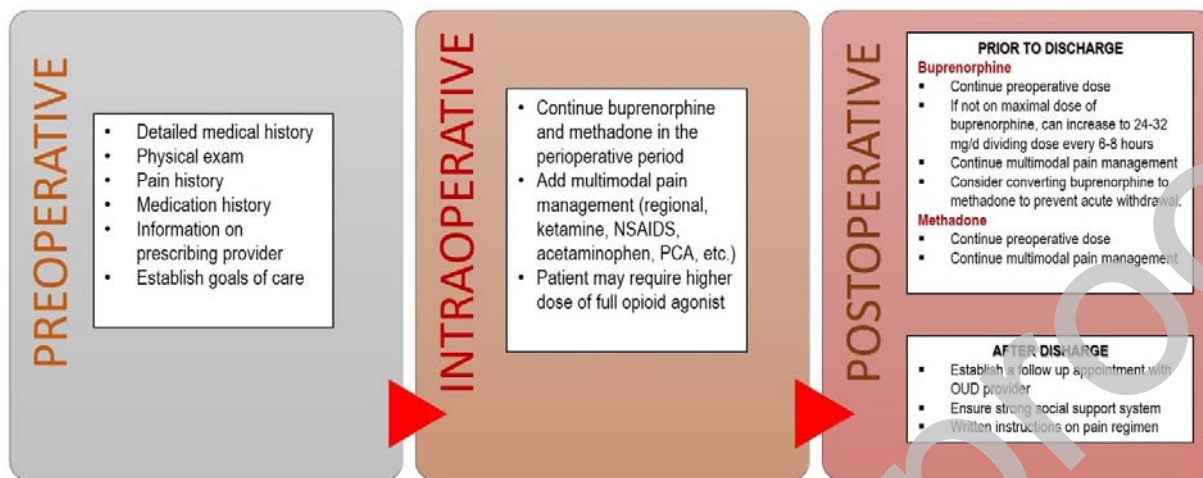


FIG. 1. Outline of recommendation for management of patients presenting for surgery with Opioid Use Disorder (OUD)