Buprenorphine, Buprenorphine/Naloxone (Suboxone)

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Abbreviations

CNS	Central nervous system
CYP	Cytochrome P450
FDA	US Food and Drug Administration
HPA	Hypothalamic-pituitary-adrenal
NMDA	N-Methyl-D-aspartate
NSAIDs	Non-steroidal anti-inflammatory drugs
ORL	Opioid receptor-like
OUD	Opioid use disorder

1 Essential Basics

1.1 Introduction

Buprenorphine is a semi-synthetic opioid derived from thebaine, an alkaloid of the opium poppy, *Papaver somniferum*, that has been on the market in various forms since the 1970s. Given the current state of the opioid crisis, alternatives to Schedule II full

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mu-agonists are increasingly needed. Characterized as a Schedule III opioid, buprenorphine is approved by the United States Food and Drug Administration (FDA) for the treatment of opioid use disorder and chronic pain. Its structure allows buprenorphine to interact with several opioid receptors—mu, kappa, and delta, as well as opioid receptor-like 1. As an agonist-antagonist at those opioid receptors, buprenorphine exhibits a unique pharmacological profile making it potentially an ideal choice for the treatment of chronic pain states as well as providing an option for those with opioid use disorder.

1.2 Pharmacodynamics of Buprenorphine

At first, the concept of buprenorphine can seem confusing. It is described as a partial opioid agonist at the traditional mu receptors, but it exhibits analgesic efficacy that rivals the traditional full-agonist opioids such as morphine and fentanyl [1]. When buprenorphine binds to the mu-opioid receptor, it causes receptor phosphorylation, promoting the release of G-protein subunits, inhibition of adenylyl cyclase, reduction of intracellular cyclic adenosine monophosphate levels, and regulation of ion channels. This cascade of events limits release of neurotransmitters, resulting in hyperpolarization of the cell membrane and preventing activation of nociceptors, leading to the desired analgesic effect. Traditional opioids such as morphine, fentanyl, and methadone also recruit beta-arrestin to the opioid receptor in addition to G-protein subunits. Beta-arrestin signaling has been associated with opioid-related adverse effects, such as respiratory depression, constipation, nausea, and abuse potential [1, 2]. Since buprenorphine does not recruit beta-arrestin to the receptor, these undesired side effects of traditional opioids are largely avoided. This unique mu-receptor activation profile for buprenorphine confers the concept of "partial agonism" due to its unique structural binding and the subsequent receptor activity level it conveys. Its analgesic efficacy is maintained while the chance of respiratory depression is decreased, and abuse potential is lessened by preventing the excessive signaling of the mu-opioid receptor.

In addition to being an agonist at the mu-receptor, buprenorphine also exhibits antagonism at the delta opioid receptor and inverse agonist activity at the kappa receptor [1, 2]. Antagonist effects at these receptors confers additional protection by limiting unwanted effects typically observed with mu-opioid receptor activation. Respiratory depression, constipation, anxiety, and addiction potential are all decreased, in contrast to pure mu-opioid receptor agonists. Furthermore, there is less sedation and euphoria associated with buprenorphine due to these receptor interactions compared to drugs such as morphine and fentanyl. It is thought that the inverse-agonist activity, meaning that binding induces the opposite effect of an agonist at the same receptor, is responsible for buprenorphine-associated antihyperalgesic activity [2]. This interaction also contributes to less sedation and euphoria, in conjunction with the antagonistic interactions at the delta receptor. Some studies have investigated tissue specificity of buprenorphine as well, suggesting that buprenorphine primarily exerts it analgesic effects on the lower central nervous system (CNS) (spinal cord) rather than the higher CNS (brain) [1]. Such findings support the notion that buprenorphine's lack of supraspinal effects may help limit the risk of respiratory depression and euphoria and maximize the analgesic effects at spinal opioid receptors. Table 1 provides a succinct overview of the basic effects of buprenorphine at each receptor at which it interacts.

An important characteristic of buprenorphine to note is its high binding affinity at various opioid receptors. Binding affinity is the ability of a drug to bind to a receptor and is measured by determining the equilibrium dissociation constant (K_i) [1]. While it does exhibit high affinity for kappa and delta receptors, its high binding affinity (having a low K_i value) for the mu-opioid receptor due to its unique structure and binding position is what most contributes to its place among other opioids. While this affinity might contribute to increased receptor occupation by buprenorphine, it does not necessarily correspond to superior activity at those receptors. As such, buprenorphine exhibits slower dissociation from the mu-opioid receptor compared with other opioids. This characteristic may contribute to prolonged analgesia while limiting the potential for withdrawal when used to manage patients

Table 1 The pharmacodynamics of buprenorphine [1]

Receptor	Mu	Delta	Kappa	ORL1
Activity	Partial agonist	Antagonist	Antagonist	Agonist
Effects	• Potent analgesia • Limited CNS effects—dysphoria, respiratory depression, euphoria • Limited physical dependence and abuse potential • Limited impact on GI system—less nausea, dysmotility • Reduced impact on HPA axis and immunosuppression • Reduced risk of anxiety, depression, and suicidal ideation	• Anti-opioid effects • Limited CNS effects	• Reduced risk of anxiety, depression, and suicidal ideation • Reduced immunosuppression	• Enhanced spinal analgesia • Reduced supraspinal effects • Limited tolerance potential

Table 2 Representative binding affinity at the μ-opioid receptor [1]

Medication	Binding affinity (K_i)
Buprenorphine	0.22
Hydromorphone	0.37
Morphine	1.17
Fentanyl	1.35
Oxycodone	25.87
Hydrocodone	41.58
Codeine	734.20

with chronic pain. Table 2 demonstrates a comparison between binding affinity of buprenorphine and several other commonly prescribed opioids.

1.3 Pharmacodynamics of Buprenorphine Metabolites

The major metabolite of buprenorphine is norbuprenorphine. It is formed from the catabolism of buprenorphine through the cytochrome P450 (CYP) 3A4. Norbuprenorphine acts as a mu receptor agonist and has high affinity for both kappa and delta receptors. Similar to its precursor, norbuprenorphine triggers mu receptor G-protein binding but to a greater degree than buprenorphine, and paradoxically, exhibits only 1/50th the analgesic potency of buprenorphine [2]. Norbuprenorphine also interacts with the beta-arrestin receptor with high affinity and subsequently activates it, which is associated with opioid-related adverse effects, such as constipation and respiratory depression seen with traditional opioids. In part, this metabolite is responsible for the minor side effects seen with buprenorphine administration [2].

Table 3 Bioavailability of buprenorphine [1]

Administration route	Bioavailability
Intravenous	100%
Buccal	46–65%
Sublingual	28–51%
Transdermal	15%

1.4 Pharmacokinetics

The bioavailability of buprenorphine is largely determined by properties such as low molecular weight, high lipophilicity, and high potency. However, its oral bioavailability is very poor, only about 10–15%, largely due to high first-pass hepatic metabolism [2]. Other routes of absorption, such as sublingual, buccal, transdermal, and illicit conversion to intranasal or intravenous routes, have greater bioavailability since they bypass first-pass metabolism. Table 3 provides relative bioavailability based on route of administration. After absorption, buprenorphine remains approximately 96% protein bound, primarily to α- and β-globulin. Due to its high lipophilicity, tissue penetration, and protein binding, it has a large volume of distribution—approximately 430 L [2]. Half-life varies depending on the route of administration, but averages about 37 h due to slow receptor dissociation. Onset of action remains relatively fast—5–15 min intravenously and 30–60 min via the sublingual route. The transdermal delivery system confers the slowest onset, valued at approximately 72 h [3].

1.5 Metabolism

Buprenorphine is metabolized through CYP3A4 and CYP2C8 to the active metabolite norbuprenorphine. The major rate-limiting step involves glucuronidation of both buprenorphine and norbuprenorphine to buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide. Interestingly, the metabolites are not known to cause major interactions with other drugs metab-

olized by the cytochrome P450 system, thereby minimizing drug-drug interactions with buprenorphine [1]. Buprenorphine and its metabolites are subsequently excreted mainly via the biliary system through enterohepatic recirculation. A small amount may be eliminated via feces or urine. Because of this, buprenorphine is suitable for patients with both renal and hepatic impairment. These characteristics make buprenorphine a good choice for treatment of chronic pain in elderly patients who often have liver and kidney impairment. Additionally, since buccal and transdermal formulations bypass first-pass metabolism, those routes of administration may be helpful in patients with gastrointestinal comorbidities who are unable to tolerate oral pain medicines well.

1.6 Indications, Formulation and General Dosing

To date, there are only two approved US FDA indications for the use of buprenorphine—the management of chronic pain and for treatment of opioid use disorder. Patients may be receiving treatment for either indication separately, but it is not uncommon for a patient to have overlapping indications. It is important for the anesthesiologist to be familiar with the indications and dosing in order to help formulate a perioperative pain management strategy.

Presently there are close to a dozen branded formulations approved by the FDA. Given the poor oral bioavailability, multiple alternative routes of administration have been developed. For chronic pain, buprenorphine is approved in transdermal and buccal formulations. For OUD and opioid dependence, approved formulations include buccal, sublingual, intramuscular depot, and subdermal implants. Some patients may be receiving off-label sublingual buprenorphine for chronic pain as well. *Naloxone* is included in some buccal and sublingual formulations. Naloxone is poorly absorbed when taken buccally or sublingually; however, if it is injected intravenously, it is highly bioavailable and subsequently blocks buprenorphine's ability to bind to target receptors. This helps to decrease the potential for illicit abuse. It is important to note that, compared to the half-life of buprenorphine, the half-

life of naloxone in the buccal and sublingual combinations is only approximately 2–12 h compared to upwards of 42 h for buprenorphine itself [3]. This underlies the fact that if someone were to require naloxone for management of a buprenorphine overdose, close monitoring for an extended period of time is essential.

The dosing of buprenorphine varies among formulations due in large part to their routes of administration and associated bioavailabilities. It is also characterized as either high-dose or low-dose. High-dose formulations are approved by the FDA for the treatment of OUD. These doses are defined as any dose that equals or exceeds an equivalent dose of 24 mg of daily sublingual buprenorphine. Low-dose formulations are defined by any equivalent daily dose less than or equal to 8 mg sublingually [4]. The FDA has approved two formulations, a transdermal patch and a buccal product, for the treatment of chronic pain. Therefore, patients being treated with buprenorphine for chronic pain are receiving formulations that fall into the low-dose category.

2 Perioperative Use

2.1 How to Choose Among Similar Medications Within the Same Class

Considering that there are a multitude of options within the opioid class of medications to use perioperatively, it is important to discuss unique properties of buprenorphine that could confer benefits to the patient. The applications of buprenorphine are far from confined to intravenous administration for acute pain management. An extremely versatile opioid, buprenorphine can be administered by a variety of routes including intravenous, intramuscular, neuraxial, subcutaneous, sublingual, and transdermal. Additionally, buprenorphine could be an acceptable alternative in those patients that cannot tolerate morphine or other opioids due to allergy or sensitivity. Given its liver metabolism, buprenorphine would be an excellent choice for those patients with renal insufficiency with the major metabolites primarily excreted via the fecal route.

Buprenorphine has demonstrated a ceiling effect with respect to respiratory depression but not analgesia [5, 6]. This property could be particularly beneficial in those patients susceptible to respiratory depressant effects of opioids, such as those with obstructive sleep apnea or the elderly, as additional doses administered for analgesia would be less likely to blunt respiratory drive. In fact, one study examining the effects of buprenorphine on postoperative pain in over 7500 patients demonstrated good or adequate pain relief for at least 4 h with an incidence of drug-associated respiratory depression of less than 1% [7].

Patients with inflammatory pain may benefit from buprenorphine in comparison to traditional opioids, as buprenorphine has been reported to have anti-inflammatory activity. In fact, it has been reported to be efficacious when administered intra-articularly; one such study of patients undergoing knee arthroscopy demonstrated a significant reduction of analgesic requirement with intra-articular buprenorphine [8]. Lastly, there exists a role for buprenorphine in regional anesthesia as perineural buprenorphine has been demonstrated to prolong the effect of local anesthetics in peripheral nerve blockade [9, 10].

2.2 Indications and Contraindications

Buprenorphine is indicated for the treatment of moderate to severe pain. As mentioned previously, there are some nonconventional applications that have been described successfully such as intra-articular and perineural administration. Official FDA-approved indications for buprenorphine remain solely for the treatment of chronic pain and opioid use disorder at this time.

With regards to contraindications, the only absolute contraindication is hypersensitivity or anaphylaxis to the drug buprenorphine itself. However, there exists a variety of relative contraindications. Caution should be used in administering buprenorphine to patients with pre-existing central nervous system depression (including concomitant use with benzodiazepines and other CNS depressants) and/or altered mental status. Other relative contraindications include severe respiratory insufficiency

(albeit potentially safer than conventional opioids due to the ceiling effect described above), known or suspected gastrointestinal obstruction, hypotension, morbid obesity, pregnancy, and seizure disorders. Buprenorphine has been reported to prolong the QT interval and thus should be used with caution in patients with congenital long QT syndrome (or with concomitant use of other QT prolonging medications) due to the risk of life-threatening arrhythmias such as Torsades de pointes [2]. Caution should be used and/or dose adjustment should be considered in those with severe liver dysfunction (due to hepatic metabolism), the elderly, and opioid-naïve patients.

2.3 Dosing/How to Titrate Up or Down

Buprenorphine has been described as about 30 times as potent as morphine [11]. A starting intravenous dose of 0.3 mg every 6 h is often used, with an additional dose of 0.3 mg given as indicated. Doses up to 7 mg have been given intravenously for postoperative analgesia without associated respiratory depression [12].

Perineural buprenorphine is dosed at 0.2–0.3 mg with the local anesthetic. For neuraxial use, epidural buprenorphine is also typically given at doses of 0.3 mg with pain relief for up to 12–24 h [13]. Intrathecal dosing is typically reduced to 1/10th the parenteral dose with dosages of 0.03 or 0.045 mg producing long-lasting analgesia with nausea and vomiting as the predominant side effects.

The buccal film form of buprenorphine is usually initiated at 75 μg once daily and titrated up to twice daily if tolerated. The dose can be increased incrementally to 150 μg every 12 h with a maximum dose of 900 μg every 12 h. Sublingual buprenorphine is typically dosed in 2–12 mg tablets, dosed up to a typical maximum of 32 mg daily in divided doses. When naloxone is added, it is generally dosed at 1/4th the dose of buprenorphine (for example, 8 mg/2 mg buprenorphine/naloxone) [2].

Transdermal buprenorphine is typically initiated at 5 μg/h applied once weekly. Opioid tolerant individuals may require 10 μg/h, and the dose is titrated in 5 μg/h increments up to the max

dose of 20 μg/h. For transdermal patch discontinuation, a gradual stepwise approach is recommended, such as decreasing the dose by 10–25% every 2–4 weeks.

In patients with severe hepatic insufficiency, it is recommended to reduce the starting dose and titration doses of buprenorphine by 50% with no adjustment needed in patients with only mild or moderate liver dysfunction. No dosage adjustment is required for patients with renal insufficiency given the pharmacokinetics of buprenorphine.

2.4 Withdrawal

Opioid withdrawal is considered to be less severe with buprenorphine than with other opioids, which may be attributed to its inherent nature as a partial agonist; buprenorphine can, however, displace other opioids and precipitate acute withdrawal in individuals with opioid use disorder.

When discontinuing or tapering down buprenorphine, it is important to do so in a gradual manner and/or bridge with other opioids in order to prevent withdrawal. Withdrawal symptoms can include myalgias, restlessness, anxiety, lacrimation, rhinorrhea, hyperhidrosis, insomnia, diarrhea/GI upset, nausea/vomiting, mydriasis, tachycardia, and hypertension. If these symptoms occur during a taper, it is important to increase the buprenorphine dose back to the previous level and interrupt the taper. Further attempts to taper should utilize a strategy with more gradual reduction in dose and/or frequency of such reductions.

2.5 Toxicity

Adverse effects of buprenorphine include nausea and vomiting, drowsiness, dizziness, headache, memory loss, cognitive and neural inhibition, perspiration, itching, dry mouth, miosis, orthostatic hypotension, and urinary retention. Constipation and CNS effects are seen less frequently than with morphine.

2.6 How to Continue or Stop Preoperatively and How to Restart Postoperatively

The perioperative management of patients taking buprenorphine and buprenorphine/naloxone is a complex process, and pain control in these patients can be challenging. In short, a widely accepted strategy for continuing, stopping, and restarting buprenorphine during the perioperative period does not exist. Due to high receptor binding affinity, long half-life, and the partial agonism nature of buprenorphine, traditional opioid analgesic effects may be inhibited resulting in uncontrolled postoperative pain [14].

Generally speaking, pain relief can be more readily achievable in patients when buprenorphine is discontinued, and thus traditional opioids can exert their therapeutic actions on their receptors in a more predictable way. Historically, some experts advocated discontinuation of chronic buprenorphine at least 72 h before surgery and using a bridging strategy with opioid agonists. However, pain control may still be achievable in patients continuing buprenorphine that are undergoing surgery. One study of surgical patients taking buprenorphine revealed that patients continued on buprenorphine had similar pain control within the first 24 h compared to those that discontinued buprenorphine, despite a lower dosage of morphine-equivalents in the buprenorphine continuation group [15]. Consequently, the approach to managing pain and the perioperative use of buprenorphine should be tailored to the individual patient, accounting for several major considerations: the *urgency* of the procedure, the *dose of buprenorphine* the patient takes, the *anticipated pain* from the procedure, and the *psychological implications of pain control* (or lack thereof) in this specific patient population [4]. A multidisciplinary approach involving the patient, surgeon, anesthesiologist, and the patient's buprenorphine prescriber is critical to establish a plan for tapering and restarting buprenorphine perioperatively, should tapering be necessary.

A recent editorial in 2018 recommended continuing buprenorphine through the perioperative period, especially in patients with OUD, because of the increased risk of relapse and the complexi-

ties of re-induction onto buprenorphine postoperatively should it be discontinued [16]. The most recent consensus opinion on perioperative management advocates for continuation of the patient's home dose of buprenorphine, particularly if they are being treated for OUD. Consideration for tapering can be made if patients are on particularly high doses, such as greater than 24 mg daily, and high anticipated post-surgical opioid requirements [17]. There exists the possibility that patients who present for surgery while still taking buprenorphine may require high dosages of opioids and/or monitored care settings resulting in increased length of stay, increased cost, and decreased patient satisfaction. Finally, a multimodal analgesic regimen is critical in these patients, particularly in the setting of continued buprenorphine use, including regional and epidural anesthesia and other non-opioid analgesics such as acetaminophen, NSAIDs, gabapentenoids, alpha-2-agonists such as dexmedetomidine, and NMDA antagonists such as ketamine [18].

Management strategies can be approached by identifying the urgency of the pain state. Essentially, two main avenues exist—elective procedures/non-emergent acute pain and emergency procedures/emergent acute pain. Identifying the anticipated pain and opioid requirements will further help guide perioperative management. For elective cases, it may be feasible to develop a pain management plan that involves tapering the dose closer to 8 mg daily prior to surgery in an effort to free more opioid receptors and manage breakthrough pain with traditional opioids more effectively. That may not always be the case for urgent or emergency surgeries. Along these lines, evidence suggests buprenorphine should be continued in the peripartum setting for pregnant patients [4]. Neuraxial techniques, including spinal anesthesia and/or epidurals should be employed whenever possible, and multimodal non-opioid analgesic therapy should be optimized. Table 4 provides a basic framework for practical considerations to buprenorphine management in the perioperative setting. Tapering guidelines can vary widely, but generally speaking patients on high doses can be considered candidates for tapering in collaboration with their pain management or addiction management specialist.

Table 4 Basic algorithm for buprenorphine management [4]

Elective surgery		Emergent surgery	
Low opioid requirements	Mod/high opioid requirements	Low opioid requirements	Mod/high opioid requirements
Continue @ current dose	Low-dose (≤8 mg daily) • Continue @ current dose	Continue @ current dose	Low-dose (≤8 mg daily) • Continue @ current dose
	High-dose (>16 mg daily) • Chronic pain—consider tapering to 8–16 mg daily prior to surgery • OUD—develop plan with primary prescriber—may involve continuing at current dose vs taper plan • Optimize non-opioid analgesics		High-dose (>16 mg daily) • Chronic pain—continue buprenorphine, optimize non-opioid analgesics; consider supplemental full mu agonists; consider temporary dose reduction to no lower than 8 mg daily • OUD—continue buprenorphine, optimize non-opioid analgesics; consider supplemental full mu agonists; consider involving pain/addiction specialist for temporary dose reduction to no lower than 8 mg daily

Common Pitfalls

Many practitioners may be intimidated when encountering a patient who is taking buprenorphine. Whether the indication is for opioid use disorder or chronic pain or another off-label use, there can be an underlying assumption that pain management will be quite difficult. Patients may inappropriately have their buprenorphine discontinued or inappropriately titrated, leading to undesired effects such as withdrawal or increased risk of relapse. Alternatively, providers may be hesitant to adequately treat peri-

operative pain with full mu-agonists for fear of the effects of over narcotizing. Having a baseline understanding of the pharmacodynamics and indications for buprenorphine treatment will help anesthesiologists be prepared to implement appropriate management plans when these patients present to the perioperative arena.

Clinical Pearls

- Buprenorphine binds to all three major opioid receptors—mu, kappa, and delta; binds with much less affinity to the opioid receptor-like (ORL-1)
- High first-pass clearance with oral administration, hence sublingual, buccal, and transdermal routes are preferred.
- Metabolized to norbuprenorphine through the cytochrome P450 followed by multiple rate-limited congugases.
- Buprenorphine is a preferred analgesic option in patients with renal failure, as clearance is independent of renal function and is not cleared by dialysis.
- Mild to moderate liver failure does not influence clearance of buprenorphine.
- Similar analgesic equivalence to other opioids but exhibits a dose-dependent ceiling effect on respiratory depression, less constipation, and less hypogonadism.
- A multidisciplinary approach should be employed, with involvement of the patient, surgeon, anesthesiologist, and the patient's buprenorphine prescriber to develop a tapering plan preoperatively and postoperative resumption of an appropriate buprenorphine dose.
- In general, patients undergoing procedures with low anticipated opioid requirements or low-dose therapy ($\leq$8 mg daily sublingual equivalents) may continue their buprenorphine therapy without modification.
- Patients on higher doses of buprenorphine and/or those undergoing more severe acute pain insults could be considered for a tapering of their dose.
- Caution should be taken in those at high risk of opioid use disorder relapse; therefore, complete discontinuation is not recommended in these patients.

- A multimodal pain management approach is critical in these patients, including nerve blocks with continuous peripheral catheters, epidural analgesia, and other non-opioid analgesics such as acetaminophen, NSAIDs, gabapentinoids, dexmedetomidine, ketamine and muscle relaxants.
- Ensure appropriate setting and level of monitoring perioperatively, especially when patients are receiving concomitant full mu-agonists, respiratory depressants and other sedatives.

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