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Buprenorphine And The Anesthesia Considerations: A Literature Review

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Abstract

Buprenorphine is a unique pharmaceutical in the management of chronic pain and opioid use disorder (OUD). Buprenorphine is a semisynthetic partial opioid agonist at the mu opioid receptor and an antagonist of the kappa opioid. Buprenorphine Maintenance Therapy (BMT) is utilized for the long-term treatment of patients with OUD. The attraction to this methadone alternative is increased safety profile, more convenient patient access to the drug, as well as increase of ease for the provider. The particular formula used in the US, Suboxone, has properties to discourage intravenous injection to prevent abuse and prevent negative secondary effects of intravascular injections in general. Buprenorphine, a partial agonist, has an affinity higher than that of a full agonist at the mu receptor. It has lower efficacy, slow offset, as well as a ceiling effect, making surgical analgesia difficult to control for those on a maintenance therapy. In the clinical setting, many opinions and theories have been discussed in the approach to managing perioperative pain for a patient on BMT. Use of buprenorphine is increasing, "nevertheless, there is limited and conflicting information in the literature pertaining to the optimal management of buprenorphine-stabilized patients presenting for surgery". (Huang, Katznelson, Perrot, & Clark, 2014). In a search through the literature, there has been varying protocols and theories presented intertwined with case studies. The goal of this paper is to review buprenorphine and to discuss the current literature on the perioperative management for patients on a maintenance plan.

Buprenorphine and the Anesthesia Considerations: a Literature Review

Reckitt and Colman Pharmaceuticals synthesized buprenorphine in the late 1960s as a semisynthetic opiate for the treatment of chronic pain, in particular, cancer pain. In the late 1970s, it was proposed at a treatment for opiate dependence or abuse. It was the Drug Addiction Treatment Act of 2000 (DATA 2000) that allowed a breakthrough of prescriptive authority for buprenorphine. DATA 2000 gave physicians legality in prescribing opioids for the treatment of opioid addiction. In 2002, the FDA approved a particular formulation of buprenorphine, Suboxone, for the treatment of opioid-dependent persons. Nationally there are over 16,700 providers registered to prescribe Suboxone. In Maine, there are 120 registered providers with new physicians being added weekly. According to DATA 2000, each registered physician prescribing Suboxone is limited to 30 patients in the first year of prescribing, up to 100 patients thereafter. (SAMHSA, 2015). Buprenorphine in the formulation of Suboxone is in increasing demand nationally. Its presence in the patient population is presenting the need for evidence based practice in the perioperative setting.

The pharmaceutical properties of buprenorphine create a unique challenge for the anesthesia provider in the management of pain. Many of the articles and case studies state the lack of consensus on surgical pain management in patients on BMT, thus presenting a topic with need for further exploration. "To date, there have been no randomized controlled studies published involving the effects of different pain control modalities applied to patients maintained on buprenorphine... evidence supporting recommendations is currently based on a number of case reports and the shared experience of clinicians". (Bryson, 2014). The next few paragraphs will discuss the properties, the pharmacokinetics and mechanism of action of buprenorphine;

following will be the presentation of case studies, review of current literature and discussion points.

Buprenorphine is a partial agonist of the mu receptor and potent kappa receptor antagonist. Mu receptor stimulation produces supraspinal analgesia, euphoria, respiratory depression, bradycardia, and dependence. Kappa stimulation produces spinal analgesia, sedation, miosis, and dysphoria; these latter effects are antagonized with buprenorphine. (Nagelhout, 2010). "In some patients, kappa agonists produce dysphoria. Buprenorphine's absence of kappa agonist effects may explain why dysphoria and other unpleasant mood effects are rarely produced in buprenorphine users." (Wesson & Smith, 2010). Typically synthetic opioids are designed to be highly selective for specific receptors. Most clinically used opioids are selective for the mu receptor alone.

The receptor theory, as discussed in Barash (2009), states that drugs have two independent characteristics at receptor sites, affinity and efficacy. Affinity is the ability to bind to a receptor to produce a stable complex. Efficacy is a dose effect curve resulting from the drug-receptor combination. A partial agonist has a dose-effect ceiling that is lower than that of a full agonist. Barash (2009) goes on to state, "even at a very large doses the efficacy, or maximum effect achieved by the partial agonist will be less than the maximum possible effect of a full agonist". Buprenorphine is described as "having a high affinity for the mu receptor, 1000-fold higher than morphine, with an extremely slow dissociation from the receptor". (Bryson, Lipson, & Gevirtz, 2010). Although it binds tightly, it only partially activates the receptor, reducing the efficacy. This satisfies the classification of a partial agonist. Its affinity for the mu receptor is greater than that of naloxone as well as other mu agonists and it will displace a full agonist from the mu receptor. As a result of being a partial agonist with high mu receptor affinity, slow dissociation,

and long duration of action, buprenorphine is an effective agent for treatment of OUD and addiction. (Vadivelu, Mitra, Kaye, & Urman, 2014). Buprenorphine has an increased safety profile because of the partial agonism compared to methadone, a full agonist. Less respiratory depression is noted as well as a decrease in the euphoric high associated with a full agonist. This is attributed to the ceiling effect of respiratory depression and euphoria.

As mentioned earlier, in 2002, a particular formulation of buprenorphine was released into the market, Suboxone. Suboxone is a 4:1 blend of buprenorphine and naloxone, released as a sublingual formula. The amount of naloxone in the combination drug is considered not bioavailable if the medication is taken as prescribed, sublingually. The naloxone only becomes active if the medication is snorted or injected intravascular. If abused, the naloxone will precipitate withdrawal symptoms. If Suboxone is dissolved and injected by someone who is physically dependent on a full opiate agonist, the naloxone will displace the full agonist, (not the partial agonist) precipitating withdrawal. This addition of naloxone essentially decreases the abuse potential of Suboxone, making it not ideal for abuse by those that are dependent on a full agonist. The naloxone is only present as a deterrent for abuse, not to reduce the mu receptor activation as some providers mistakenly believe. (Wesson & Smith, 2010). The patient population enrolled in BMT for OUD in the US is primarily taking the Suboxone formula.

The following is a brief overview of the pharmacokinetics and dosing. Buprenorphine as supplied in the treatment for OUD is a sublingual formula with a bioavailability of 30%-50%, the PO formula has a decreased bioavailability of 3-14% due to is extensive first pass elimination. It is metabolized in the liver by cytochrome P450 3A4 enzymes leaving norbuprenorphine as one of its metabolites. Norbuprenorphine as considered to have some opioid activity but its potency

and significance is unclear (Roberts & Meyer-Witting, 2010). Metabolites are excreted primarily in the bile and eliminated in the feces.

Buprenorphine is both lipophilic and highly protein bound. It is distributed to adipose tissue and slowly redistributed to plasma, extending the half-life. The half-life is route and dose dependent. Higher doses are utilized in BMT whereas significantly lower doses are used for chronic pain. In general, high dose buprenorphine has a half-life of 20-70 hours, low dose therapy has an approximate half-life of 2-6 hours. (Roberts & Meyer-Witting, 2005). According to the published work of Wesson and Smith (2010), the plasma half life of sublingual buprenorphine in opioid naïve healthy males was approximately 26 hours. In their analysis, considerable individual differences were apparent with computed half-lives ranging from 6-96 hours. The time from ingestion to maximum plasma level ranged from 0.5 to three hours. The literature clearly indicates a large range in the half-life of buprenorphine.

As alluded to earlier, there is a variety in dosing related to therapeutic goals. A low dose analgesic regimen for those with chronic pain or cancer pain would typically be a range of 2-4mg/24hr divided in to doses to be administered every 6 hours. A much higher dosing regimen is utilized in BMT with a reported 24-hour maximum of 32mg. "Beyond 32mg/24hr, a ceiling effect in terms of analgesia occurs due to the partial agonist effect of buprenorphine at the opioid receptor." (Huang et al, 2014). Obviously dosing is tailored to patient specific needs.

Buprenorphine is appearing more often in patient's medical regimens and due to its pharmaceutical properties it can be difficult to manage these patients in the perioperative setting. "The same properties that make buprenorphine advantageous for management of addiction and chronic pain present a challenge to anesthesiologists." (Chern, Isserman, Chen, Ashburn, and & Liu, 2012) A search through the literature was completed via Medline, Lexicomp, Cochrane

database, UpToDate, and Google Scholar. What was found was a series of case studies and publish recommendations as well as institution based protocols. What was not found was systematic reviews nor controlled studies in the search for anesthesia management for patients taking chronic buprenorphine. The articles found continue to reiterate the need for further controlled studies. The next few pages will present current case studies as well as proposed protocols.

Literature Review

In 2010 Harrington & Zaydfudim presented a case study involving a young male stabilized on BMT who sustained multisystem trauma in a motorcycle accident. His acute pain was difficult to manage due to his BMT. The patient presented on some form of buprenorphine. Trauma evaluation revealed: right frontal lobe brain contusion, grade IV liver laceration, grade III spleen laceration, right renal hematoma, right rib fractures of 5,6,7, and a right olecranon fracture. During the initial hospitalization the patient was agitated and required high doses of narcotics. Agitation became managed with haloperidol and lorazepam; pain was treated with high dose full agonist opiates. By post injury day 3 (PID 3), the patient's analgesic needs began to decline. Additional history revealed the patient was actively on a BMT and on PID 4, his regimen was restarted with the aim of obtaining better pain management. Tapering of narcotics did not happen, and on PID 6 the patient's requirements increased to 50mg of morphine, 37 mg haloperidol, 8mg of lorazepam and 17mg of midazolam. The hospitals medical-psychiatry service evaluated the patient and determined the diagnosis of delirium was attributed to the TBI. The buprenorphine was also thought to contribute to insufficient analgesia leading to further agitation. The buprenorphine was discontinued resulting in a marked reduction in narcotic demand. The patient's mental status and related agitation improved rapidly. The patient was

discharged on daily a dose of 120mg of SR oxycodone and counseled of future re-evaluation for his BMT.

The authors note that the pain management improvement on PID 3 is consisted with the wearing off of the approximate 72-hour buprenorphine induced blockade of hydromorphone effects. In adding buprenorphine into the regimen on PID 4, pain requirements for full agonists increased, demonstrating the displacement of full agonists by the partial agonist. The follow up response by the authors is discouraging the continuation of buprenorphine during an acute pain syndrome. In reinstating the BMT, it may perpetuate the problem. "In addition, attempt to treat acute pain with incrementally greater doses of buprenorphine may precipitate frank opiate withdrawal due to kappa receptor antagonism that predominates at higher doses" (Harrington & Zaydfudim, 2010).

In 2012, the American Journal of Emergency Medicine published a case report that demonstrated buprenorphine inhibiting remifentanil. A 22-year-old male presented to the ER with a work related injury to his right forearm. He was in severe pain, ashen, diaphoretic, and writhing on the stretcher. His right wrist was deformed, no palpable pulse, and fingers were dusky. X-ray revealed a severe distal radial and ulnar fracture. The patient denied any other significant medical history. Morphine 10mg was injected SQ while IV access was obtained but resulted in no pain relief. A remifentanil infusion was initiated at 0.7mcg/kg/min with no apparent beneficial effect at 8 minutes into the infusion. The patient continued to writhe in pain and 1mg of lorazepam was administered. A bolus of remifentanil 1mcg/kg was administered with no effect. That particular order was given verbally to which the patient responded, "fentanyl won't work on me, I'm taking Suboxone". Apparently he was prescribed suboxone for chronic back pain. The remifentanil infusion was stopped and a Bier block was successfully

administered. The patient had complete anesthesia to the affected limb within 5 minutes. The patient calmed down, ashen appearance reversed and was no longer diaphoretic. The fracture was reduced and the patient was discharged with a prescription for Percocet.

The authors of this particular report conclude that patients in need of emergent pain relief taking suboxone should be given some form of non-opioid pain management. Recommendations included ketamine, propofol, nitrous oxide, and etomidate. Regional anesthesia highly recommended as well as NSAIDS, acetaminophen and tramadol. (Gilmore, Saccheti, & Cortese, 2012).

The Journal of Anesthesia and Clinical Research published a more complicated case study in 2012 involving a 37-year-old patient with a Type 1 Chiari malformation who was receiving buprenorphine, 8mg TID, for chronic pain management. This patient underwent two separate but similar gynecologic procedures 6 months apart. The patient had chronic pelvic pain and was scheduled for removal of vaginal mesh. She had developed erosion and pain from the mesh and already had prior office visits for trimming of the mesh.

At the most recent vaginal mesh trimming, at an outside hospital, the patient was instructed to continue her buprenorphine up to the day of surgery, but reported that this resulted in severe pain in the post-operative period. She requested a pre-operative consultation for perioperative pain management before her upcoming gynecologic procedure at the author's facility. She was instructed to stop her buprenorphine 5 days prior to surgery and start hydromorphone PO, 4mg Q4-6hours. Upon the morning of surgery the patient reported adequate pain control on the hydromorphone and experienced no difficulty in transitioning from the buprenorphine to the full agonist. In the pre-operative area, a fentanyl challenge was started. The patient was given 100mcg of fentanyl IV and was given additional boluses of 50mcg of fentanyl every 1-2 minutes,

up to 400mcg. The patient remained alert and conversational and was then transported to the OR with the fentanyl challenge still being administered. She had received a total of 1000mcg of fentanyl before induction and was still conversational. Induction included 80mg of lidocaine IV, 200mg propofol IV, and 100mg succinylcholine IV. Tracheal intubation was performed and GA was maintained with sevoflurane, an additional 100mcg of fentanyl IV was given as well as 30mg toradol IV.

Upon emergence the patient complained of severe, unbearable right hip pain after being taken out of lithotomy. The patient was re-sedated with propofol and fentanyl and an urgent orthopedic consult was completed and a dislocated hip was ruled out. Again, 100mcg boluses of fentanyl were administered ever 1-2 minutes in the PACU, again adding up to 1000mcg of fentanyl. The anesthesia team was consulted for additional pain management in the PACU. She continued to report the pain as a 7-8/10. Hydromorphone 8.5mg IV was given and a PCA with the same opioid was set up with a basal rate of 2mg/hour and a demand dose of 0.6 mg every 10 minutes, toradol 30mg every 6 hours was also included in the regimen. After 24 hours, she was transitioned back to her pre-op dose of hydromorphone, 4mg every 3 hours, with acceptable pain control. She was able to ambulate, void and tolerate a regular diet. She was then discharged on a limited amount of hydromorphone and was instructed to follow up with her buprenorphine prescriber to transition back to buprenorphine. This study is interesting in that the authors were aiming to create a case study of comparing two similar procedures with 2 different buprenorphine regimens. The post-op extreme hip pain created an entirely different scenario with an unpredicted outcome.

In the discussion section of the case report, the authors state there is no consensus in the literature as to how to best manage acute pain in patients taking buprenorphine. They do

however present and discuss 3 options in this setting. The first option is to continue the baseline regimen and supplement with additional buprenorphine. This is considered ideal because in the patient that is avoiding re-exposure to full agonist opioids. The concern is that the ceiling effect will prevent sufficient analgesia. The second option is to continue the pre-op buprenorphine and if pain control is not sufficient after adding more buprenorphine, traditional full agonist opioids should be added to supplement. The caveat is that very large doses of opioids will be required and sedation and respiratory depression can be very concerning at those high doses, thus requiring higher levels of close monitoring. The third option is to convert the buprenorphine to a full agonist preoperatively with resuming of prior buprenorphine following the acute perioperative period. While there is no antagonist effect to overcome, large doses of opioids may be required as described in this particular case due to significant opioid tolerance. The last recommendation by this author group is the encouraged use of multimodal pain control with administration of local anesthesia, regional anesthesia, and NSAIDS. The challenge of this case was that there was no wound or incision to infiltrate and a regional technique was not considered given the theoretical risk of exacerbating the symptoms of a Type 1 Chiari malformation. (Chern, Isserman, Chen, Ashburn & Liu, 2012).

The Canadian Journal of Anesthesia published an interesting case report in 2014 involving a patient on suboxone for chronic pain. The patient was a 47-year-old female with a history of chronic pain that presented to the authors facility for a Clagett window closure procedure. She had a bronchopleural fistula following a right upper lobectomy for pulmonary aspergillosis. Her pain management was complicated by nociceptive and neuropathic pain in both her chest and right arm that had persisted for several months. Several regimens had been attempted including oxycodone up to 260mg per day, fentanyl patch (100mcg/hour), Cymbalta, cyclobenzaprine,

NSAIDS, tricyclic antidepressants, and a transcutaneous electrical nerve stimulation unit. These were all discontinued due to lack of benefit or due to side effects. The patient's pain was primarily chest wall pain at the site of the Clagett window involving a burning and aching sensation that often radiated to her right shoulder and jaw. She reported her baseline pain to be a 7/10 with frequent episodes of 10/10 pain. Her chronic pain had caused her functional status to deteriorate and she required assistance with her activities of daily life.

At the time of her closure surgery, her pain regimen included suboxone 16mg bid, gabapentin 1,200mg tid, venlafaxine 225mg daily, and nabilone 1mg bid. A thoracic epidural was placed at T6 and a general anesthetic used. Intraoperatively she received ketamine 45mg IV and hydromorphone 1.6mg IV. The procedure was 2.5 hours and she was extubated in the OR and brought to the PACU without any issues. On post op day 1 (POD 1) she continued to receive a thoracic epidural infusion of 0.2% ropivicaine at 5ml/hr and also had a hydromorphone PCA with bolus doses of 0.6-0.8mg every 5 min. In the immediate post op period, her pain was well controlled with the above therapy. She did however start to develop new right shoulder pain with radiation to her hand and numbness to her fingers. The neurology team was consulted and with their findings, it was determined the patient had a right brachial plexus stretch injury.

By POD 5, the thoracic epidural began to fail, and she began experiencing profound pain at the surgical site requiring 15-20mg/24hr of hydromorphone via her PCA. She began to experience sharp and burning pain, rating it a 7-8/10 with episodes of 10/10 again. The epidural catheter was removed on POD 7, followed by increasingly difficult to manage pain, using 30-40 mg/24hr of hydromorphone via her PCA. The authors make a note here to state that at this time, she was still continuing to receive her usual home analgesics including her Suboxone. On POD 11, in addition to her PCA doses, the patient began taking Hydromorph Contin 12mg bid; shortly

thereafter it was increased to 24mg bid with little benefit. By this time, her PCA doses of hydromorphone were increased to 50-70mg/24hr for nearly persistent 10/10 pain. The possibility of interference from her maintenance suboxone was considered at this point. The decision to reduce her Suboxone from 16mg bid to once daily was made and her Hydromorph Contin was discontinued. According to the article, immediately after the suboxone dose was reduced, her pain control markedly improved. She was reporting pain back down to a 7-8/10 from 10/10 in the first couple days post the suboxone taper. Her PCA requirements were also decreased back down to 15-25mg/24hr. Within 10 days of reducing her suboxone, the PCA was discontinued and she was transitioned to PO hydromorphone. Again, her suboxone was reduced from 16mg once daily to 8 mg once daily. The patient was finally discharged on POD 41 and her regimen consisted of Hydromorph Contin 9mg tid, baclofen 10mg tid, gabapentin 1,200mg tid, venlafaxine 225mg once daily, and nabilone 1mg bid. At the time of discharge, her pain was a 3-5/10, which as the authors emphasize, was lower than her preoperative values. She was evaluated 3 weeks post discharge and was offered to transition back to Suboxone. She declined. She was more satisfied with the current regimen and due to nausea and anorexia she experienced with the Suboxone, she refrained from getting back on it.

In discussing this particular patient's course, the authors state that the refractory nature of her pain was likely due to the saturation of opioid receptors by buprenorphine, which limited the effect of additional opioids administered. The receptor affinity of buprenorphine is sufficiently strong enough to displace the full opioid agonists, minimizing their effect. The authors conclude that overpowering buprenorphine occupied receptors is very challenging. They agree with other literature that recommends considering taking a patient off buprenorphine between 3-7 days preoperatively; meanwhile converting the patient to a full agonist for pain treatment as well as to

avoid opioid withdrawal. The pitfall being that post-operatively these patients are typically reintroduced to buprenorphine at some point and consequentially may have difficult to manage pain. Of note, this patient was on the suboxone formulation, not straight buprenorphine. As described earlier, suboxone is a 4:1 ratio with naloxone. Whereas the sublingual dose of naloxone is not considered significant enough to cause systemic effect, the authors contemplated that with her high dose of buprenorphine at 32mg/day, her naloxone dose was 8mg/day. According to literature, sublingual doses >4mg have been shown to precipitate withdrawal symptoms. This suggests that higher doses of sublingual naloxone can produce antagonist effects at the opioid receptor. This larger amount of absorbed naloxone may have contributed to the ineffectiveness of IV hydromorphone in this particular case.

Again these authors state the limited recommendations in the literature regarding perioperative management of patients on buprenorphine. This is the first case report of a thoracic-specific report involving a patient stabilized on buprenorphine. This was a complicated case in that the patient had such high and difficult to manage pain to start with, plus she sustained a brachial plexus injury, and the frequency of this type of procedure is not common. In closing statements, the authors state the need for further research and more evidence based protocols and guidelines. (Huang, Katznelson, Perrot & Clark, 2014).

In the search through the literature, a few recommendations were described in how to manage perioperative pain in patients stabilized on BMT. In an article published in Anesthesiology News, four options are described. First, maintain BMT as prescribed and add short acting opioids, titrating to effect. Be prepared that the patient will require significantly higher doses of full agonist opioids to achieve an expected effect. The second option is to divide the patients BMT dose into 3 times daily dose to take advantage of its analgesic properties. This approach is

recommended if the anticipated procedure is not likely to be too invasive or typically not very painful. Third option is to stop the BMT and administer full opioid agonists while assessing for withdrawal. The authors again stress that 5 days may be required to free up the opioid receptors from the last dose of buprenorphine. The final fourth option is to convert to methadone 30-40mg/day. This is the recommended dose to deter withdrawal symptoms. It is noted that because methadone cannot be prescribed for withdrawal apart from a methadone clinic, the dose needs to be prescribed for treating pain, not managing withdrawal. (Vaghari, Baratta, & Gandhi, 2013).

Bryson (2014) published an article discussing the perioperative management of patients on various pharmaceuticals for opioid addiction. He states again that there are no randomized controlled studies published involving the effects of pain control modalities applied to patients on BMT; current guidelines are based on case reports and shared experience of clinicians. Bryson's work involved reviewing case studies and current guidelines based on collective experience. His overall recommendation is to stop buprenorphine therapy before surgery with a gradual tapper down over a period of two weeks, with a final stop 3 days before surgery. In the event that time does not permit, the provider should have the patient hard stop 3 days prior to surgery omitting the taper. If withdrawal precipitates, convert to methadone or another full agonist opioid before surgery.

If the patient is to be maintained on buprenorphine, supplement with short acting opioids and titrate to achieve reasonable pain control understanding that effective doses will be much higher, putting the patient at risk for respiratory depression. An alternate choice is to maintain the patient on their daily dose of buprenorphine, but divide the dose and administer it every 6-8 hours to achieve the peak analgesic mechanism of the buprenorphine. This method is considered

appropriate for only mild-moderate anticipated pain. This author does emphasize that if the patient is at high risk for relapse, the plan should be to replace the BMT with methadone before surgery. Other general recommendations are to maximize regional techniques, utilize indwelling peripheral nerve catheters, NSAIDS, and low-dose ketamine infusions. (Bryson, 2014).

In 2006 Annals of Internal Medicine published an article with recommendations for treating acute pain in patients receiving BMT or methadone therapy. Their recommendations were very similar to the Bryson (2014) recommendations including that the ideal approach is to taper buprenorphine gradually. In an inpatient setting, the recommendation is to convert to methadone 30-40mg/day to abate withdrawal. Because methadone binds less tightly to the mu receptor, additional opioid analgesics will be effective as expected allowing for adequate titration as needed. When the acute pain is resolved, the full agonists should be discontinued as well as the methadone. The patient should resume their previous BMT once the early signs of mild opioid withdrawal manifest. This particular article emphasized collaboration with the primary prescriber of the buprenorphine to best manage the individual patient. (Alford, Compton, & Samset, 2006).

Wasson & Beirne (2013) published their work related to buprenorphine therapy and it's challenge in the outpatient setting for oral and maxillofacial surgery. A typical outpatient deep sedation regimen for oral and maxillofacial surgery combines benzodiazepines with opioids such as fentanyl or remifentanil. This technique achieves the synergistic effect for the ideal depth of sedation as well as analgesia. Administration of opioids to patients taking buprenorphine will not yield these benefits. Their recommendation is to anticipate opioids to not be effective and instead adjunct the benzodiazepines with propofol. A ketamine infusion maybe useful, but in this setting excessive salivation must be addressed and the prolonged recovery time is not ideal,

thus propofol is superior. Another recommendation is to utilize dexmedetomidine, the selective alpha2 agonist. Because of its long loading dose timing and prolonged recovery dose, it may not be ideal in the office setting, again suggesting the superiority of propofol.

Post-operative pain management strategies are also described in this article. Similar to other pieces mentioned above, an ideal approach is to collaborate with the buprenorphine prescriber, stop the buprenorphine and transition to a full agonist, recognizing the period to free the mu receptors may take up to 60 hours. To transition back to buprenorphine, the patient should have an opioid free period of 12-24 hours. Again, another approach is to maintain the patient on their buprenorphine daily dose, but divide it in to doses to be given every 6-8 hours to rely on the analgesic property alone. This approach is considered appropriate if the anticipated pain is mild to moderate. In patients expected to have ongoing need for pain management, replacing buprenorphine with methadone provides the flexibility of supplementing full opioid agonists on top of the methadone without fear of a ceiling effect in analgesic therapy. In the office setting of maxillofacial surgery use of local anesthetics is the normal approach, leaving an indwelling nerve catheter is not logistical. Multimodal therapy is recommended in this setting with use of preoperative and postoperative NSAIDS, acetaminophen, as well as corticosteroids. The corticosteroids have been shown to decrease pain, edema, and trismus associated with oral surgery. The authors note that the benefits of corticosteroids have not been found for all types of surgery or in all instances. (Wasson & Beirne, 2013).

In 2014, Best Practice & Research Clinical Anesthesiology published an article discussing perioperative analgesia in the OUD patient. This author group does describe the approach of discontinueing the buprenorphine 72 hours prior to surgery as well as transitioning to a full agonist preoperatively. Also, they suggest the option of staying on the maintenance

buprenorphine and supplementing additional sublingual buprenorphine post-operatively, stating that buprenorphine is intrinsically a strong analgesic. In this article buprenorphine is described as having a potency of 30 times greater than that of morphine. Yet the analgesic half-life is shorter than the half-life of the drug, thus supplementing additional doses more frequently is an adequate approach. This article does not however address the ceiling effect of 32mg/24hr and the limitations in dosing additional buprenorphine in patients maintained on high does BMT. Multimodal therapy is encouraged with low dose ketamine infusions intraperatively (60-120mcg/kg/hr), as well regional/local techniques. Anti-inflammatory medications, anti-depressants, and anti-convulsants are useful adjuncts to opioids as well. (Vadivelu, Mitra, Kaye, & Urman, 2014).

As the search through the literature continued, an actual protocol was found, as opposed to guidelines and recommendations. The Acute Pain Services (APS) at the University of Michigan created a protocol (Figure 1 &2) with the assistance of physicians specializing in Suboxone management. It is a detailed protocol with considerations for elective surgery and urgent/emergent surgery, as well as considerations for levels of anticipated pain. The protocol is prefaced by encouraging collaboration with APS as well as the patient's primary suboxone prescriber in order to tailor an individual plan. Prolonged admissions should be anticipated for pain management, as post-operative pain will likely still be difficult to manage. Pathways on the protocol included maintaining BMT if appropriate as well as withholding it for 5 days to transition to full agonists, all similar to the previous works presented but with further detail and direction as protocols typically function. Multimodal approaches are described and strongly recommended as well as continued collaboration with the buprenorphine prescriber. (University of Michigan Health Systems).

In 2014 a published pain physician, from Boston Medical Center countered the University of Michigan's protocol stating that the "5 day rule" of ceasing buprenorphine 5 days out is based on theoretical concern of pharmacological principles and has never been evaluated. His concern with the protocol is that it risks causing a disruption in the patient's recovery from opioid addiction by stopping buprenorphine during a high anxiety preoperative period. According to Alford's work, patients should take the last dose of buprenorphine on the morning of the day prior to surgery, hold buprenorphine of the day of surgery, and give an extended release opioid pre-operatively. Post-operatively, continue to hold the buprenorphine and give supplemental opioids such as fentanyl, while maintaining an extended release opioid. In approximately one week post operatively, the patient should be seen by their buprenorphine provider to be considered to restart their BMT. In his publication, Alford debates the certainty of the ceiling effect of buprenorphine stating there is no published data indicating an analgesic ceiling in humans. Alford's work, endorsed by Boston Medical Center really stands to confirm that there is not yet a consensus in the literature or among providers in the management of patients stabilized on BMT in the perioperative setting. (Alford, 2014).

Discussion

This literature review presents a variety of recommendations as well as actual case studies involving perioperative approaches and experiences to managing patients on buprenorphine whether its use is for OUD or chronic pain. Over and over again, it is discussed that there is a lack of consensus, lack of randomized controlled studies, therefore a lack of systematic reviews for this topic. The articles found are based on pharmacologic principles, case studies, and various suggestions based on clinical experiences.

It is clear that buprenorphine, in the form of Suboxone, is increasing in presence in the patient population as it's safety profile increases ease of access, ease of providers, and contains appropriate deterrent for abuse. Pharmacologically, it is a unique drug in its potent yet partial agonizing effects of the mu receptor. The half-life of buprenorphine varies in the 20-72 hour range with an affinity higher than that of any full agonist. When analyzing the properties of the drug, it is clear that managing acute pain and surgical pain in this population is difficult. What is not clear is the perfect formula for optimizing pain management in this population. That being said, the literature presented offers consistencies in recommendations, providing options for the provider to consider for each patient.

Consistencies are observed in that multi-modal approaches should be utilized. Many authors recommend ketamine, an NMDA antagonist, as an opioid alternative peri-operatively. Also consistent is the recommendation of infiltration of local anesthesia, promoting indwelling peripheral nerve catheters when possible, as well as use of non-opioid adjuncts such as NSAIDS, acetaminophen, Celebrex, Cox 2 inhibitors, and gabapentin. Consulting a facility's pain specialist and team collaboration is consistently recommended.

Overall the significant weaknesses of the article guidelines are that they are generalized and not tailored to specific surgeries, complexities of surgery, co-existing diseases, age populations, or individual addiction complexities. In an ideal setting, there is excellent communication between a surgeon, a primary care physician, and the BMT physician to establish the perfect plan. In the real world setting of a busy surgical setting, not every patient enrolled in a BMT program gets evaluated days in advance to create an optimized plan. Communication with the patient is paramount as well setting realistic pain management goals.

Ultimately, the anesthesia provider ought to remain informed in multimodal therapies, remain alert for additional literature to surface as well as continue to practice the art and science of anesthesia in creating an individualized care plan for each patient.

Figure 1

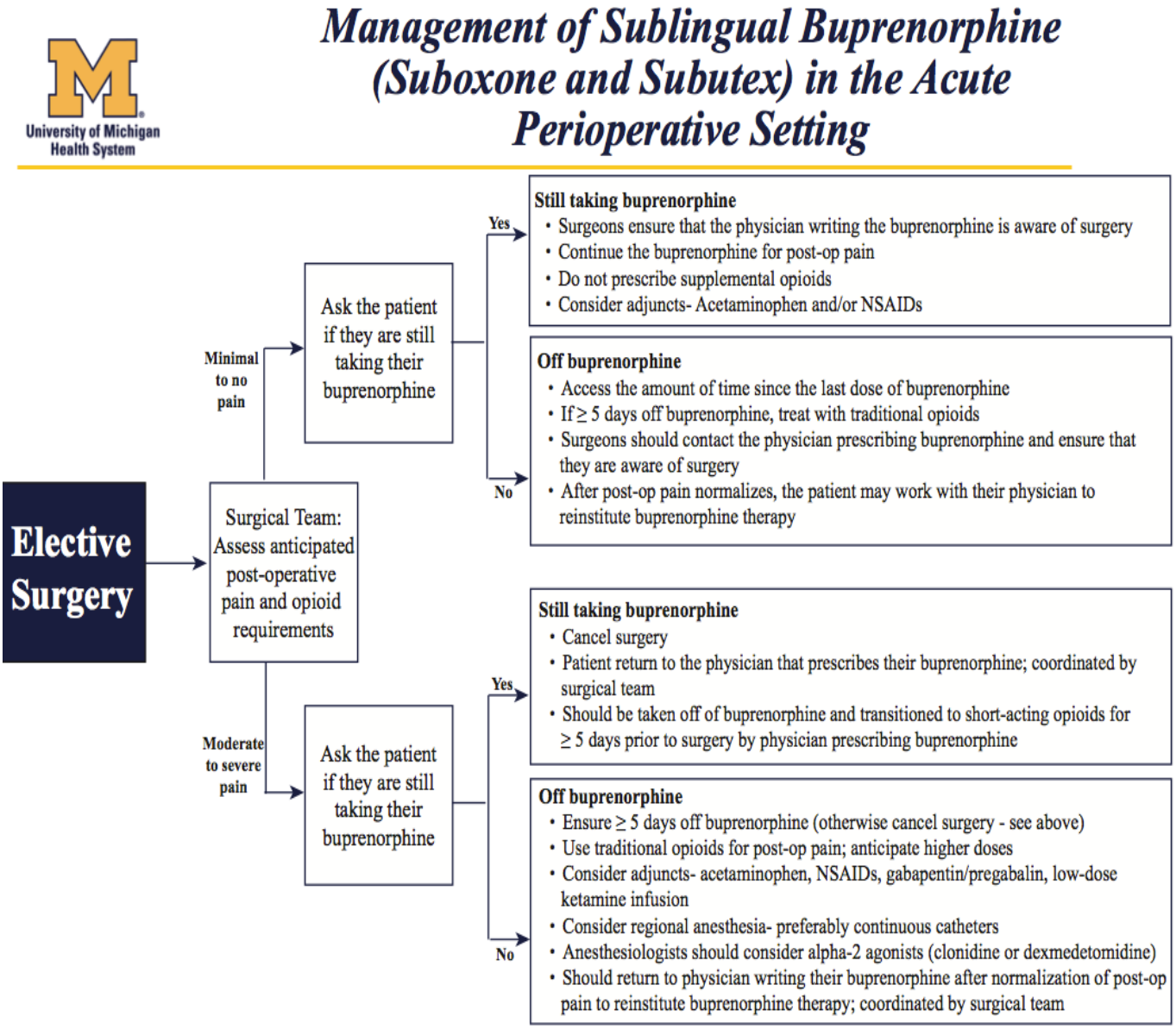
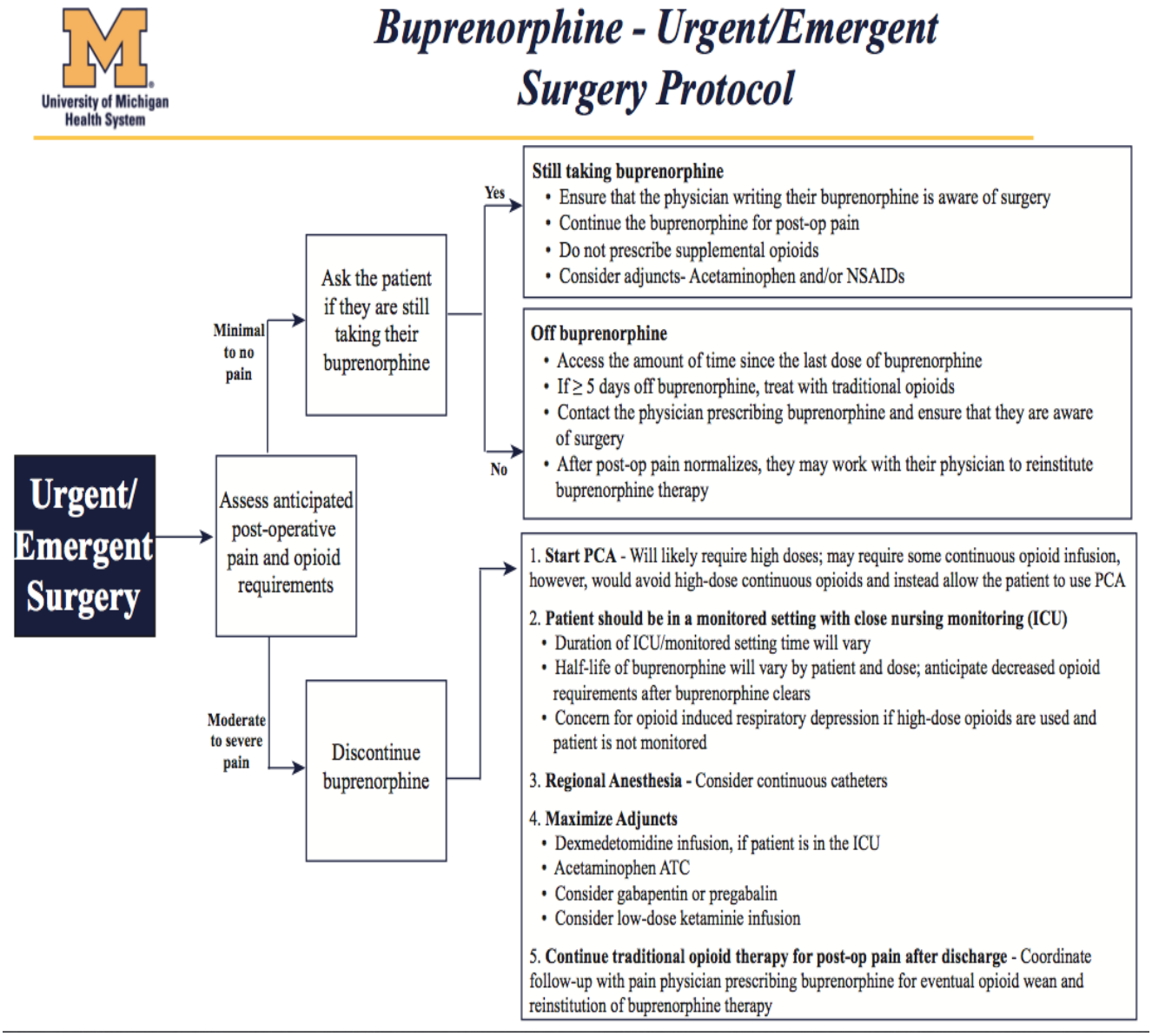

Management of Sublingual Buprenorphine (Suboxone and Subutex) in the Acute Perioperative Setting
University of Michigan Health System
Elective Surgery
Surgical Team: Assess anticipated post-operative pain and opioid requirements
Minimal to no pain
Moderate to severe pain
Ask the patient if they are still taking their buprenorphine
Ask the patient if they are still taking their buprenorphine
Yes
No
Yes
No
Still taking buprenorphine
• Surgeons ensure that the physician writing the buprenorphine is aware of surgery
• Continue the buprenorphine for post-op pain
• Do not prescribe supplemental opioids
• Consider adjuncts- Acetaminophen and/or NSAIDs
Off buprenorphine
• Access the amount of time since the last dose of buprenorphine
• If ≥ 5 days off buprenorphine, treat with traditional opioids
• Surgeons should contact the physician prescribing buprenorphine and ensure that they are aware of surgery
• After post-op pain normalizes, the patient may work with their physician to reinstitute buprenorphine therapy
Still taking buprenorphine
• Cancel surgery
• Patient return to the physician that prescribes their buprenorphine; coordinated by surgical team
• Should be taken off of buprenorphine and transitioned to short-acting opioids for ≥ 5 days prior to surgery by physician prescribing buprenorphine
Off buprenorphine
• Ensure ≥ 5 days off buprenorphine (otherwise cancel surgery - see above)
• Use traditional opioids for post-op pain; anticipate higher doses
• Consider adjuncts- acetaminophen, NSAIDs, gabapentin/pregabalin, low-dose ketamine infusion
• Consider regional anesthesia- preferably continuous catheters
• Anesthesiologists should consider alpha-2 agonists (clonidine or dexmedetomidine)
• Should return to physician writing their buprenorphine after normalization of post-op pain to reinstitute buprenorphine therapy; coordinated by surgical team

Figure 2


University of Michigan Health System
Buprenorphine - Urgent/Emergent Surgery Protocol
Urgent/ Emergent Surgery
Assess anticipated post-operative pain and opioid requirements
Minimal to no pain
Ask the patient if they are still taking their buprenorphine
Yes
Still taking buprenorphine
• Ensure that the physician writing their buprenorphine is aware of surgery
• Continue the buprenorphine for post-op pain
• Do not prescribe supplemental opioids
• Consider adjuncts- Acetaminophen and/or NSAIDs
No
Off buprenorphine
• Access the amount of time since the last dose of buprenorphine
• If ≥ 5 days off buprenorphine, treat with traditional opioids
• Contact the physician prescribing buprenorphine and ensure that they are aware of surgery
• After post-op pain normalizes, they may work with their physician to reinstitute buprenorphine therapy
Moderate to severe pain
Discontinue buprenorphine
1. Start PCA - Will likely require high doses; may require some continuous opioid infusion, however, would avoid high-dose continuous opioids and instead allow the patient to use PCA
2. Patient should be in a monitored setting with close nursing monitoring (ICU)
• Duration of ICU/monitored setting time will vary
• Half-life of buprenorphine will vary by patient and dose; anticipate decreased opioid requirements after buprenorphine clears
• Concern for opioid induced respiratory depression if high-dose opioids are used and patient is not monitored
3. Regional Anesthesia - Consider continuous catheters
4. Maximize Adjuncts
• Dexmedetomidine infusion, if patient is in the ICU
• Acetaminophen ATC
• Consider gabapentin or pregabalin
• Consider low-dose ketaminie infusion
5. Continue traditional opioid therapy for post-op pain after discharge - Coordinate follow-up with pain physician prescribing buprenorphine for eventual opioid wean and reinstitution of buprenorphine therapy

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