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Opioids for Surgery or Acute Pain in Patients on Chronic Buprenorphine

Background and Pharmacology

As of this chapter submission date, there are no controlled prospective human studies to determine the best approach for treating acute pain in a patient receiving buprenorphine chronically for a substance abuse disorder and/or chronic pain in the form of Suboxone®, Sebutex®, any generic alternatives, or Butans® Transdermal patch. At best, all publications to date have multiple deficiencies, confounds, and preconceptions that are discussed in greater detail herein.

There are several questions that one needs to ponder when preparing for post-surgical analgesia for patients currently receiving chronic buprenorphine. These include…

1. For scheduled elective surgery should the patient continue buprenorphine or stop it in advance of the surgery?
2. If it is stopped, what are the risks regarding rebound substance abuse?
3. If it is not stopped, what are the post-operative dilemmas for treating acute pain with pure opioid agonists?
4. If the patient stops buprenorphine prior to surgery, how far in advance should it be discontinued?
5. If the patient presents for acute surgery, do I continue the buprenorphine or stop it in anticipation of required opioid therapy?
6. And perhaps most important, why should I even be asking these questions?

We’ll start with the answer to question #6 above. To truly understand buprenorphine, one needs to fully understand its pharmacology and pharmacokinetics in order to make an informed decision on how to approach the decisions for 1-5 above.
Buprenorphine is FDA approved for treating substance abuse and moderate to severe chronic pain. It is available in sublingual (SL) tablets or transmucosal film (Subtex® and Suboxone®) for substance abuse, or transdermal patches (Butrans®), and parenteral formulations (Buprenex®) for pain. Suboxone® is a combination product of buprenorphine with naloxone. Clinically, there is substantial controversy around this topic because naloxone was packaged with buprenorphine ostensibly to mitigate the abuse potential if the originally tablets were to be crushed and injected. However, as we will see, buprenorphine has about five times the affinity for µ-opioid receptors compared to naloxone.\textsuperscript{1}

Buprenorphine is a dehydroxylated phenanthrene; just like its counterparts hydrocodone, oxycodone, levorphanol, hydromorphone, oxymorphone, naloxone, and butorphanol.\textsuperscript{2} However, unlike its counterparts, buprenorphine is a partial agonist at the mu(μ)-opioid receptor (MOR) and an antagonist at the kappa(κ) receptors.\textsuperscript{3} Basically what this means is that when buprenorphine acts on the MOR, it elicits a partial analgesic response and at the κ receptors, it binds tightly but elicits no response and thus leaves the κ receptors inactive. Analgesia occurs at multiple opioid receptors, the most common of which are the various μ receptor subtypes.\textsuperscript{3-5} There are many μ-receptor subtypes, and μ-1 receptors are thought to be the most important for attaining analgesia.\textsuperscript{4-5} Buprenorphine is highly bound to μ-1 receptors, hence its usefulness in treating pain.\textsuperscript{6}

To better understand the concept of a partial agonist, consider the analogy of a lock and key. The lock represents the MOR and the key is represented by the drug. If a full μ-opioid agonist such as morphine is administered, the key turns the whole lock and full analgesic effects are experienced. However if a partial agonist, such as buprenorphine is administered, the lock turns roughly half way and only partial analgesic effects are experienced. Moreover, for a pure agonist (such as morphine), the receptor undergoes a significant conformational change and closes tightly around the drug. In contrast, partial agonists (such as buprenorphine) cause less conformational change and as a result the receptor (lock) closes less tightly around the drug. The change in receptor shape achieved by a full agonist is a reflection of its analgesic potential as demonstrated in figure 1 which represents this relationship by plotting the percent response versus log dose of opioid.\textsuperscript{7} As seen in figure 1, initially both the full agonist and partial agonist produce an indistinguishable response at low doses. However, when the doses are titrated upward, we see that the partial agonist exhibits what is called a “ceiling effect” in which the response eventually plateaus without regard to the increasing concentration of the drug.

A unique aspect of buprenorphine is the strength to which it binds with the MOR, which is far greater than any other opioid and can disallow access by a pure agonist such as morphine\textsuperscript{3} “Affinity” and “binding” are important concepts to understand. Affinity is the pull that a drug has towards the receptor and binding capacity is the opioid’s ability to hold onto that receptor.\textsuperscript{3}

Buprenorphine is said to have high affinity and binding capacity, but low intrinsic activity at the μ-opioid receptors. Buprenorphine has a very long half-life which is the time required for a drug to decrease to 50\% of its initial concentration. For example, if the blood level of a drug is 100ng/mL and four hours later it is 50ng/mL, the half-life is 4 hours. Buprenorphine’s half-life is between 24-42 hours depending on the individual, and half-life of dissociation from the receptors of buprenorphine is about 166 minutes. In contrast to the pure opioid agonist fentanyl, buprenorphine’s activity extends well beyond the plasma half-life.\textsuperscript{1} Fentanyl dissociates from receptors rapidly and completely, but buprenorphine dissociates slow and incompletely. In short, fentanyl responses are dependent on high plasma concentrations, but that is not the case for buprenorphine.\textsuperscript{9} These pharmacokinetic parameters are key concepts to remember when we discuss how to treat patients that are candidates for elective versus emergency surgery and are receiving chronic buprenorphine therapy.
The metabolism of buprenorphine occurs in the liver through the cytochrome P450(CYP3A4) system, although CYP2C8 also plays a minor role. Buprenorphine’s active metabolite, norbuprenorphine undergoes glucuronidation carried out by UGT1A1 and UGT2B7. In other words, the metabolite norbuprenorphine, is made more water soluble by the process of glucuronidation through the action of UGT1A1 and UGT2B7 enzymes so that the body may eliminate it through urine and/or feces.

To review, buprenorphine is a partial μ-1 receptor opioid agonist with very high affinity (or draw towards the receptor) and is also very tightly bound to these receptors. In fact, it is so tightly bound, that it can displace pure opioid agonists such as morphine. Similarly, a pure opioid antagonist, such as naloxone, fits snugly at the receptor, has a very high affinity, and is not easily displaced; these drugs are used to reverse pure opioid agonists if a patient presents overdosed on drugs such as morphine or heroin. Although buprenorphine is a partial agonist/antagonist, pharmacologically it actually has a higher binding affinity to the μ-1 receptor when compared to naloxone (Narcan®) and therefore could theoretically also be used to reverse the effects of morphine. In fact, van Dorp and colleagues demonstrated this well showing that although naloxone can reverse burpenorphine, the naloxone dose must be huge and continuous. But even then, the reversal is short-lived.

Now that we have some sense of buprenorphine’s pharmacology and the pharmacokinetic parameters involved, we may begin to ponder how to best treat patients who are on chronic buprenorphine therapy and require surgery. If you are still wondering why buprenorphine poses a problem for these patients, the answer is in the pharmacology and pharmacokinetics of buprenorphine. As stated previously, buprenorphine is a partial μ opioid agonist and κ antagonist, and has a higher affinity for the MOR than any other opioid. Therefore, if an opioid such as morphine was administered along with buprenorphine for analgesia, the morphine would have no chance of competing with buprenorphine for the MOR. Therefore, patients on chronic buprenorphine therapy that require a surgical intervention present a conundrum to anesthesiologists, physicians and pharmacists because it is very difficult to provide opioid analgesia for this subset of individuals. Moreover, there are no published controlled studies to provide clinicians a validated protocol to reference and provide adequate and safe analgesia. All of the articles published are case studies, experiential opinions, and/or non-validated presumptions. However, until such evidence exists, this chapter provides information outlining the pros and cons of the various treatment options and how to address the dilemmas. The scenarios will be divided into 2 types: 1) Patients on chronic buprenorphine therapy that choose elected surgery and 2) Patients on chronic buprenorphine therapy that require emergency surgery.

Practicality

Imagine bringing a patient to surgery on a naloxone continuous intravenous infusion that you cannot stop for at least 2-3 days post-operatively, or perhaps longer. Envision trying to treat that severe pain with acute opioid therapy (AOT) but that with each sequential dose escalation, your attempts remain futile because naloxone is blocking the AOT from combining at the site of action, the μ-1 opioid receptors. Essentially, this is what’s happening when you perform surgery on a buprenorphine(Suboxone®) patient, but with some inherent analgesic activity from the buprenorphine. [AOT examples include morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, and others.]

Adjuvant therapeutic options (regional nerve blocks, ketamine, IV acetaminophen and ibuprofen, pregabalin, SNRIs, sedative-hypnotics, etc.) become the principal analgesic treatments, and AOT becomes the adjuvant – exactly opposite to what we’re all used to. One of the most misunderstood opioids among clinicians is buprenorphine for the reasons previously outlined, and even more especially when combined with naloxone in the branded form of Suboxone®.
If a patient has a scheduled or elective surgery with an active prescription for any buprenorphine product, the approach is complex and requires an understanding of pharmacology, various options, rational polypharmacy, but most importantly, common sense.

Providing Analgesia for Chronic Buprenorphine Therapy Patients: Elective Surgery

It is theoretically easier to treat patients who are on chronic buprenorphine therapy that choose to have elective surgery rather than emergent surgery. The primary reason is because in this situation, time is a medical provider’s best friend. We know exactly when the patient is scheduled to have surgery, and therefore have time to set up a game plan. This game plan helps to assess the patient’s protocol and assess beforehand what the postoperative situation might be depending on how minor or major the surgery. If it is minor surgery and minimal pain is expected, we can often treat the patient’s postoperative pain by continuing the buprenorphine regimen along with standard adjuvant therapy such as acetaminophen and/or NSAID’s. However, the recommendations change for major surgery when considerable pain is expected postoperatively. Referring back to buprenorphine’s pharmacology and pharmacokinetics, concurrent opioid therapy with buprenorphine could result in suboptimal analgesia. This is especially true for major surgery with resultant moderate to severe pain. As outlined above, the administered opioid would have little to no chance [theoretically] of competing with buprenorphine at the MOR. The most recent government guidelines for buprenorphine state that until buprenorphine clears the body, it may be difficult to achieve analgesia with short-acting opioids in patients who have been maintained on buprenorphine therapy. Therefore, one would expect that buprenorphine therapy should be discontinued for surgeries that provoke moderate to severe pain postoperatively if there is an expected requirement to use full opioid agonists.

Currently, primary literature suggests tapering off buprenorphine gradually 2-4 weeks prior to surgery in order to treat the postoperative pain routinely with opioids and adjuvants. This should allow adequate time to clear buprenorphine from the body thereby allowing adequate analgesia with standard opioid therapy. During the buprenorphine taper process as an outpatient, patients may be prescribed short acting opioids if they were on a chronic buprenorphine product for pain. (i.e. Butrans® Transdermal Patch) It should be noted that patients will require significantly higher than usual doses of short-acting agents if buprenorphine remains in their body. Therefore, extreme caution and patient counseling are advised if short-acting combination products containing acetaminophen, ibuprofen, or aspirin are prescribed in order to avoid toxicity from the non-opioid component. Once the patient has been completely switched off of the buprenorphine and it is time for surgery, a standard pain protocol commensurate with the institution’s pain management policy may be initiated pre, intra, and post operatively. Immediately following surgical recovery, and after the patient’s pain is adequately controlled, the patient may be reintroduced to buprenorphine and the dose may be gradually titrated up to the therapeutic dose the patient was on previously receiving; or a higher dose may be used to compensate for the surgical pain. Seems easy enough, right? Well it may seem simple; however, we recommend that a multidisciplinary team, including pain specialists, be formed for these patients to achieve successful outcomes. Table 1 outlines benefits versus risks based on our review of the literature and experience.

These patients should be monitored vigilantly because validation data is lacking and there are potential pitfalls. One major consequence of this recommendation is the potential for relapse in patients receiving buprenorphine for a substance abuse disorder. Buprenorphine’s unique pharmacology and
pharmacokinetics render it particularly useful as replacement therapy for heroin users or other opioid abuse. The potential for relapse is presumably very high for the patient with comorbid substance abuse disorder and chronic pain that is being weaned from their treatment regimen and instead given substantial doses and quantities of short-acting opioids.

Another important concern is patients that are illegally obtaining buprenorphine from non-medical sources to self-treat their substance abuse disorder. If these patients do not disclose their transgression, the patient could enter into surgery with blocked μ receptors which to the healthcare team is assessed as a high level tolerance to opioids. But, after 2-3 days of high dose opioid therapy which unbeknownst to the care team is required to overcome buprenorphine, the buprenorphine disassociates from the μ receptors, and the patient is at risk of opioid overdose – this is even more problematic if the patient is sent home within 24 hours and prescribed a higher than average opioid dose, and the buprenorphine dissociates from the receptors while the patient is at home. This dilemma is nicely outlined by Marcucci et. al.16

Providing Analgesia for Chronic Buprenorphine Therapy Patients: Emergent Surgery

Patients that present in need of emergency surgery on buprenorphine therapy are a bit more challenging therapeutically. Hypothetically it is very difficult to attain analgesia with opioids alone for a patient that is receiving buprenorphine therapy because of the manner in which the buprenorphine acts on the MOR. There are very few recommendations in the literature to guide the clinician for achieving sufficient analgesia in these patients. Most, if not all published recommendations are contentious at best. For example, Macintyre et al suggest that patients who received methadone or buprenorphine therapy post-operatively required much less PCA morphine equivalents compared to patients who did not receive methadone or buprenorphine therapy postoperatively.17 The authors concluded that buprenorphine behaves as a full μ-opioid agonist and that there is a synergistic effect seen in analgesia when buprenorphine is given with other μ-opioid agonists. This is counterintuitive, since the science tells us just the opposite.15,7-8,12 In this study, the authors admittedly were unable to quantify adjuvant drug analgesic benefit received perioperatively, some of which included anti-inflammatories, acetaminophen, tramadol (consider NE reuptake inhibition), and IV ketamine.17

Although Macintyre’s conclusions are vulnerable, considering sample size and other limitations, she surely demonstrated that treating post-op pain in the buprenorphine patient is possible, especially by employing medications other than opioids with variable pharmacological mechanisms. Thus, adjuvant therapy can provide significant benefit. As mentioned before, there are no reliable studies for treating through buprenorphine, however there are options that are recommended and published specific to emergency surgery.13-14,16,18-21 Nevertheless, we have created an easy to follow flow chart (figure 3) outlining the major recommendations and benefits versus risks table for each recommendation made.

We suggest that it is important to form a multidisciplinary care team since pain affects so many areas of a patient’s life and condition. In addition, current literature recommends assessing post-op needs of the patient.13-14,18 We recommend to preoperatively assess the type of pain anticipated and ascertain analgesic dilemmas in advance. Once the anticipated pain has been assessed preoperatively, the decision to either continue or discontinue the buprenorphine therapy needs to be made. If we are dealing with moderate-severe pain, as most emergency surgeries will present, it is recommended to maximize adjuvant therapy. This is a key point because we need to utilize and maximize medications other than those targeting μ-opioid receptors.

Other literature recommends high doses of short acting opioids while buprenorphine is still present in the patient.7,13-14,16,18-21 Many of these studies employed fentanyl, hydrocodone, morphine, or
oxycodeone by various routes of administration and/or by patient controlled analgesia (PCA) with adjuvant therapies. The theory behind this is that high dose of short acting agents will compete against buprenorphine for the MOR. This may be supported by science in that analgesia in drugs such as fentanyl are concentration-dependent. Again we note that buprenorphine is very lipophilic with a terminal half-life of 26-42 hours and dissociation half-life from the MOR of 166 minutes; thus even if we gave high doses of short acting opioids, it would be very difficult to compete with buprenorphine. We suggest that in order for a pure opioid agonist to compete with buprenorphine, it would be logical to prescribe a drug with similar lipophilicity that is equally or more potent. If we consider for example that doses of parenteral buprenorphine and fentanyl are almost identical (0.3 mg and 0.25 mg respectively), perhaps fentanyl offers a viable option – still we have no proof that fentanyl can or will substantially compete with buprenorphine without scientific evidence in the clinical setting. But, several authors have suggested this as an option and report positive analgesic outcomes with fentanyl and other opioids.

Once the post-op pain has been stabilized, the patient may be discontinued from short-acting opioids and resume the buprenorphine. It is crucial that the post-op pain is stabilized before we discontinue the short-acting opioid and adjuvant therapies.

If buprenorphine is discontinued, then extra cautionary steps are recommended. Once the patient has been given the high doses of short acting opioids, the patient needs counseling that continued high dose short-acting opioid therapy is not required 2-3 days postoperatively as the buprenorphine begins to dissociate from the MOR. Failure to recognize this concept can lead to potential opioid overdose and could prove fatal. Therefore, it is recommended that for the first 24-72 hours especially, the patient should be monitored vigilantly and appropriate adjustments be made with opioid therapy if buprenorphine is discontinued. Once appropriate adjustments have been made and the patient’s post-op pain is stabilized by opioid and adjuvant therapies, buprenorphine may be re-initiated by escalating to the patient’s original admission dose. A summary of the recommendations is represented in figure 3. In addition, a table presenting the benefits and risks associated with the recommendations made by published articles is outlined in table 2.

Is methadone an option to replace buprenorphine?

One of the greatest risks of discontinuing buprenorphine is the risk of relapse for patients that are on buprenorphine therapy for their opioid dependency. Now you may be saying to yourself “methadone is a full μ-agonist and approved for opioid dependency, why not just switch the patient from buprenorphine to methadone and call it a day?” Methadone is of course a full μ-opioid agonist and is FDA approved for treatment of opioid addiction and also for pain, and there are published articles that recommend switching patients from buprenorphine to methadone periopetatively. However, most of these articles directly or indirectly reference back to a single article in support of this decision, and that article was published in 1975, long before buprenorphine gained popularity for the treatment of opioid abuse. Although there are recommendations to switch buprenorphine therapy to methadone, we advise otherwise. Converting the patient from buprenorphine to methadone is a poor choice for short-term pain management because of methadone’s complex pharmacokinetics requires weeks to safely titrate to an effective dose and even longer to discontinue safely. Methadone’s half-life is variable (15-60 hours), significantly longer than buprenorphine, it’s extensively tissue bound and released slowly back into plasma, has potential cardiac toxicity leading to dangerous arrhythmias, and numerous drug interactions some of which are only now being characterized. Dose conversions to methadone are not standardized and failing to perform accurate conversions can lead to drug overdose deaths of which methadone (30%) is consistently responsible for more than any other opioid even though accounting for such a small percentage of overall opioid prescriptions (2%). Moreover, if methadone was favored perioperatively, based on then pharmacokinetics, it would begin to accumulate in the body tissue due to
its high volume of distribution. At the same time as methadone begun sequestering within the tissues, buprenorphine would be blocking lethargy and respiratory depression. Buprenorphine is now stopped, it dissociates from the receptors after days, but now you’re left with a potential methadone overdose as the receptors become occupied by methadone.

**Buprenorphine during gestation**

Opioid prescription use among pregnant women has been exponentially increasing. In the nine years from 2000 to 2009, live births increased from 1.2 per thousand to 5.6 per thousand. Similarly, the incidence of Neonatal Abstinence Syndrome (NAS) also increased from 1.2 to 3.4 per thousand hospital live births.\(^2\) Methadone was the recommended treatment of choice in opioid dependent pregnant women for decades prior to approval of buprenorphine. Until 2004, methadone was the only generally accepted medication initiated during pregnancy for treatment of opioid dependence. In 2008, the amount of patients treated with either methadone or buprenorphine in this patient population stabilized.\(^3\) Women maintained on buprenorphine sublingual (SL) (Mean dose at delivery = 15.4 mg/day) as opposed to methadone oral (Mean dose at delivery = 87.4 mg/day) were more likely to initiate opioid agonist treatment before pregnancy or begin treatment earlier in pregnancy.\(^4\) Meyer et al. developed a retrospective cohort study comparison of 609 pregnant opioid dependent women treated with methadone (\(n=248\)) or buprenorphine (\(n=361\)). They demonstrated that women treated with buprenorphine as opposed to methadone displayed superior positive outcomes in neonates delivered including likelihood of delivering at term (\(P<0.001\)), extended period of gestation (\(P<0.001\)), delivering neonates that are larger in size (\(P<0.001\)) with a larger head circumference (\(P<0.001\)), delivering neonates who do not require treatment for NAS (\(P<0.001\)) and requiring NAS treatment for a shorter duration (\(P<0.001\)).\(^5\) Accordingly, there is sufficient data to support that prescription use of methadone and buprenorphine is not considered “off-label” during pregnancy. American College of Obstetrics and Gynecology specifies that the current standard of care for pregnant women with opioid dependence should be referred for an opioid-assisted therapy employing methadone or buprenorphine, which is also supported by current and emerging evidence.\(^6\) Both methadone and buprenorphine are compatible with breast feeding, as there are low levels present in breast milk.\(^7\)

**Delivery**

Labor analgesia is usually administered per the patient’s request while the type (spinal, epidural, combination) and timing of the analgesia is determined by the anesthesiologist.\(^8\) Meyer et al. demonstrated little difference regarding intrapartum pain perception between groups (No difference seen [buprenorphine treated mothers versus control]) for pain scores at cervical dilation, rate of delivery without analgesia, proportion of women choosing neuroaxial analgesia, efficacy of regional analgesia, time from admission to delivery, pain score to or following neuroaxial analgesia placement and initial PCA settings. At the time of delivery, patient’s average SL buprenorphine dose was 13.7 mg +/- 6.2 per day. Morphine was used for parenteral analgesia in buprenorphine maintained patients for pain management, whereas the control group received nalbuphine or morphine. Of Note; all buprenorphine was administered to patients by the SL route. Any patient that received epidural analgesia also received PCA.

Pain management varies for women who deliver vaginally versus by cesarean section. In Hoffich et al.\(^9\) for vaginal delivery, patients were given bupivacaine bolus, bupivacaine infusion and additional fentanyl in the epidural space (at anesthesiologist’s discretion). Also, IV nalbuphine was usually given for pain control at 5-10 mg per dose, and/ or infusion of NSAIDs or acetaminophen. Buprenorphine maintained patients required peridural anesthesia more often than the comparison group (\(P=0.048\)). At delivery, patients were on a daily average methadone dose of 56.25 +/- 33.35 mg (20-100 mg) and 71.54 +/- 37.15 mg (20-130 mg) or a daily average SL buprenorphine dose of 12.77 +/- 5.32 mg (6-22 mg) and 15.33 +/- 7.86 mg (8-28 mg) for vaginal and cesarean section deliveries respectively. In Hoffich et al., spinal
Anesthesia was performed for women delivering by cesarean section. Bupivacaine with or without supplemental fentanyl was given. There was no difference in medication use seen with spinal anesthesia. Additional IV analgesics given for pain management included NSAIDs (diclofenac, metamizol), benzodiazepines (diazepam) and/or opioid analgesics (tramadol, piritramid). Meyer et al. demonstrated, intrathecal opioid use of morphine or meperidine administered for buprenorphine maintained women significantly more than the control group. In Hoflich et al., spinal anesthesia was performed for women delivering by cesarean section (bupivacaine with or without supplemental fentanyl). The buprenorphine cohort requested more frequent administration of opioids which we should expect, since here again we note that pure opioids do not displace buprenorphine from the mu receptor unless extremely high doses by continuous infusion are administered. Tramadol has no place in therapy for this patient population during delivery or post-partum because it’s binding affinity to the mu receptors is 6000x less than that of morphine with the only possible benefit coming from norepinephrine reuptake blockade, as serotonin offers no analgesic benefit. Likewise, neither meperidine nor morphine will displace buprenorphine.

The authors of this chapter are in agreement with non-opioid adjuvants such as the NSAIDs, acetaminophen, bupivacaine, and other non-opioids, and particularly with use of neuroaxial analgesia. From a pharmacological standpoint it makes little sense to use pure opioids parenterally or by PCA because of the reasons listed above and earlier in this chapter. A more practical approach would be to employ IV buprenorphine available as 0.3mg/mL in standard dosage regimens rather than having to deal with excessively large doses of pure opioids parenterally that potentially are exposing the neonate to increased unnecessary harm. Unfortunately there are no studies to support this presumably safer alternative.

**Post-partum:**
During the first 2 days post-partum period for vaginal delivery, there was no difference seen for pain management between groups. Meyer et al. demonstrated that post-vaginal delivery pain scores were elevated in women who were maintained on buprenorphine without any differences in the amount or frequency of opioid use. This is concerning because although there was a significantly elevated pain score for these patients, they were not treated optimally according their pain level. Pure opioids theoretically would afford no analgesic benefit, as they will not displace buprenorphine from the mu receptor at usual doses. The frequency of pain score assessment was similar in both groups following vaginal delivery. During the post-partum period, Hoflich et al analyzed patients with respect to the first 3 days post-partum and the administration of opioid and non-opioid analgesics. The most commonly used analgesics administered during this period were NSAIDs and acetaminophen, both by the oral and IV routes.

In Meyer et al., buprenorphine was maintained postpartum. The use of pain medication following vaginal delivery was on an “as-needed” basis with use of acetaminophen, ibuprofen, and oxycodone. Following a cesarean section delivery, pain medications were ordered for continuous dosing (for the first 48 hours) and as needed (>48 hours). Medication use included acetaminophen, oxycodone/acetaminophen, ibuprofen and morphine sulfate (breakthrough pain). Again, commensurate with the mu binding affinities, opioid dosing/potency given in excess of the standardized order were required significantly more frequently by women maintained on buprenorphine compared to controls (P=0.02), with most changes seen within the first 24 hours post-cesarean section. Meyer et al. demonstrated that buprenorphine could safely be maintained throughout the labor and delivery period. Again, we point out neither morphine nor oxycodone will overcome buprenorphine at the receptors, therefore, “as needed” use seems like a futile option.

Following cesarean section, women maintained on opioids for day 0, 1 and 2, post-partum received significantly less opioid analgesic (day 0 (P=0.038), day 1 (P=0.02), day 2 (P=0.031), day 3 P=0.142). During the first 2 days post-partum, there were no differences seen with pain management therapy, but on postpartum day 3, a greater number of opioid dependent patients received NSAIDs (P=0.029).
statistically significant frequency of IV analgesic given between groups were as follows; diclofenac (P=0.006), metamizol (P=0.012). In contrast, women maintained on SL buprenorphine post-cesarean section in Meyer et al., had higher post-op pain scores and exhibited a 47% increase in opioid use even after the immediate post-op period. In both groups, opioid utilization decreased 24 to 48 hours post-op but the number of pain assessments were significant greater for buprenorphine controlled patients as opposed to the control group.

Neonate
Kraft et al. 2008\textsuperscript{36} was a pilot study that reviewed the use of SL buprenorphine for the treatment of Neonatal Abstinence syndrome (NAS). According to the authors, SL buprenorphine had never been given in a child less than 4 years old. All mothers were maintained on methadone during pregnancy and neonates were treated for NAS with buprenorphine versus standard treatment (Neonatal opium solution [NOS]). Neonates treated with buprenorphine as opposed to NOS had a 31% reduction in length of treatment, 22 versus 32 days (P=0.077), and 29% reduction in length of stay, 27 versus 38 days (P=0.068). Kraft et. al 2010,\textsuperscript{37} was a randomized clinical trial that reviewed the use of SL buprenorphine versus standard treatment (morphine) in neonates born to methadone maintained mothers during pregnancy. Opioid dependent mothers were on a daily maternal methadone dose of 124 mg (SD=60) and 157 mg (SD=57) respectively when compared to NAS treatment of their newborn with either morphine or buprenorphine. The neonate’s length of treatment was significantly reduced for infants on buprenorphine, 23 days versus morphine 38 days (P=0.001). Additionally, length of hospital stay was significantly reduced for buprenorphine versus morphine maintained infants 32 and 42 days (P=0.05) respectively.

There are several beneficial factors to buprenorphine use in neonates which could favor its use, including a more predictable and longer analgesic half-life (decreased rapid change in receptor occupancy), limited abuse liability (beneficial shorter hospital stay in regards to accessibility for outpatient use,) decreased toxicity, ceiling effect of respiratory depression,\textsuperscript{38} and decreased dosing interval (for nursing convenience). Norbuprenorhine was not present in two-thirds of samples, which did suggest impaired N-dealkylation in neonates receiving buprenorphine treatment, which could demonstrate less toxicity then the use of morphine or methadone to treat NAS. Although IV administration would be theoretically ideal, allowing more pain to the newborn who is already withdrawing from opioids and introducing another means for infection by IV access in a NICU setting realistically raises an ethical dilemma without supportive evidence. It is also necessary that buprenorphine be converted from IV (very predictable pharmacokinetics) to SL (erratic pharmacokinetics) before discharge home, at which time the caregivers would be faced with the difficulties of buccal or SL buprenorphine administration while attempting to minimize swallowing. Considering that SL pharmacokinetics are less precise than IV administration, we suggest that IV or perhaps continuous subcutaneous buprenorphine\textsuperscript{39,40} could be far more preferable approach in the neonate – unfortunately there are no studies or data to support this approach.

Summary
In closing this chapter, we wish to make clear again that there is no evidence to recommend that buprenorphine always be stopped or always be continued in any patient. But, we hoped to clarify what considerations are important in making these decisions for each patient. The answers to our original questions are as follows:

1. For scheduled elective surgery should the patient continue buprenorphine or stop it in advance of the surgery? This depends on our ability to adequately manage pain and/or substance abuse in the days leading up to surgery.
2. If it is stopped, what are the risks regarding rebound substance abuse? The risks are potentially very real, and this is at least one reason why it is important to employ an interdisciplinary team in advance of elective surgery.

3. If it is not stopped, what are the post-operative dilemmas for treating acute pain with pure opioid agonists? The largest risk here is presumably that reintroduction of pure opioids could trigger craving of pure opioid agonists upon discharge and relapse of substance abuse.

4. If the patient stops buprenorphine prior to surgery, how far in advance should it be discontinued? Based on the half-life, at least a week, but two weeks gives us some flexibility and time to adjust therapy.

5. If the patient presents for acute surgery, do I continue the buprenorphine or stop it in anticipation of required opioid therapy? Either is possible. If you continue buprenorphine, very high doses of pure opioid agonists will be needed and fentanyl may be the best option. If buprenorphine is discontinued, high doses of pure opioid agonists will still be needed for at least up to three days (perhaps longer if a Butrans® patch was used because of residual drug in the transdermal tissue) after discontinuation. After such time that buprenorphine dissociates from the receptor, keen monitoring is necessary to adjust the pure opioid agonist doses downward as the buprenorphine stops blocking the pure opioid agonist activity.

6. In the neonate, there is sufficient evidence to support that buprenorphine is a superior option to methadone in terms of efficacy, safety, toxicity, and overall outcomes. Although treatment of acute pain in the buprenorphine patient remains controversial, satisfactory analgesic outcomes are not insurmountable if the clinician has a keen understanding of the pharmacology and pharmacokinetics.

References

Addiction. [Rockville, MD]: U.S. Dept. of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, 2005.


Figure 1

*Conceptual representation only, not to be used for dosing purposes.

Figure 2
The University of Michigan Protocol for the Management of Sublingual Buprenorphine (Suboxone and Subutex) in the Acute Perioperative Setting for Emergent Surgery

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Emergency surgery protocol for patients on buprenorphine therapy

Table 1: Benefits vs Risks

- **Buprenorphine patient requiring emergency surgery**
  - **Assess post-op pain**
    - **Mild**
      - Continue buprenorphine + maximize adjuvant therapy
    - **moderate/severe**
      - Decide to continue or D/C buprenorphine
        - Provide high doses of short acting opiates + maximize adjuvants
          - Monitor vigilantly to decrease dose of short acting opiates as buprenorphine dissociates
          - Once post-op pain stabilized assess patient for re-initiation of buprenorphine
        - Provide high doses of short acting opiates + maximize adjuvants
          - Once post-op pain stabilized short acting opiates may be stopped
          - Consider increasing buprenorphine dose to compensate for post-op pain and assess weekly

Especially for 2-3 days after buprenorphine is stopped!
Pros

Time! We, as clinicians have the ability to adjust when the patient can have surgery. This is probably the major benefit!

Logical and simple plan if buprenorphine is being tapered.

Pain management protocol is simpler when buprenorphine is cleared from the patient’s system.

Once buprenorphine is cleared, patient can be considered as opioid naive and receive normal or slightly higher opioid regimen.

Cons

Long $T_{1/2}$ = variability. Very difficult to taper patients since not everyone clears the drug in the same manner. Re-initiation can also be difficult because of the variable half-life.

Tapering of “opioid dependence medication” can create an ethical dilemma for physicians restarting a pure opioid agonist in a vulnerable patient.

Risk of relapse if the patient is receiving opioids post-op.

<table>
<thead>
<tr>
<th>Table 2: Benefits vs Risks</th>
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<tbody>
<tr>
<td><strong>Buprenorphine Continued</strong></td>
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<tr>
<td><strong>Pros</strong></td>
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<tr>
<td>Continued opioid dependence therapy.</td>
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<tr>
<td>No need for re-initiation post-op</td>
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<tr>
<td>Less risk of relapse</td>
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<tr>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>Difficult to achieve full analgesia</td>
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<tr>
<td>Cost to the patient regarding extensive adjuvant therapy and continued use of high dose opioid therapy.</td>
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