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To Stop or Not, That Is the Question

Acute Pain Management for the Patient on Chronic Buprenorphine

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In Brief

The management of acute perioperative pain in patients on chronic buprenorphine as opioid maintenance therapy is a complex process. We describe pain management approaches for patients on buprenorphine who present for elective and urgent/emergent surgery.

Background

Opioid use disorder, a chronic neurobehavioral disease, is difficult to manage and accompanied by extensive psychologic and physical comorbidity, as well as a high mortality rate, when untreated.[1] Over the past two decades, opioid-related deaths and admission to treatment facilities have risen substantially. Of the 21.5 million Americans experiencing substance use disorders in 2014, an estimated 1.9 million had opioid use disorder, and more than 0.5 million were addicted to heroin.[2] Similarly, the number of patients on medication-assisted treatment is on the rise.

Most medication-assisted treatment strategies for patients with opioid use disorder consist of either buprenorphine or methadone. Methadone is a full μ-receptor agonist and *N*-methyl-D-aspartate receptor antagonist developed in the late 1930s. Methadone was subsequently approved for use in the United States as an analgesic alternative to more highly addictive opioids. Following World War II, an influx of heroin into U.S. metropolitan areas led to increased rates of illicit drug use. Consequently, narcotics maintenance programs were established with federal resources; methadone was the primary opioid replacement agent prescribed due to its slow onset of action and long elimination half-life. Patients who subscribe to methadone therapy must adhere to strictly regulated clinic visits and comply with established protocols to remain enrolled in addiction treatment plans.

Buprenorphine for Addiction Treatment

Buprenorphine has been available since the 1970s in parenteral and sublingual formulations.[3–6] Since the passage of the Drug Addiction Treatment Act of 2000, buprenorphine (Suboxone [buprenorphine/naloxone sublingual tablet] and Subutex [buprenorphine sublingual tablet], Reckitt Benckiser Pharmaceuticals Inc., USA) have been used for outpatient opioid detoxification, addiction therapy, and chronic pain treatment.[3,5–7] Approximately 30 times as potent as morphine, buprenorphine produces effective analgesia at low receptor occupancy (5 to 10%).[4,5,8,9] Sublingual doses of 16 mg reduce μ opioid receptor binding by 79 to 95%, and doses greater than 24 to 32 mg do not produce any greater opioid effect despite up to 95% occupancy of receptors.[10,11] It is a partial agonist at the μ receptor and an antagonist at the κ and Δ receptors, with a wide safety profile including less potential for abuse and respiratory depression compared with traditional opioids.[12–16] Buprenorphine has broad interpatient half-life variability (24 to 60 h) with high affinity for, low intrinsic activity at, and slow dissociation from the μ receptor.[5,6,13,17,18] The long half-life in the clinically available sublingual and buccal formulations may be due to a depot effect from buprenorphine sequestered in the oral

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mucosa.[18] Low doses of buprenorphine will competitively displace traditional opioids from the opioid receptors; the displacement of buprenorphine by traditional opioids is only accomplished with extremely high doses.[17]

To obtain a unique Drug Enforcement Agency identification number allowing the prescription of sublingual buprenorphine, a physician must meet at least one of the following requirements: hold a subspecialty board certification in addiction psychiatry or addiction medicine, hold an addiction certification, or have completed at least 8 h of training on the management of patients with opioid use disorder.

Buprenorphine has several advantages over methadone for the treatment of opioid use disorder, including less potential for abuse compared with methadone, and as an office-based treatment option, greater flexibility in buprenorphine prescribing. Serious side effects from higher doses of methadone include potentially fatal respiratory depression and arrhythmias due to lengthening of the corrected QT interval. Methadone is the opioid associated with the highest rate of accidental overdose death, contributing to one of three overdose deaths in 2009.[19] The risk of respiratory depression is considerably less with buprenorphine, even when large doses are taken, given its ceiling effect. Buprenorphine reduces opioid cravings and rates of addiction relapse.[3]

Buprenorphine for Chronic Pain and Other Indications

Buprenorphine is increasingly prescribed for chronic pain treatment.[7] Hence, many patients using buprenorphine regularly do not have an opioid misuse history. Both intravenous and transdermal formulations of buprenorphine are U.S. Food and Drug Administration approved to treat chronic pain; the sublingual and oral formulations are U.S. Food and Drug Administration approved only for opioid use disorder therapy and are often used off label for chronic pain treatment. In a study of opioid-naïve patients with chronic, noncancer pain, the use of transdermal fentanyl or buprenorphine resulted in similar analgesic effects.[20] Likewise, studies have concluded that patients with a history of opioid use disorder had reductions in chronic pain when started on buprenorphine therapy. Tolerance to both buprenorphine and methadone occur at a slower rate than to morphine.[21,22] Buprenorphine may treat opioid-induced hyperalgesia, in part, through its antagonism of κ receptors and improve pain control in patients with opioid-induced hyperalgesia.[23–25]

Buprenorphine can relieve treatment-resistant depression,[26] a potentially important benefit for patients experiencing chronic pain and opioid use disorder due to the vicious, synergistic cycle linking these conditions. Chronic pain, opioid use disorder, and addiction have the potential to contribute to depression that, if not recognized and adequately treated, is associated with higher suicide rates, worsened physical health, and increased rates of opioid abuse.[27] In a study of 15 middle-aged adults, low-dose buprenorphine rapidly improved treatment-resistant depression.[26] This is consistent with reports of patients on buprenorphine for treatment of opioid use disorders who developed improvement of depressive symptoms.[28] The mechanism of action is thought to be, in part, due to buprenorphine-mediated κ receptor antagonism. κ receptor antagonism has been implicated in treating forms of stress, depression, and addiction disorders.[29]

Perioperative Management of Patients Using Buprenorphine

The treatment of acute pain in patients taking buprenorphine is particularly challenging.[7,30,31] The high receptor binding affinity, long half-life, and partial agonism of buprenorphine may inhibit the analgesic actions of traditional opioids, hence the potential for uncontrolled postoperative pain and serious adverse events (fig. 1).[4–7,30–32]

Review of Published Reports of Perioperative Analgesia Strategies for Patients on Buprenorphine

The pharmacokinetic properties contributing to the safety of buprenorphine interferes with the effectiveness of other opioids used simultaneously; limited data exist on optimal acute pain management strategies for these patients. Therefore, suggestions are generally made based on case reports and provider opinion. The core issue appears to be an elevated but indeterminate opioid requirement to compete with μ-receptor buprenorphine binding. One report describes a 50-yr-old man with acute limb compartment syndrome on buprenorphine therapy for chronic pain and opioid dependence with poorly controlled postoperative pain. Adequate pain relief was not achieved until 48 h after discontinuation of buprenorphine.[33] Another report describes a 47-yr-old woman on buprenorphine for chronic pain who underwent open window thoracoscopy for pulmonary aspergillosis. Her postoperative pain was ineffectively controlled despite high doses of intravenous hydromorphone. After buprenorphine was discontinued, her pain improved and her opioid requirement was reduced.[34] Another report describes a patient taking buprenorphine preoperatively who underwent a posterior spinal fusion and had uncontrolled postoperative pain. His pain improved after buprenorphine was discontinued and he was transferred to the intensive care unit (ICU) for dexmedetomidine and high-dose opioid therapy.[35] The authors of these and other case reports suggest that buprenorphine should be discontinued at least 72 h before elective surgery and replaced with opioid agonists in the interim.[33,34,36,37] However, perioperative pain management for patients on chronic buprenorphine may be difficult regardless of whether buprenorphine is discontinued before surgery. Another report describes a 37-yr-old woman taking buprenorphine for chronic pain who underwent two separate urogynecologic procedures. With one procedure, the patient took buprenorphine up to the day of surgery; for

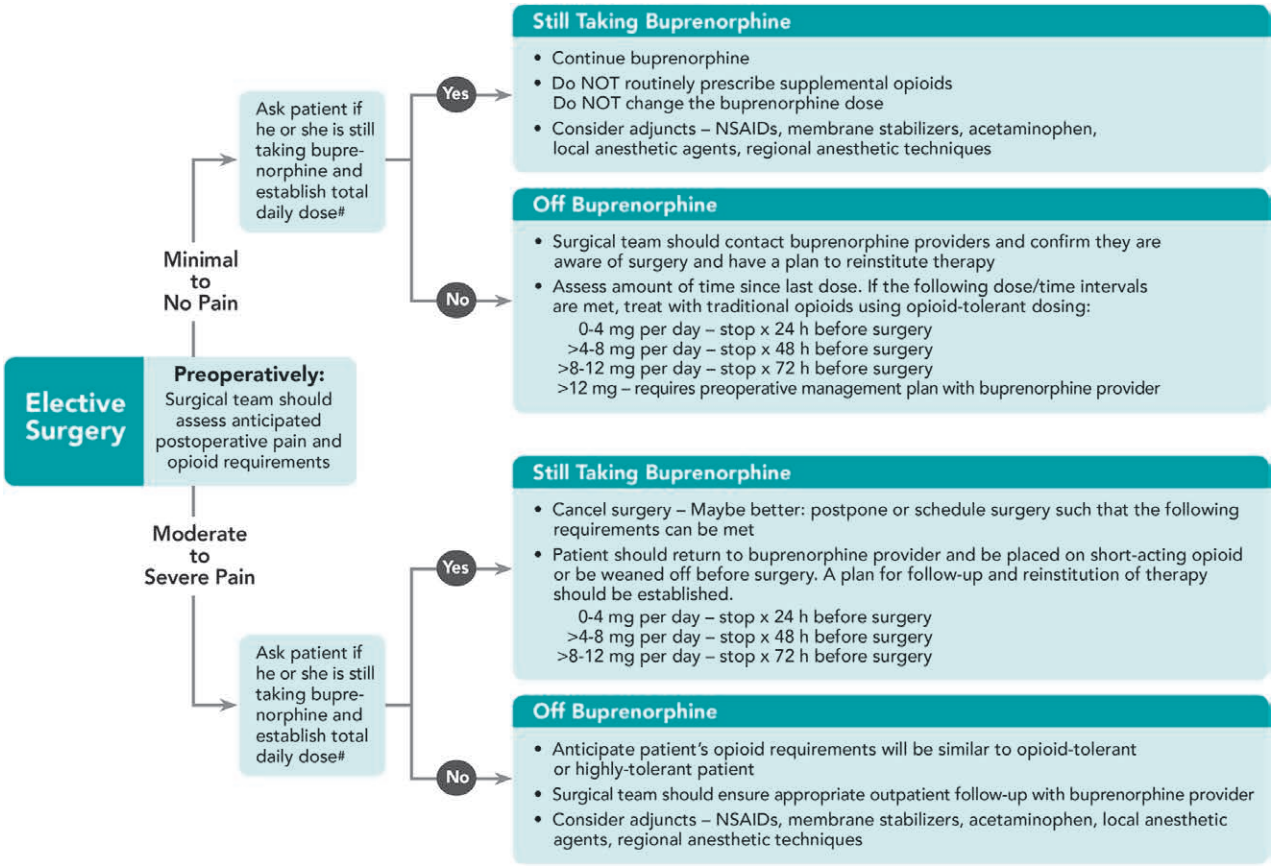

Fig. 1. Suggestions are outlined for patients presenting for elective surgeries taking buprenorphine. NSAIDs = nonsteroidal anti-inflammatory drugs. #Transdermal buprenorphine need not be discontinued prior to elective surgery regardless of dose.

the subsequent procedure she discontinued buprenorphine five days before surgery, substituting hydromorphone in the interim. Pain management was challenging after both surgeries.[38]

Not all experts agree that buprenorphine therapy requires discontinuation before elective surgery. Kornfeld and Manfredi[39] reported adequate pain control in five patients maintained on buprenorphine perioperatively and given supplemental opioids as needed for breakthrough pain. In a retrospective cohort study of 22 patients presenting for surgery and taking buprenorphine, half were maintained on buprenorphine and the remainder had their buprenorphine doses held postoperatively. On postoperative day one, pain control was similar between groups. In the group that had buprenorphine withheld after surgery, the average morphine-equivalent dose given in the first 24 h postoperatively was 246 *versus* 155 mg in the group where buprenorphine was continued.[40] The authors concluded that buprenorphine can be continued perioperatively, and coadministered opioid agonists can effectively treat acute pain. Similarly, in an observational study of patients maintained on buprenorphine or methadone in the peripartum period, acetaminophen-oxycodone was effective at treating acute pain after vaginal delivery in both groups.[41] Average pain scores were similar in both groups. Comparing opioid consumption between those continued on buprenorphine *versus* those who were not is inherently flawed given that buprenorphine itself is an opioid. Therefore, adequate acute pain management may be achievable in patients when the postoperative opioid requirements are reasonable.

Perioperative Management Strategy for Patients Taking Buprenorphine

Currently, no consensus or high-level evidence exists on optimal acute pain management strategies for patients taking buprenorphine. Except for urgent and emergent situations, buprenorphine therapy and transitioning preoperatively and postoperatively should be handled by a specialist in the field. Abrupt discontinuation of buprenorphine in the highly stressful, emotionally charged perioperative period risks precipitation of opioid use disorder relapse.[42] Also, patient fear of postsurgical pain and the ubiquitous prescribing of opioids that produce high levels of euphoria for acute pain treatment may serve as strong triggers for relapse. Since evidence points toward buprenorphine as effective in treating pain, depression, and opioid-induced hyperalgesia, providers may consider strategies for continuing buprenorphine therapy perioperatively in some patients. Patients on chronic buprenorphine therapy, especially those with a history of opioid use disorder or depression, should have their

perioperative care coordinated with specialists in addiction medicine or mood disorders.[43]

Given the limited and mixed data regarding the clinical outcomes of patients taking buprenorphine after surgery, the protocol created for the University of Michigan Health System (figs. 1 and 2) was based on pharmacology, published reports, and clinical experience. Separate protocols for elective (fig. 1) *versus* urgent/emergent (fig. 2) surgery were created. The buprenorphine patch (Butrans, Purdue Pharma, USA) was not included in this protocol because of the very low doses of buprenorphine delivered.

The protocols are intended to give guidance and expectations for the patient, nurses, surgeons, anesthesiologists, and pain physicians. Patients taking buprenorphine and presenting for elective surgery must be evaluated preoperatively to determine the best perioperative management course (fig. 1). It may be appropriate to continue buprenorphine in patients undergoing surgeries with only mild pain expected postoperatively, surgeries where continuous regional anesthesia is very likely to minimize postoperative pain, or patients at high risk for perioperative substance abuse relapse. If the buprenorphine is to be continued, it can be increased in patients who are not on a maximal dose (24 to 32 mg orally daily), or traditional μ agonists can be used as well. In patients taking buprenorphine for chronic pain or if it is anticipated that postoperative pain may be difficult to control, buprenorphine may be discontinued preoperatively after consultation with the prescribing clinician, although this is no guarantee of ease of postoperative pain management.

Patients with severe postoperative pain that is unresponsive to opioid treatment frequently require monitored care settings, increasing the cost of care and patient length of stay while decreasing patient satisfaction. Thus, if a patient who is anticipated to have moderate-to-severe postoperative pain presents for elective surgery and is still taking buprenorphine, it may be best to postpone surgery until the patient has consulted with the prescribing clinician and a perioperative analgesia plan is determined that may include buprenorphine discontinuation. Consensus and evidence-based guidelines for the management of stopping

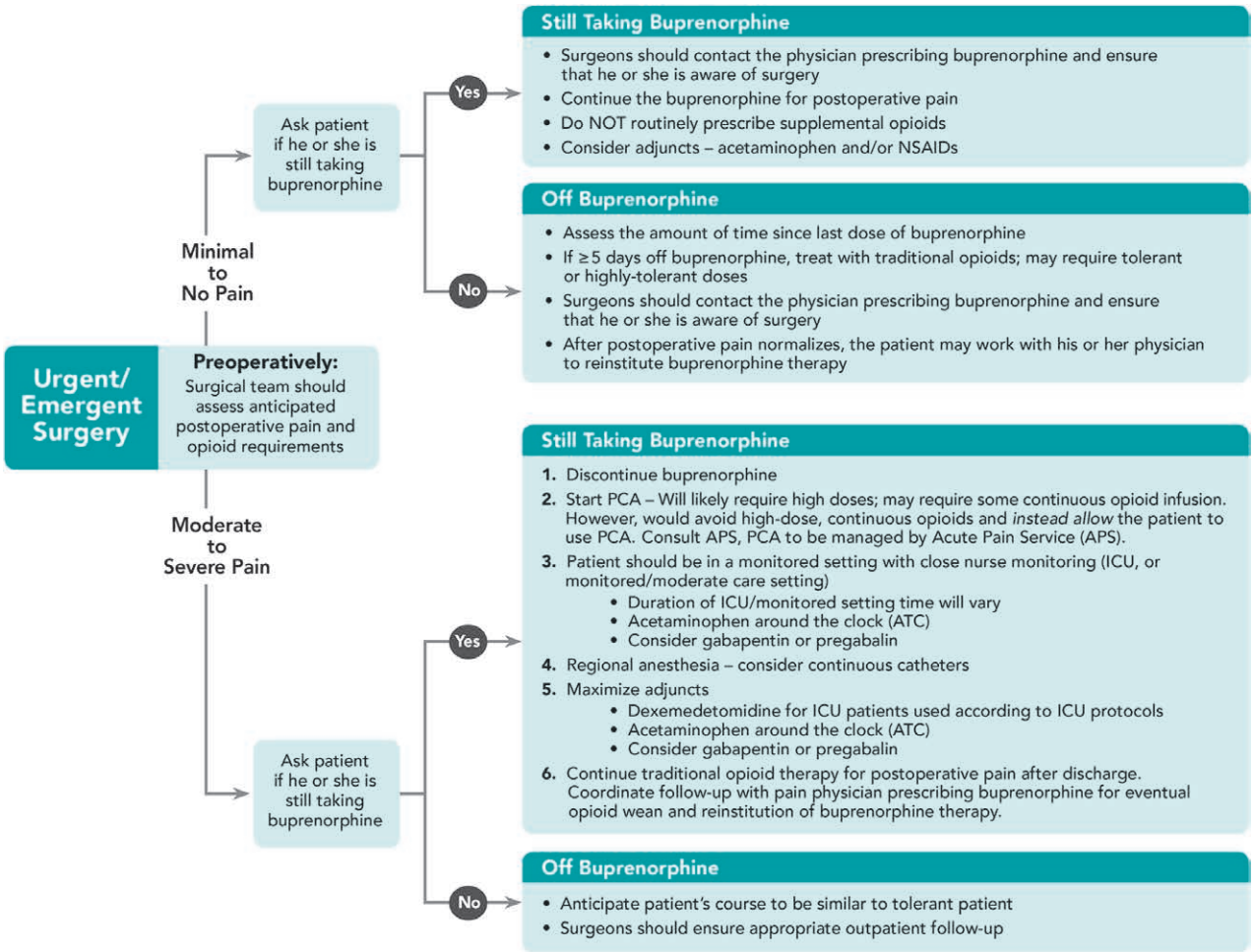

Fig. 2. Suggestions are outlined for patients presenting for urgent and emergent surgeries taking buprenorphine. APS = Acute Pain Service; ATC = acetaminophen around the clock; ICU = intensive care unit; NSAIDs = nonsteroidal antiinflammatory drugs; PCA = patient-controlled analgesia.

and restarting buprenorphine can be found in a treatment improvement protocol published by the Substance Abuse and Mental Health Services Administration.[44] Patients may also present for surgery with a buprenorphine subcutaneous implant (trade name Probuphine [buprenorphine implant], Braeburn Pharmaceuticals, USA), which delivers buprenorphine equivalent to a daily sublingual or transmucosal dose of 8 mg or less. Therefore, moderate-to-severe postoperative pain may be difficult to manage. Maximizing pharmacologic and nonpharmacologic analgesia strategies, including continuous regional anesthesia, is recommended when possible. Such patients may require large amounts of opioids, and it may be best to have the patient in a monitored care setting.

Suggestions are outlined for patients presenting for urgent and emergent surgeries who are also taking buprenorphine (fig. 2). For the urgent/emergent situation, ICU admission or a monitored setting should be considered postoperatively to maximize adjunct therapy (*i.e.,* dexmedetomidine infusion or ketamine infusions) and to monitor respiratory status given the anticipated need for large amounts of opioid. Even if no other indication is present for ICU admission, large doses of buprenorphine in the context of a large trauma or surgery should be considered as an indication for ICU care. There is a theoretical risk of respiratory depression in the patient who has discontinued buprenorphine at admission and requires high doses of a μ receptor agonist. Pain may be adequately controlled without significant respiratory depression on the first postoperative day when buprenorphine is still binding a majority of μ receptors; yet, as more buprenorphine is metabolized and more μreceptors become available to be bound by the μ receptor agonist, respiratory depression can occur.

Treatment Options

There is a clear lack of agreement on approaches for the perioperative management of patients on buprenorphine, largely due to the paucity of data and inconsistencies regarding the clinical relevance of the established pharmacokinetics of buprenorphine. However, the consensus recommendations of the American Pain Society; the American Society of Regional Anesthesia and Pain Medicine; and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council should be considered for all patients taking buprenorphine in the perioperative period.[45] These recommendations include the appropriate use of preoperative pain management planning, perioperative patient education, perioperative use of a validated pain assessment tool, multimodal analgesia including both pharmacologic and nonpharmacologic strategies, consideration of physical modalities (transcutaneous electrical nerve stimulation), oral over intravenous opioids, patient-controlled analgesia when systemic analgesics are necessary, avoidance of basal opioid infusions, local anesthetic infiltration, single-injection or continuous regional analgesia, suitable patient monitoring to avoid adverse events, presence of an organizational structure to allow safe and efficacious postoperative pain control, and patient access to a pain specialist. For those surgeries where regional anesthesia and analgesia are not appropriate, high doses of opioids should be anticipated.

Perioperative analgesia should include the use of regional and systemic opioid-sparing treatment modalities whenever possible. Multimodal analgesic combinations that simultaneously target pain pathways at different sites using different mechanisms are associated with superior pain relief and decreased opioid consumption. Regional anesthesia and analgesia, nonopioid analgesics, and nonpharmacologic agents should be considered and used, depending on the surgical procedure and patient comorbidities, as possible. Nonopioid analgesics that should be used when appropriate for acute pain include nonsteroidal antiinflammatory drugs, gabapentinoids, ketamine, α2 agonists, and *N*-methyl-D-aspartate receptor antagonists. Continuous regional anesthesia techniques should be strongly considered when appropriate, because they provide superior postoperative analgesia to opioid-based analgesics.[46–48] A suitable regional anesthesia technique may abrogate the need to discontinue buprenorphine preoperatively and the provision of additional analgesics for acute postoperative pain.

A critical part of the protocol is the early discussion with the buprenorphine provider to ensure that the appropriate support is in place after surgery. Avoiding the psychologic stress of perioperative pain as much as possible in all patients, particularly those with a history of opioid use disorder, is important. Each patient's social and psychiatric issues should be addressed and optimally treated. Management should begin early, at the time of preoperative assessment, and a collaborative multidisciplinary approach, incorporating pain management specialists and mental health professionals, including the clinician currently prescribing buprenorphine, should be used when necessary. Patients with opioid use disorder should be encouraged to be active participants in their treatment plans, and providers should address patient substance abuse history early to aid in elucidating optimal treatment plans. The risks and benefits of discontinuing or continuing buprenorphine preoperatively should be explicitly discussed with patients, as well as the risks and benefits of the use of opioid agonists for postoperative pain management. Similarly, these discussions should include inquiry of each patient's beliefs regarding pain, coping strategies effective during stressful situations, and fears and concerns regarding surgery and postoperative recovery. If opioid agonists are necessary for postoperative pain control after discharge from the hospital, a plan for safe use should be developed, including such features as limiting the number of pills prescribed, having a family member hold the medication, and/or use of a locked medication box at home. Patients should be educated on what to expect after surgery, including the typical time course for acute pain and realistic goals for pain control. Even with an analgesic strategy that includes a combination of nonopioid agents and techniques, patients taking buprenorphine for opioid use disorder may

require supplemental opioids for acute perioperative pain management. Treatment goals should be aimed at using the minimal opioid dose required.

Conclusions

The pharmacokinetic and pharmacodynamic properties of buprenorphine make it particularly appealing for the treatment of pain and addiction, and its use continues to grow. Although its properties are ideal for outpatient maintenance therapy, it poses unique challenges in the setting of acute pain. Inappropriate perioperative pain management in patients taking buprenorphine can lead to prolonged hospital stays with significant postoperative pain and can increase the risk for severe adverse effects from high-dose opioid therapy, including precipitating patient cravings and subsequent relapse. Perioperatively, nonopioid analgesic strategies should be maximized, recognizing that management recommendations for this patient population are based on pharmacology with conflicting clinical data. As such, perioperative protocols developed specifically for the management of these patients are highlighted here. When possible, a thoughtful pain management strategy involving the entire perioperative team of surgeons, nurses, anesthesiologists, addiction specialists, and the patient should be assembled as early as possible.

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Competing Interests

The authors declare no competing interests.

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