REVIEWS

Treating Perioperative and Acute Pain in Patients on Buprenorphine: Narrative Literature Review and Practice Recommendations

Megan Buresh, MD[1], *Jessica Ratner, MD*[1], *Aleksandra Zgierska, MD, PhD*[2,3], *Vitaly Gordin, MD*[3], *and Anika Alvanzo, MD, MS*[4,5]

[1]Division of Addiction Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA; [2]Department of Family and Community Medicine, Penn State College of Medicine, Hershey, PA, USA; [3]Department of Anesthesiology and Perioperative Medicine, Penn State Hershey Medical Center, Hershey, PA, USA; [4]Divisions of General Internal Medicine and Addiction Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA; [5]Pyramid Healthcare, Inc., Duncansville, PA, USA.

Opioid use disorder (OUD), a leading cause of morbidity and mortality in the USA, can be effectively treated with buprenorphine. However, the same pharmacologic properties (e.g., high affinity, partial agonism, long half-life) that make it ideal as a treatment for OUD often cause concern among clinicians that buprenorphine will prevent effective management of acute pain with full agonist opioid analgesics. Because of this concern, many patients are asked to stop buprenorphine preoperatively or at the onset of acute pain, placing them at high risk for both relapse and a difficult transition back to buprenorphine after acute pain has resolved. The purpose of this review is to summarize the existing literature for acute pain and perioperative management in patients treated with buprenorphine for OUD and to provide practical management recommendations for generalist practitioners based on evidence and clinical experience. In short, evidence suggests that sufficient analgesia can be achieved with maintenance of buprenorphine and use of both opioid and non-opioid analgesic options for breakthrough pain. We recommend that clinicians (1) continue buprenorphine in the perioperative or acute pain period for patients with OUD; (2) use a multi-modal analgesic approach; (3) pay attention to care coordination and discharge planning when making an analgesic plan for patients with OUD treated with buprenorphine; and (4) use an individualized approach founded upon shared decision-making. Clinical examples involving mild and severe pain are discussed to highlight important management principles.

KEY WORDS: buprenorphine; perioperative; acute pain; opioid use disorder

J Gen Intern Med 35(12):3635–43
DOI: 10.1007/s11606-020-06115-3

Jessica Ratner contributed equally to the work.

Received January 28, 2020
Accepted August 5, 2020
Published online August 21, 2020

Opioid use disorder (OUD) is a chronic disease affecting 2.1 million Americans,[1] and opioid-related overdose is one of the leading causes of preventable mortality for Americans.[2] Many patients with OUD also suffer from pain. Buprenorphine, a semi-synthetic opioid, was first developed in the 1970s as an analgesic with parenteral and sublingual formulations.[3] It was subsequently found to be an effective treatment for OUD, decreasing opioid withdrawal and craving, illicit opioid use, and mortality.[4–7] The passage of the Drug Addiction Treatment Act (DATA) of 2000 allowed for buprenorphine to be prescribed in outpatient settings for treatment of OUD.[3] There are now several formulations of buprenorphine approved by the FDA for OUD and chronic pain. Sublingual (brand names Subutex [buprenorphine alone], Suboxone or Zubsolv [buprenorphine-naloxone]), injectable (Sublocade), and implantable (Probuphine) preparations are FDA-approved for OUD only. Buccal (Bunavail) and transdermal (Butrans) formulations are FDA-approved for treatment of chronic pain. Sublingual buprenorphine has also been used for off-label treatment of chronic pain,[8] particularly in those with chronic pain who develop higher risk prescription opioid use[9, 10] and for those in whom the pain-approved formulations are of inadequate analgesic dose.

While its high binding affinity to the mu-opioid receptor and long half-life make it ideal for treatment of OUD, there is concern among clinicians that buprenorphine will prevent effective analgesia if other opioids are required for the management of acute pain due to surgery, injury, or acute illness. The following are two typical scenarios that might be encountered by the general practitioner in clinical practice:

Case 1: A 24-year-old patient with OUD, stable on buprenorphine-naloxone 12–3 mg SL twice daily, is scheduled for dental extraction. Should the patient continue on buprenorphine on the day of the procedure and how should pain be managed after the procedure?

Case 2: A 36-year-old patient with OUD, on buprenorphine-naloxone 8–2 mg SL twice daily, is admitted for right foot osteomyelitis with overlying soft tissue infection. Orthopedic

surgery recommends surgical debridement. The patient is currently experiencing severe pain. How should the patient's acute pain and postoperative pain be managed?

There is still mixed guidance in literature on how to manage buprenorphine perioperatively, with some guidance (particularly in anesthesia literature) recommending that patients taper off or stop buprenorphine preoperatively, particularly in cases where moderate to severe pain is expected.[11–14] In our clinical experience, some practitioners still ask patients to taper off buprenorphine up to 2 weeks prior to planned surgery. However, among all patients with OUD treated with buprenorphine, those who are tapered off rather than maintained on buprenorphine have been found to be at higher risk of relapse and overdose.[15] This increased risk of relapse, as well as the difficulty of transitioning back of buprenorphine postoperatively, has led many, including SAMHSA and the American Society of Addiction Medicine (ASAM), to question the routine practice of perioperative buprenorphine dose disruption.[16, 17] The purpose of this narrative review is to summarize the existing literature for acute pain and perioperative management in patients treated with buprenorphine for OUD and to provide practical recommendations regarding perioperative pain management for the general practitioner based on evidence and clinical experience.

PHARMACOLOGY OF BUPRENORPHINE

Properties at Mu-Opioid Receptor

Mu Receptor Agonist Properties. Buprenorphine is a semisynthetic partial (low intrinsic efficacy) agonist at the mu-opioid receptor, which mediates effects on opioid craving and withdrawal, analgesia, and respiratory depression. Given its partial agonism, the maximum analgesic effect produced by buprenorphine is less than that produced by a full agonist opioid, particularly in patients with opioid tolerance.[18] Sublingual doses of 16 mg occupy 79 to 95% of mu-opioid receptors, and doses greater than 24 to 32 mg occupy up to 95% occupancy of receptors.[19] While earlier studies showed ceiling effect for respiratory depression,[20] a recent systematic review of 28 randomized controlled studies involving 2210 patients comparing buprenorphine and morphine in acute pain management showed no difference in pain, respiratory depression, or sedation.[21]

Mu Receptor Affinity. Buprenorphine has a higher binding affinity at the mu receptor than other opioids: 1.7 times that of hydromorphone, 5.4 times that of morphine, 6.2 times that of fentanyl, and 120 times that of oxycodone.[22] This high affinity means that when buprenorphine is administered too soon after full agonist opioids, it will competitively displace them from the mu receptor, leading to a precipitated withdrawal.[23] Precipitated withdrawal can be avoided by waiting to administer buprenorphine until the patient develops symptoms of opioid withdrawal (a sign of low receptor occupancy). Buprenorphine's high binding affinity has led to the misperception among many clinicians that it is impossible to treat perioperative pain in patients treated with buprenorphine maintenance. However, receptor theory and clinical observations have shown that this blockade can be overridden with higher doses of full agonist opioids.[24, 25] In a study by Mercadante et al. of 29 patients with chronic cancer pain on transdermal buprenorphine, all acute pain events were successfully managed with IV morphine without discontinuing buprenorphine.[26]

Mu Receptor Dissociation. Buprenorphine has slow dissociation kinetics (approximately 166 min),[27] contributing to its long half-life and allowing for once or twice daily dosing in maintenance therapy for OUD. The half-life for transmucosal buprenorphine is variable and ranges from 24–42 h (based on package inserts), with broad interpatient half-life variability (24 to 60 h).[18] Half-life for transmucosal preparations is longer than for intravenous (IV) ones (3 h), possibly due to sequestration in the oral mucosa and lipid storage sites when administered transmucosally.[28] In general, the analgesic half-life is shorter than the half-life of the drug, such that three or four times daily dosing is often preferable for analgesia.[29]

Kappa, Delta, and ORL-1 Receptor Antagonism. Buprenorphine and its active metabolite norbuprenorphine have both agonist and antagonist properties at the kappa- and delta-opioid receptors and ORL-1 receptor.[30] Kappa-opioid antagonism is thought to contribute to some of the reversal of opioid-induced hyperalgesia with buprenorphine noted in preliminary studies.[31] ORL-1 effects at higher doses may be an important mediator of buprenorphine's ceiling effect in vivo.[30, 32]

REVIEW OF ORIGINAL RESEARCH

For this narrative review, a selection of relevant research studies is summarized in the following section to provide insight into changing practices regarding perioperative buprenorphine management and serve as a foundation for management decisions for the general practitioner. The authors used PubMed to identify English-language articles related to buprenorphine, OUD, and perioperative management including case studies, comparative studies, and review articles. Articles were selected based on expert opinion regarding relevance to the general practitioner. Given limited studies specifically comparing perioperative cessation and continuation of buprenorphine for patients with OUD, literature was also included that compared patients maintained on buprenorphine with opioid-naive or methadone-maintained controls.

Table 1 Descriptive Studies and Case Reports on Perioperative Pain Management of Patients on Buprenorphine

Study	Type of study	Patient population	Intervention	Outcome
Book et al., 2007	Case report	32-year-old (yo) woman on 24 mg buprenorphine for 6 months who underwent surgical removal of breast implants	Continued baseline buprenorphine and prescribed additional 2–4 mg q4-6 prn for post-op pain control	Adequate pain control on post-op days 1 and 2 with 12 mg buprenorphine q6h in addition to baseline 24 mg daily
Chern et al., 2013	Case report	37-yo woman on buprenorphine 8 mg q8h with multiple prior pelvic surgeries and history of poorly controlled post-op pain after continuing buprenorphine up to day of prior surgery, undergoing vaginal mesh trimming	Discontinued buprenorphine 5 days prior and started oral hydromorphone 4 mg q4-6 h	Suboptimal pain control (persistent scores 7–8 out of 10) despite significant opioid dosing, including more than 1100 mcg fentanyl and 8.5 mg hydromorphone in the several hours post-op followed by initiation of hydromorphone PCA
Gilmore et al., 2012	Case report	22-yo man on buprenorphine (unknown dose) who presented with severe right forearm fracture	On buprenorphine (patient presented emergently)	Unable to achieve pain control with SQ morphine 10 mg, remifentanil infusion 1.7 μg/kg/min over 8 min, lorazepam 1 mg, and remifentanil bolus 1 μg/kg. Pain control achieved with Bier block
Harrington and Zayfudim, 2010	Case report	30-yo man on 2 mg buprenorphine who presented with multi-organ trauma sustained in motorcycle accident	Discontinued buprenorphine at admission, restarted on hospital day 4, and then subsequently discontinued again	Unable to continue tapering full-agonist opioids after restarting buprenorphine on day 4; full-agonist opioid demand decreased after discontinuing bupe
Huang et al., 2014	Case report	47-yo woman on buprenorphine 16 mg BID for chronic pain who underwent Clagett window closure	Continued baseline buprenorphine perioperatively and then decreased dose from BID to daily on post-op day 11	After removal of thoracic epidural, escalating pain and IV PCA doses (nearly 10/10 pain despite 50–70 mg/24 h dilaudid); improvement to 15–25 mg/24 h dilaudid after buprenorphine dose decreased
Israel and Poore, 2013	Case report	37-yo woman on buprenorphine (unknown dose) who underwent bilateral mastectomies	Discontinued buprenorphine and applied fentanyl patch 3 days prior to surgery	Inadequate pain control post-op day 1 with fentanyl patch and PCA and ketorolac; improved after transition to oxycodone 10–30 mg q3h and acetaminophen 1000 mg q8h
Khelemsky et al., 2015	Case report	44-yo woman on 24 mg buprenorphine daily who underwent emergent cervical spine surgery for fracture and cord compression followed by planned spinal surgery 5 days later	On buprenorphine before first surgery (patient presented emergently); discontinued buprenorphine 5 days prior to second surgery	Significantly higher doses of anesthesia required to maintain motionless surgical field during first surgery (propofol 200 mcg/kg/min, remifentanil 0.4 mcg/kg/min, ketamine 100 mg/h) compared with second surgery (propofol 125 mcg/kg/min and remifentanil 0.2 mcg/kg/min)
Kornfeld and Manfredi, 2010	Case series	5 patients on sublingual buprenorphine for chronic pain for at least one year who underwent 7 major surgeries	Continued baseline buprenorphine	Adequate pain control with combination of buprenorphine, full agonist opioids, and local anesthetics
Leighton and Crock, 2017	Case series	4 women on prescribed or illicit buprenorphine who underwent cesarean section or tubal ligation	Continued baseline buprenorphine in 3 out of 4 patients	All patients achieved adequate pain control with some combination of buprenorphine (if continued), bupivacaine epidural, ketorolac, and hydromorphone PCA
McCormick et al., 2013	Case report	50-yo man with McArdle's disease on buprenorphine (unknown dose)	On buprenorphine (patient presented emergently); buprenorphine discontinued in	Required high doses of hydromorphone PCA both pre-op (0.5 mg bolus

(continued on next page)

Table 1. (continued)

Study	Type of study	Patient population	Intervention	Outcome
		who underwent bilateral fasciotomies for compartment syndrome	postoperative period due to inadequate pain control and restarted 2 months later	with 15-min lockout, no basal rate) and post-op (0.8 mg bolus with 15-min lockout, basal rate 0.5 mg/h)
Silva and Rubinstein, 2016	Case report	53-yo man on 8 mg TID buprenorphine when he underwent first total knee arthroplasty (TKA) and on high-dose hydromorphone when he underwent his second TKA	Continued buprenorphine perioperatively during first TKA; not on buprenorphine at time of second TKA	Achieved adequate pain control with buprenorphine and hydromorphone PCA after first TKA. After second TKA (not on buprenorphine), similar PCA doses provided inadequate pain control

Perioperative Pain Management in Patients on Buprenorphine

Tables 1 and 2 summarize the existing literature on perioperative pain management of patients on buprenorphine. Nine case reports[33–41] and two case series,[42, 43] comprising a total of 17 cases, were identified that described perioperative course or pain management after traumatic injury among patients treated with buprenorphine for chronic pain or OUD (Table 2). In 12 of the 15 cases where buprenorphine was continued (5 case reports, plus 8 cases from the 2 case series), adequate pain control was achieved.[33, 38, 41–43] Discontinuing buprenorphine was only required in three of the cases.[36, 39, 40] Of note, pain control in these patients required multi-modal management and titration of medication, including regional pain blocks[35] and adjustment of buprenorphine dose.[38] In the two cases where buprenorphine was discontinued 3–5 days preoperatively, it was difficult to achieve adequate pain control in the perioperative period.[34, 37] Many of the patients in these cases were noted to require high doses of opioids (with or without buprenorphine), which is consistent with known opioid tolerance among patients with OUD.

Five studies compared the adequacy of postoperative pain control in patients maintained on baseline buprenorphine versus other patient populations (Table 2). Two of the five studies retrospectively evaluated pain care outcomes in pregnant women maintained on buprenorphine[44] or methadone[45] for OUD compared with opioid-naive controls. Meyer et al. found no difference in intrapartum pain control or efficacy of regional anesthesia between pregnant women continued on their baseline buprenorphine through delivery compared with matched opioid-naive controls. Among patients treated with buprenorphine maintenance, they found mildly higher pain scores without increased opioid use after vaginal delivery and higher pain scores with 47% increase in opioid use after delivery by cesarean section.[44] However, Hoflich et al. found no difference in post-partum pain control after vaginal delivery, and increased non-steroidal anti-inflammatory drug (NSAID) use with decreased opioid use after cesarean section among patients maintained on buprenorphine or methadone compared with opioid-naive controls. They found that patients receiving buprenorphine or methadone required epidural anesthesia more often during vaginal delivery but this was accounted for by differences in smoking status between the two groups in regression analyses.[45] Prior literature has suggested that chronic nicotine use may reduce mu-opioid receptor availability resulting in greater difficulty controlling pain.[46] These studies suggest that maintenance of buprenorphine does not introduce significant complications to pain control after vaginal or cesarean delivery compared with those unexposed to opioids.

Three additional studies compared analgesic requirements of patients with OUD on buprenorphine to those on methadone undergoing surgery,[47] vaginal delivery,[48] or C-section.[49] In two of these studies, all participants were continued on their maintenance therapy through the perioperative/peripartum periods. Jones et al. found that, after vaginal delivery, there was no significant difference in pain ratings (which were in the mild range), use of acetaminophen, or use of oxycodone between patients continued on buprenorphine and those on methadone; patients on buprenorphine used less ibuprofen than those on methadone.[48] Similarly, Vilkins et al. found adequate pain control and no significant differences in opioid requirements between patients maintained on buprenorphine and methadone after delivery by cesarean section.[49] These studies suggest that similar pain management strategies can be used for patients with OUD on methadone and buprenorphine.

Macintyre et al. performed a retrospective analysis of patients on baseline buprenorphine and methadone, some of whom had their doses held and some of whom had their doses continued on the day of and day after surgery.[47] They found no correlation between PCA-based opioid requirement in the first 24 h after surgery and the preoperative dose of either buprenorphine or methadone. Additionally, patients who did not receive their buprenorphine dose on the day after surgery required longer duration of PCA and supervision by the pain medicine service and had higher opioid requirements than those who did. Of note, there were no differences in opioid requirement between those who did versus those who did not receive their baseline methadone on the day after surgery.

Table 2 Comparative Studies on Perioperative Pain Management of Patients Maintained on Buprenorphine

Study	Type of study	Patient population	Intervention	Outcome
Maintaining buprenorphine preoperatively: comparison of patients on buprenorphine with opioid-naive patients				
Meyer et al., 2010	Retrospective cohort-control study	63 women on buprenorphine during pregnancy (44 delivered via vaginal birth, 19 via C-section), matched with opioid-naive controls	Continued baseline buprenorphine	No difference seen intrapartum in pain perception or efficacy of regional anesthesia after vaginal delivery, mildly higher pain scores among patients on buprenorphine but no difference in opioid use. After C-section, higher pain scores among patients on buprenorphine and 47% increase in opioid use
Hoflich et al., 2012	Retrospective evaluation of RCT data	37 women randomized to buprenorphine or methadone during pregnancy as part of study who underwent vaginal delivery or C-section, compared with 80 matched non-opioid dependent controls	Continued baseline buprenorphine or methadone	During vaginal delivery, opioid-dependent patients required peridural anesthesia more often; no difference in pain management post-partum. During C-section, no differences in use of spinal anesthesia between groups; post-partum, opioid-dependent patients used NSAIDs more often but opioids less often than opioid-naive patients. Smoking status accounted for differences in peridural anesthesia during vaginal delivery and NSAID use after C-section
Maintaining buprenorphine preoperatively: comparison of patients on buprenorphine and methadone				
Jones et al., 2009	Secondary observational study of RCT data	18 women randomized to buprenorphine or methadone during pregnancy as part of study who underwent vaginal delivery	Continued baseline buprenorphine or methadone	Pain ratings in mild range for both groups. No significant difference in pain ratings, use of acetaminophen, or use of oxycodone between group; less ibuprofen use among patients on buprenorphine compared with those on methadone
Macintyre et al., 2013	Retrospective cohort study	51 patients on buprenorphine (43%) or methadone (57%) who were managed by acute pain service after surgery and required IV PCA without concurrent regional analgesia	In the buprenorphine group, about 2/3 received baseline dose on day of surgery and 1/2 received dose on day after surgery. In the methadone group, about 4/5 received baseline methadone dose on day of surgery and 3/4 received dose on day after surgery	No significant correlation between the first 24-h PCA opioid requirement and preoperative buprenorphine or methadone dose. Patients who did not receive baseline buprenorphine or methadone dose on day after surgery required longer duration of PCA and supervision by pain service. Higher opioid requirement in patients who did not receive baseline buprenorphine on during and after surgery compared with those who did; no difference in the methadone group
Vilkins et al., 2017	Retrospective cohort study	273 women on buprenorphine (32%) or methadone (68%) during pregnancy who underwent delivery by C-section	Continued baseline buprenorphine or methadone	No significant difference in opioid requirements between patients on buprenorphine and patients on methadone during the postoperative period

CURRENT PRACTICE RECOMMENDATIONS AND CONTROVERSIES

In the absence of sufficient data, there has been a lack of consensus on the best approach to perioperative management of patients maintained on buprenorphine.[11, 50–52] As such, existing recommendations on perioperative management of buprenorphine-maintained patients have largely arisen out of expert opinion based on the pharmacologic principles of buprenorphine, case reports, and clinical experience. The recommendations often differ based on the type of surgery (e.g., emergent vs. elective), the degree of anticipated postoperative pain, the patient's baseline dose, and the age of the publication. In general, earlier publications often recommend discontinuation of buprenorphine for elective procedures, citing concerns for a ceiling effect of buprenorphine's analgesic properties and inability to achieve sufficient analgesia from full agonist opioids due to buprenorphine's high affinity for the receptor and the potential for competition at the mu-opioid receptor.[50, 51] However, in response to emerging evidence of ability to achieve sufficient analgesia in buprenorphine-maintained patients (reviewed above) as well as concerns of predisposing patients with OUD to an increased risk of relapse and overdose with discontinuation of buprenorphine—particularly when exposing them to full agonist opioids used for acute pain care—continuation of buprenorphine in the perioperative period is increasingly common in clinical practice and recent publications.

Table 3 Recommendations for Acute Pain and Perioperative Management of Patients on Buprenorphine

Recommended management of buprenorphine	Recommended management of acute breakthrough pain	Discharge planning
Continue buprenorphine without dose reduction, including the following: • On morning of a planned surgery or procedure (whether minor or major) • During the postoperative period • During periods of acute, non-operative pain	Mild pain (pain scores 4 or less) or minor procedure (e.g., case 1): 1) Start with non-opioid analgesics (e.g., NSAIDs, acetaminophen). 2) Consider splitting buprenorphine dose into Q6-8h dosing; can increase total daily dose up to 32 mg for better pain coverage.* Moderate to severe pain (5 or more) or major procedure (e.g., case 2): In addition to recommendations for mild pain above, 1) If needed, add one short-acting full agonist opioid (e.g., oxycodone or hydromorphone) for breakthrough pain. Given underlying tolerance, higher doses will be required compared with opioid-naive patients (e.g., oxycodone 15–20 mg PO instead of 5–10 mg). Pain control should be reassessed after every dose. 2) IV opioids or PCAs without basal component (buprenorphine will play role of basal rate) may be considered in addition to patient's buprenorphine if pain is not adequately controlled or if patient is not tolerating POs. 3) Regional blocks and non-opioid analgesia should also be encouraged.	Patient's outpatient buprenorphine prescriber should be contacted prior to discharge to notify them of opioids received while in hospital and to arrange for follow-up appointment and should be informed of any doses changes and if patient will be discharged on additional opioids for pain. An X-waivered buprenorphine prescriber will need to write a discharge prescription to bridge to their next outpatient appointment.

**Some insurance companies do not approve outpatient doses of SL buprenorphine above 24 mg; however, it is FDA-approved up to 32 mg daily and can be increased to this dose while patient is inpatient*

Variability remains with respect to the circumstances under which discontinuation of buprenorphine is discouraged or recommended, as well as the timing of discontinuation. Some authors recommend continuation of buprenorphine for anticipated minimal to mild pain, but discontinuation of buprenorphine and transition to short-acting full agonist opioids in situations where moderate to severe pain is anticipated.[11, 12, 18, 53] In contrast, many clinicians and several authors have recommended continuing buprenorphine without interruption regardless of severity of expected pain, including administration of the maintenance dose on the morning of the surgery and continuation postoperatively.[13, 14, 41, 54] However, among those authors and institutional guidelines that recommend continuation of buprenorphine, there remains variability in recommendations regarding the maximum dose of buprenorphine that should be given. For example, in their 2005 paper, Roberts and Meyer-Witting recommend increasing the buprenorphine dose by 25% for major surgeries.[55] Conversely, a recent editorial by Lembke and colleagues recommends that those patients on buprenorphine doses higher than 12 mg be tapered down to 12 mg in the 2–3 days prior to surgery, with return to the maintenance dose as early as 3 days postoperatively.[52] A recent review from Quaye and Zhang recommends continuing home buprenorphine dose for minor procedures and decreasing buprenorphine to 8 mg sublingual daily for major procedures.[56] The authors of these articles consistently recommend continuation of buprenorphine through perioperative period and management of breakthrough acute pain with multi-modal approaches, including as-needed full agonist opioids, as well as non-pharmacologic options, non-opioid medications, and regional anesthesia.

SUMMARY AND RECOMMENDATIONS

In our clinical experience as addiction medicine and pain specialists, in cases in which buprenorphine is stopped preoperatively, patients are typically discharged from the hospital on full agonist opioids alone, requiring re-initiation of buprenorphine in the outpatient setting, which is challenging for the patients and puts them at high risk of relapse. In contrast, patients with OUD on buprenorphine maintenance do best when buprenorphine is continued through the perioperative period and a multi-modal approach to acute breakthrough pain is utilized. Based on the previously presented literature and our clinical expertise, we make the following recommendations:

Continue buprenorphine in the perioperative period for patients with OUD who are on buprenorphine

Based on expert consensus, SAMHSA updated its guidelines in 2018 to recommend that most patients continue buprenorphine through the perioperative period due to increased risk of relapse when it is discontinued.[17] A recent review of literature supports continuation of buprenorphine[56] and clinical protocols at many leading US medical centers are now reflecting this approach.[52, 57] While more research is needed, our recommendation is to continue buprenorphine through the perioperative period, including in peripartum management in obstetrical populations, regardless of whether additional full agonist opioids are needed. In our clinical practice, we continue buprenorphine without dose reduction (similar to management of methadone); however, further research is needed on optimal dose of buprenorphine in the

perioperative period. As buprenorphine formulations are either sublingual, buccal, transdermal, or implantable, there is no need to hold this medication while a patient is NPO either pre- or postoperatively.

Use a multi-modal analgesic approach

An effective analgesic plan requires a multi-modal approach, inclusive of appropriate anesthesiology techniques (e.g., regional anesthesia); non-pharmacologic interventions; non-opioid analgesics; and, when appropriate, short-acting opioid analgesics. Non-opioid modalities should be used to reduce opioid requirements in the perioperative period. Non-opioid medications with pain modulating properties, including NSAIDs, acetaminophen, duloxetine,[58] gabapentinoids, ketamine, IV lidocaine, and alpha-agonists, such as clonidine, prazosin, and dexmetomidine,[59] have been shown to be effective as opioid-sparing approaches during the postoperative period. Continuous regional/neuraxial blocks have been utilized successfully for the relief of severe postoperative pain.[60] Mind-body therapies, such as mindfulness meditation and hypnotic suggestion, have been shown to decrease pain in hospitalized patients by up to 29% right after the practice.[61] Patients can be safely discharged on oral non-opioid analgesic medications for ongoing postoperative pain. NSAIDs, acetaminophen, and duloxetine have good safety profiles and low risk for abuse and are preferred medications for discharge. Gabapentinoids have more potential for abuse, particularly in patients with substance use disorders, and should be used with caution.[62]

As part of a multi-modal approach, buprenorphine and short-acting full agonists can also be utilized for pain control. Given the shorter analgesic half-life of buprenorphine, a patient's total daily dose (TDD) can be divided into three to four times daily dosing for better analgesic effect. In addition, the buprenorphine TDD can be increased in cases of mild pain (pain score less than 4). Patients with moderate to severe pain (pain score greater than 5) will likely need short-acting full agonist opioids in the immediate postoperative period. In these cases, continue the patient's home buprenorphine dose and select one short-acting full agonist (either PO or IV, depending on pain severity), reassessing the patient's response after each dose and titrating as needed. Consider transition to IV PCA if pain cannot be controlled with PO or IV options (PCA settings should include boluses only, as the patient's baseline buprenorphine should take the place of a basal infusion). Notably, starting doses of short-acting full agonists will be higher than those required for an opioid-naive patient (ex. oxycodone 10–15 mg by mouth every 4–6 h rather than 5 mg; see Table 3 for detailed recommendations). Decisions about discharging a patient on full agonist opioids should be individualized, with consideration of expected duration of acute pain and patient stability and ability to safely take opioids as prescribed; these decisions should be communicated to the patient's outpatient buprenorphine prescriber to improve continuity of care. In our practice, we generally discharge patients requiring ongoing full-agonist opioids with 1–2-week supply of medication, plan for taper, and close follow-up with outpatient provider.

Care coordination and discharge planning are essential components of an effective perioperative analgesic plan for patients with OUD treated with buprenorphine

We recommend multi-disciplinary care coordination, inclusive of collaboration with the outpatient buprenorphine prescriber and, when possible, expert consultation from addiction medicine and/or anesthesia/pain medicine colleagues. Finally, for elective surgeries, we recommend preoperative patient assessment with development of the planned intraoperative and postoperative analgesic approaches and post-discharge planning.

An individualized approach to perioperative pain management should be based on shared decision-making

There are many factors influencing perioperative pain management that vary between patients, including stability on buprenorphine treatment, pain tolerance, preference for pain modalities, and degree of psychosocial support. With the above three recommendations as a guide, decisions regarding perioperative pain management should be individualized and based on shared-decision making between the patient and provider.

The cases are revisited below as illustrations of our approach to management of buprenorphine when there is acute pain due to surgery, injury, or acute illness, including when and how to use additional short-acting full agonist opioids. Table 3 includes a summary of general management principles applicable to each case.

Case 1—Mild Pain or Minor Procedure. A 24-year-old patient with OUD, stable on buprenorphine-naloxone 12–3 mg SL twice daily, is scheduled for dental extraction.

Recommendation:

- Continue home buprenorphine without dose reduction and advise patient to take NSAIDs (such as ibuprofen 800 mg three times daily) and acetaminophen 500–1000 mg three times daily for pain. The dentist can use local anesthesia for this routine dental procedure.
- If patient reports inadequate pain relief, buprenorphine dose can be split into 6 mg (1/2 film or tab) four times daily.

Case 2—Severe Pain or Major Procedure. A 36-year-old patient with OUD, on buprenorphine-naloxone 8–2 mg SL twice daily, has severe pain from osteomyelitis with overlying soft tissue infection, awaiting surgical debridement.

Recommendation:

- Continue home buprenorphine 8 mg SL twice daily for opioid dependence, including on the day of surgical debridement. After surgery, dosing can be split into 4 mg SL four times daily if needed.
- Start around-the-clock NSAIDs and acetaminophen, per above dosing, for baseline pain control. For severe pain, start short-acting full agonist opioid such as oxycodone or hydromorphone (e.g., start with oxycodone 10–15 mg PO every 4 h or hydromorphone 4–6 mg PO every 4 h as needed). Re-assess after each dose to determine if pain control is adequate and increase dose until pain is tolerable.
- Strongly consider consulting anesthesia/pain medicine for initiation of a regional block of the affected limb.

Thoughtful management of acute perioperative pain among patients on buprenorphine for OUD is of critical importance, given the risks of destabilization during the perioperative period. Maintaining buprenorphine and utilizing an individualized, multi-modal, and multidisciplinary approach to analgesia are key components of a successful strategy. Notably, this field of knowledge, at the intersection of addiction medicine, pain medicine, and anesthesia, is rapidly evolving with wide variability in practice. More research, particularly on such topics as ideal perioperative buprenorphine dosing and the most effective modes of non-opioid analgesia in this population, is needed to further optimize perioperative strategies for acute pain management for patients with OUD maintained on buprenorphine.

Corresponding Author: *Megan Buresh, MD; Division of Addiction Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA (e-mail: mburesh2@jhmi.edu).*

Compliance with Ethical Standards:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

REFERENCES

1. SAMHSA. Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD; 2018.
2. **Hedegaard H, Miniño AM, Warner M**. Drug Overdose Deaths in the United States, 1999-2017. NCHS Data Brief. 2018;(329):1-8.
3. **Johnson RE, Fudala PJ, Payne R**. Buprenorphine: Considerations for pain management. J Pain Symptom Manage. 2005;29(3):297-326.
4. **Cornish R, Macleod J, Strang J, Vickerman P, Hickman M.** Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010;341:c5475.
5. **Fudala PJ, Bridge TP, Herbert S, et al**. Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone. N Engl J Med. 2003;349(10):949-958.
6. **Mattick RP, Breen C, Kimber J, Davoli M**. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;(2):1-85.
7. **Schackman BR, Leff JA, Polsky D, Moore BA, Fiellin DA**. Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. J Gen Intern Med. 2012;27(6):669-676.
8. **Roux P, Sullivan MA, Cohen J, et al**. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: Reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. Pain. 2013;154(8):1442-1448.
9. **Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM**. A Clinical Trial Comparing Tapering Doses of Buprenorphine with Steady Doses for Chronic Pain and Co-existent Opioid Addiction. J Addict Med. 2010;4(3):140-146.
10. **Malinoff HL, Barkin RL, Wilson G**. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. Am J Ther. 12(5):379-384.
11. **Jonan AB, Kaye AD, Urman RD. Buprenorphine Formulations**: Clinical Best Practice Strategies Recommendations for Perioperative Management of Patients Undergoing Surgical or Interventional Pain Procedures. Pain Physician. 2018;21:E1-E12.
12. **Childers J, Arnold R**. Treatment of Pain in Patients Taking Buprenorphine. J Palliat Med. 2012;15:613-614.
13. **Mehta V, Langford RM**. Acute pain management for opioid dependent patients. Anaesthesia. 2006;61:269-276.
14. **Ward EN, Quaye AN-A, Wilens TE**. Opioid Use Disorders: Perioperative Management of a Special Population. Anesth Analg. 2018;127(2):539-547.
15. **Williams AR, Samples H, Crystal S, Olfson M**. Acute Care, Prescription Opioid Use, and Overdose Following Discontinuation of Long-Term Buprenorphine Treatment for Opioid Use Disorder. Am J Psychiatry. 2020;177(2):117-124.
16. ASAM. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. J Addict Med. 2020;14(2S):1-91.
17. SAMHSA. Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 19-5063FULLDOC. Rockville, MD; 2018.
18. **Anderson TA, Quaye ANA, Ward EN, Wilens TE, Hilliard PE, Brummett CM**. To Stop or Not, That Is the Question. Anesthesiology. 2017;126(6):1180-1186.
19. **Greenwald MK, Johanson CE, Moody DE, et al**. Effects of Buprenorphine Maintenance Dose on μ-Opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-Dependent Volunteers. Neuropsychopharmacology. 2003;28(11):2000-2009.
20. **Dahan A, Yassen A, Romberg R, et al**. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627-632.
21. **White LD, Hodge A, Vlok R, Hurtado G, Eastern K, Melhuish TM**. Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2018;120(4):668-678.
22. **Volpe DA, Tobin GAM, Mellon RD, et al**. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol. 2011;59(3):385-390.
23. **Coe MA, Lofwall MR, Walsh SL**. Buprenorphine Pharmacology Review. J Addict Med. 2019;13(2):93-103. https://doi.org/10.1097/ADM.0000000000000457
24. **Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE**. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. J Pharmacol Exp Ther. 1988;247(1):47-53.
25. **Strain EC, Walsh SL, Bigelow GE**. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. Psychopharmacology (Berl). 2002;159(2):161-166.
26. **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(2):175-179.
27. **Boas RA, Villiger JW**. Clinical Actiions of Fentanyl and Buprenorphine: The Significance of Receptor Binding. Br J Anaesth. 1985;57(2):192-196.
28. **Welsh C, Valadez-Meltzer A**. Buprenorphine: A (Relatively) New Treatment For Opioid Dependence. Psychiatry (Edgmont). 2005;2(12):29-39.
29. **Vadivelu N, Mitra S, Kaye AD, Urman RD**. Perioperative analgesia and challenges in the drug-addicted and drug-dependent patient. Best Pract Res Clin Anaesthesiol. 2014;28(1):91-101. https://doi.org/10.1016/j.bpa.2014.02.003

30. **Lutfy K, Eitan S, Bryant CD, et al**. Buprenorphine-Induced Antinociception Is Mediated by μ-Opioid Receptors and Compromised by Concomitant Activation of Opioid Receptor-Like Receptors. J Neurosci. 2003;23(32):10331-10337.
31. **Chen KY, Chen L, Mao J**. Buprenorphine–Naloxone Therapy in Pain Management. Anesthesiology. 2014;120:1262-1274.
32. **Lutfy K, Cowan A**. Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol. 2004;2(4):395-402.
33. **Book SW, Myrick H, Malcolm R, Strain EC**. Buprenorphine for Postoperative Pain Following General Surgery in a Buprenorphine-Maintained Patient. Am J Psychiatry. 2007;164(6):979.
34. **Chern S-YS, Isserman R, Chen L, Ashburn M, Liu R**. Perioperative Pain Management for Patients on Chronic Buprenorphine: A Case Report. J Anesth Clin Res. 2013;3(250).
35. **Gilmore T, Saccheti A, Cortese T**. Buprenorphine/naloxone inhibition of remifentanil procedural sedation. Am J Emerg Med. 2012;30(8):2009-2010.
36. **Harrington CJ, Zaydfudim V**. Buprenorphine maintenance therapy hinders acute pain management in trauma. Am Surg. 2010;76(4):397-399.
37. **Israel JS, Poore SO**. The Clinical Conundrum of Perioperative Pain Management in Patients with Opioid Dependence: Lessons from Two Cases. Plast Reconstr Surg. 2011;127:2141-2150.
38. **Huang A, Katznelson R, de Perrot M, Clarke H**. Gestion périopératoire d'un patient subissant la fermeture d'une fenêtre de Clagett stabilisé par Suboxone® pour douleur chronique: une étude de cas. Can J Anesth. 2014;61(9):826-831.
39. **Khelemsky Y, Schauer J, Loo N**. Effect of Buprenorphine on Total Intravenous Anesthetic Requirements During Spine Surgery. Pain Physician. 2015;18:E261-E264.
40. **McCormick Z, Chu SK, Chang-Chien GC, Joseph P**. 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(8):1187-1191.
41. **Silva MJ, Rubinstein A**. Continuous Perioperative Sublingual Buprenorphine. J Pain Palliat Care Pharmacother. 2016;30(4):289-293.
42. **Kornfeld H, Manfredi L**. Effectiveness of Full Agonist Opioids in Patients Stabilized on Buprenorphine Undergoing Major Surgery- A Case Series. Am Jounral Ther. 2010;17:523-528.
43. **Leighton BL, Crock LW**. Case Series of Successful Postoperative Pain Management in Buprenorphine Maintenance Therapy Patients. Anesth Analg. 2017;125(5):1779-1783.
44. **Meyer M, Paranya G, Keefer Norris A, Howard D**. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. Eur J Pain. 2010;14:939-943.
45. **Höflich AS, Langer M, Jagsch R, et al**. Peripartum pain management in opioid dependent women. Eur J Pain. 2012;16(4):574-584.
46. **Greenwald MK, Comer SD, Fiellin DA**. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. 2014;144:1-11.
47. **Macintyre P, Russell R, Usher K, Gaughwin M, Hutable C**. Pain Relief and Opioid Requirements in the First 24hrs After Surgery in Patients Taking Buprenorphine and Methadone Opioid Substitution Therapy. Anaesth Intensive Care. 2013;41(2):222-230.
48. **Jones HE, O'Grady K, Dahne J, et al**. Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. Am J Drug Alcohol Abuse. 2009;35(3):151-156.
49. **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;11:397-401.
50. **Alford DP, Compton P, Samet JH**. Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. Ann Intern Med. 2006;144:127-134.
51. **Bryson EO**. The perioperative management of patients maintained on medications used to manage opioid addiction. Curr Opin Anaesthesiol. 2014;27:359-364.
52. **Lembke A, Ottestad E, Schmiesing C**. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. Pain Med. 2019;20(3):425-428.
53. **Sen S, Arulkumar S, Cornett EM, et al**. New Pain Management Options for the Surgical Patient on Methadone and Buprenorphine. Curr Pain Headache Rep. 2016;20:1-8.
54. **Warltier DC, Mitra S, Sinatra RS**. Perioperative Management of Acute Pain in the Opioid- dependent Patient. Anesthesiology. 2004;101:212-227.
55. **Roberts DM, Meyer-Witting M**. High-dose buprenorphine: Perioperative precautions and management strategies. Anaesth Intensive Care. 2005;33:17-25.
56. **Quaye AN-A, Zhang Y**. Perioperative Management of Buprenorphine: Solving the Conundrum. Pain Med. 2019;20(7):1395-1408.
57. Johns Hopkins Division of Addiction Medicine. Recommendations for Management of Acute Pain for Patients on Medications for Opioid Use Disorder (mOUD) Presenting to ED and Inpatient Settings. 2019.
58. **Castro-Alves LJ, Oliveira de Medeiros ACP, Neves SP, et al**. Perioperative Duloxetine to Improve Postoperative Recovery After Abdominal Hysterectomy: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Study. Anesth Analg. 2016;122(1):98-104.
59. **Ramaswamy S, Wilson JA, Colvin L**. Non-opioid-based adjuvant analgesia in perioperative care. Contin Educ Anaesth Crit Care Pain. 2013;13(5):152-157.
60. **Suksompong S, von Bormann S, von Bormann B**. Regional Catheters for Postoperative Pain Control: Review and Observational Data. Anesthesiol Pain Med. 2020;10(1). https://doi.org/10.5812/aapm.99745
61. **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):1106-1113.
62. **Smith R V., Havens JR, Walsh SL**. Gabapentin misuse, abuse and diversion: a systematic review. Addiction. 2016;111(7):1160-1174. https://doi.org/10.1111/add.13324