

C-42 Perioperative Management of Buprenorphine/Naloxone

Moderator(s)/Facilitator(s): Nyla Azam, M.D.

Objective

After completion of this session, the participant will be able to:

- Manage the use of buprenorphine in the perioperative period for the opioid-dependent patient.

Case Stem Question

A 30-year-old female with a past medical history significant for anxiety, bipolar disorder, chronic pain and opiate dependence presents to the Emergency Department by air medical transport after jumping out of a third story window. She reports pain in her hips and lower abdomen. She states that she was not on anticoagulation but states she took buprenorphine/naloxone that morning, as prescribed. En route to the emergency room the patient receives 40mg of ketamine.

In the emergency room, she is hemodynamically stable, protecting her airway and found to have equal bilateral breath sounds. She has 2+ central and distal pulses. Her pelvis is stable but tender on exam. She has a negative FAST exam, and chest X-ray is negative for rib fractures. She still continues to have severe pain. She was initially given morphine for pain control; however, this provided no relief. After receiving an additional dose of ketamine, she was able to lay still for CT scan of the chest and pelvis.

Past Medical history: Kidney stones, chronic low back pain, opiate dependence

Allergies: No known drug allergies

Past Surgical History: None

Social History: Current smoker, reports alcohol use 1-2 drinks on the weekends, reports history of former drug use, last use three years ago of heroin

The patient was found to have a separation of her pubic symphysis and a right femur fracture. She was admitted to the orthopedic trauma service, and the acute pain service was consulted.

Guiding Questions for Discussion

1. What is buprenorphine, and how do its characteristics make it a good candidate for treating opiate dependence?
2. How does buprenorphine differ from buprenorphine/naloxone?
3. What are the different forms of buprenorphine available?
4. Which patients are best suited for buprenorphine treatment?
5. How will buprenorphine affect acute pain management?
6. How do you manage this patient's buprenorphine/naloxone prior to an urgent surgery?
7. How would your management change if she were coming in for elective surgery?
8. What concerns do you have regarding adverse effects when transitioning from buprenorphine to traditional opioids?

1. What is buprenorphine, and how do its characteristics make it a good candidate for treating opioid dependence?

Buprenorphine is a semi-synthetic partial opioid agonist, a derivative of the morphine alkaloid thebaine.^{1,2} Buprenorphine was initially developed as an analgesic, but its pharmacologic properties led it to become a popular choice for treating opioid dependence and addiction. These include:¹

- a. High affinity for the mu opioid receptor, for which buprenorphine will compete with and displace other opioid analgesics. This in turn can trigger withdrawal symptoms if introduced concurrently with other opioids.
- b. Partial agonism at the mu opioid receptor, reproducing the effect of an opioid but to a lesser degree. This creates an analgesic and euphoric ceiling effect.
- c. Slow dissociation from the mu opioid receptor, with a mean half-life of about 37 hours. This extends its duration of action relative to other opioids and prevents withdrawal symptoms.
- d. Full antagonism of the kappa opioid receptor, which is responsible for many of the dysphoric and psychotomimetic side effects of opioids. This may also be a mechanism for treating depression.
- e. Large volume of distribution, high protein binding and extensive hepatic metabolism, with greater potency than morphine in both intravenous and oral forms; buprenorphine is about 30x more potent than morphine.

Buprenorphine has been used to treat patients for opioid addiction, opioid maintenance, and more recently chronic pain management. About 2.5 million people have OUD in the US. Medication assisted treatment, as a supplement to psychosocial counseling and behavioral treatment for OUD, has shown improved outcomes with increased retention in treatment and decreased morbidity and mortality. There are three FDA approved medications for treating OUD: methadone, buprenorphine, and naltrexone. Methadone and buprenorphine are opioid agonists and have the ability to both curb withdrawal symptoms and provide analgesia. A Cochrane meta-analysis showed no difference in retention of treatment between methadone and buprenorphine, while a recent National Institute on Drug Abuse study found higher retention rates for methadone. Methadone had been the drug of choice for treating addiction, but with strict requirements of treatment centers, medication side effects and surrounding social stigma, treatment has been limited.⁷ Buprenorphine can be prescribed discreetly in a regular clinic but does require an X-waiver if the physician is treating more than 30 patients at a time. With its unique pharmacologic profile, buprenorphine can be used to slowly wean down and replace abused opioids. The maximum daily effective dose of buprenorphine is 24-32 mg daily, equating to about 60-70 mg morphine daily. Buprenorphine may not be as effective in patients on higher doses of opioids. But with its ceiling analgesic effect, lower abuse potential secondary to naloxone, fewer respiratory complications and lesser likelihood of withdrawal, buprenorphine is becoming a drug of choice treatment for addiction and maintenance over methadone.¹

Buprenorphine was approved by the FDA in 2002 for clinical use and became the first medication that could be prescribed from an outpatient clinic setting for opioid dependence and addiction, increasing access to treatment.³ More recently, it had been approved for the treatment for acute and chronic pain.² The Substance Abuse and Mental Health Services Administration/Center for Substance Abuse Treatment is the body that qualifies physicians for prescribing of buprenorphine for treating opioid dependence and addiction. Physicians must meet specific requirements prior to applying for a second DEA number, in the form of an X number, to be able to prescribe it.³ In order to improve accessibility, on April 28, 2021, the Department of HHS announced that qualified practitioners who are state licensed and registered by the DEA are exempt from the X-waiver training requirement. These include physicians who treat no more than 30 patients at any one time, and they still must submit a NOI to obtain an x-waiver to SAMHSA. Clinicians can order mg dosing FDA approved formulations of buprenorphine for OUD in the hospitalized setting without applying for an NOI and can increase if needed in order to maintain or detoxify as an adjunct to medical/surgical treatment of other than addiction to those with intractable pain in which no other medications have been found to have effect after reasonable effort. Patients admitted with conditions related to drug use are all eligible for treatment with buprenorphine in the hospitalized setting. FDA formulations for chronic pain (mcg dosing) can be used for treatment of analgesia in any setting without obtaining an X-waiver. Completing x-waiver certification is an 8 hour course and training link.

2. How does buprenorphine differ from buprenorphine/naloxone?

Similar to other opioids, buprenorphine has the potential to be abused. For this reason, naloxone is added as an abuse deterrent. buprenorphine/naloxone is a combination of buprenorphine and naloxone in the form of a sublingual film.² Naloxone is a short-acting, competitive opioid receptor antagonist. At low doses, it is used to reverse side effects such as respiratory depression and sedation. At high doses, it can reverse analgesia and precipitate withdrawal.⁵ Suboxone is a sublingual tablet with a 4:1 ratio of buprenorphine to naloxone. Naloxone has limited bioavailability when taken in the sublingual form, exerting its antagonistic effect when taken intravenously.⁶

3. What are the different forms of buprenorphine available?

Several formulations of buprenorphine with and without naloxone have been developed over the past decade. Buprenorphine and naloxone both have poor bioavailability when taken in oral form, and high bioavailability in intravenous form. Buprenorphine has good bioavailability in the sublingual form, while naloxone does not. FDA has approved buprenorphine in mg doses for treatment of OUD and mcg dosing for chronic pain.

Mg dosing

Buprenorphine + naloxone Buprenorphine

SL tablet (29%) SL tablet

SL film (buprenorphine/naloxone) ER Injection (70%)

Buccal film (46-65%) IV form

Mcg dosing
TD patch weekly (15%)
Buccal

The transdermal patch and intravenous formulation are FDA approved to treat chronic pain.

4. Which patients are best suited for buprenorphine treatment?

Chronic pain patients have for years been prescribed opioids, which are now known to be addictive in nature. In addition to facing issues of dependence and addiction, chronic pain patients on opioids struggle with decreasing efficacy of treatment in the form of tolerance and opioid induced hyperalgesia. Studies looking at the use of buprenorphine in the chronic pain population show decreased pain levels, withdrawal symptoms and opioid abuse.¹¹ Studies have postulated that buprenorphine reverses opioid induced hyperalgesia, improving chronic pain.¹

Of note, buprenorphine is the preferred drug over methadone for opioid dependence and addiction in two patient populations: pregnant patients, and those with renal failure. In pregnancy, buprenorphine has been shown to be safe for mom and child through gestation, delivery and breast feeding. Pregnant patients treated with buprenorphine have had babies with fewer neonatal abstinence symptoms and higher birth weights, with neonates requiring 89% less morphine, needing shorter tapers, and with decreased hospital length of stays. For pregnancy, patients are continued to continue with buprenorphine throughout their pregnancy and delivery.⁹

In the renal failure population, there is an accumulation of methadone metabolites, which are normally excreted through the kidneys. This may lead to lethal side effects.¹ Buprenorphine has minimal renal clearance and does not have to be renally dosed.¹⁰

Buprenorphine is metabolized through the CYP3A4 system, and as such, will interact with drugs cleared through the same. Serious and fatal interactions can occur in those taking buprenorphine in conjunction with benzodiazepines due to accumulation of metabolites.¹

5. How will buprenorphine affect acute pain management in an opioid tolerance patient?

In 2004, the Treatment Improvement Protocol released by the US Center for Substance Abuse Treatment stated that buprenorphine should be discontinued while patients are taking mu agonist opioids. This influenced medical practice, and it became commonplace to discontinue buprenorphine prior to surgery. The recommendation was derived from multiple case reports that described difficult to control pain in the acute pain setting in patients on buprenorphine. However, that may have reflected the challenge of managing already opioid-tolerant patients and opioid dependent patients needing analgesia as opposed to the consequences of buprenorphine alone. Follow up

case reports became available demonstrating patients not on buprenorphine still having difficulty with pain control in the perioperative setting. Further evidence became available suggesting that buprenorphine in combination with full mu agonists can still effectively treat pain. In summary, acute pain management in this population can be difficult overall. But now, in addition to having uncontrolled pain, these patients who discontinued buprenorphine preoperatively were also at risk for relapse. Patients who discontinue buprenorphine were having a 50, up to 90% chance of relapsing into OUD or death. The increased risk of inadvertent overdose was secondary to decreased opioid tolerance and concurrent introduction of a full mu agonist. Risk factors for OUD exacerbation in the perioperative period include: 1) discontinuing buprenorphine 2) introducing a full mu agonist 3) 16 mg if anticipating high levels of postoperative pain levels. Any change to the regimen should be made only after a discussion with the prescriber and patient and should include the risks of recurrence and increase in cravings during or after the hospitalization. Multimodal analgesics and regional anesthesia should be used as available. When using full mu agonists, use opioids with high mu affinity (fentanyl, hydromorphone). These recommendations are applicable regardless of whether the surgery is urgent or elective.

This is a change from prior guidelines. Previously, buprenorphine was discontinued for all patients when admitted for surgery. Recommendations then came out to stratify based on 1) whether surgery is elective or urgent, and 2) expected pain level after surgery. Urgent surgeries don't allow time to plan for a taper off buprenorphine. Now, for urgent surgeries with low levels of expected postoperative pain, such as a bronchoscopy or colonoscopy, it is recommended that buprenorphine be continued without dose adjustment. For urgent surgeries with intermediate or high levels of pain anticipated after surgery, it is recommended that the last dose of buprenorphine be determined, and further doses discontinued. An acute pain service consultation should be called to facilitate pain management. High doses of short-acting opioids would be needed to displace buprenorphine from the mu receptor. Acute surgical pain may need to be treated with higher than average doses of opioids with high activity at the mu opioid receptor (fentanyl, hydromorphone, morphine).²

7. How would your management change if she were coming in for elective surgery?

For elective surgery, buprenorphine protocols can be used to try to optimize postoperative pain control. The decision as to whether or not to continue buprenorphine depends on the expected pain level after surgery. For surgeries with low levels of postoperative pain, such as colonoscopy or bronchoscopy, buprenorphine can be continued without dose adjustment. For those with intermediate levels of postoperative pain, such as laparoscopic, thoracoscopic or arthroscopic surgery, buprenorphine can be discontinued 3 days pre-operatively without a bridge. For surgery with high levels of pain anticipated after surgery, such as open abdominal, thoracic, or orthopedic surgery, buprenorphine can be discontinued 3-5 days prior to surgery with an opioid bridge for a limited number of doses of a short-acting opioid to manage withdrawal symptoms.

These are outdated guidelines, as this was deemed impractical because patients and

prescribers were uncomfortable stopping buprenorphine for OUD, and prescribers were uncomfortable handing prescriptions for opioids to someone at risk for relapsing. Buprenorphine itself is an analgesic and may have adequate analgesic levels for surgeries with mild to moderate levels of expected postop pain. For surgeries with high levels of anticipated pain, the dose can be tapered to free up mu receptors and buprenorphine can be split into 2-3x/day dosing for immediate analgesic effect.

8. What concerns do you have regarding adverse effects when transitioning from buprenorphine to traditional opioids?

For both elective and urgent surgeries, high levels of postoperative pain may need to be treated with higher doses of short-acting opioids with high activity at the mu opioid receptor (fentanyl, morphine). These patients should be monitored for uncontrolled postoperative pain and respiratory complications. Any patient receiving an addition or increase of opioids needs a safe postoperative taper plan for when their acute surgical pain resolves. Some suggest increasing the buprenorphine dose during the perioperative period with a plan to taper back to the baseline dose as an outpatient. This would have to be discussed with the prescribing physician prior to putting into place.

Because of the adverse effects from opioids, all patients on buprenorphine undergoing surgery – elective or non-elective, with low, intermediate or high levels of pain – are recommended to maximize non-opioid adjuncts, including regional anesthesia, local anesthetic infiltration into the wound by the surgeon, NSAIDs, gabapentinoids, acetaminophen, clonidine, ketamine and dexmedetomidine whenever possible.²

References

1. Chan KY, Chen L, Miao J. Buprenorphine-Naloxone Therapy in Pain Management. *Anesthesiology* 2014; 120(5): 1262-1274.
2. Jonan AB, Kaye AD, Urman RD. Buprenorphine Formulations: Clinical Best Practice Strategies for Recommendations for Perioperative Management of Patients Undergoing Surgical or Interventional Pain Procedures. *Pain Physician* 2018; 21:E1-E12.
3. Buprenorphine. <https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine> Substance Abuse and Mental Health Services Administration. Updated 9/27/19, Accessed 9/30/19.
4. Anderson TA, Quaye AN, Ward EN, Wilens TE, Hilliard PE, Brummett CM. To Stop or Not, That is the Question. *Anesthesiology* 2017; 126:1180-6.
5. Levine JD, Gordon NC, Fields HL. Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain. *Nature*. 1979; 278:740-1.
6. Harris DS, Jones RT, Welm S, Upton RA, Lin E, Mendelson J. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. *Drug Alcohol Depend*. 2000; 61:85-94.
7. Judd LL. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *JAMA*. 1998; 280:1936-43.

8. Raisch DW, Fye CL, Boardman KD, Sather MR. Opioid dependence treatment, including buprenorphine-naloxone. *Ann Pharmacother.* 2002; 36:312-21.
9. Boyer E, McCance-Katz E, Marcus S. Methadone and buprenorphine toxicity in children. *Am J Addict.* 2010; 19:89-95.
10. Summerfield RJ, Allen MC, Moore RA, Sear JW, McQuay HJ. Buprenorphine in end stage renal failure. *Anaesthesia* 1985; 40:914.
11. Roux P, Sullivan M, Cohen J, Fugon L, Jones J, Vosburg S, Cooper Z, Manubay J, Mogali S, Comer S. 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; 154:1442-8.