



## Appendix 5

### OREGON HEALTH AND SCIENCE UNIVERSITY

#### OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

##### *PRACTICE RECOMMENDATIONS FOR THE PERIOPERATIVE MANAGEMENT OF PATIENTS ON BUPRENORPHINE-CONTAINING DRUGS*

**Background:** Opioid dependence is a significant and growing problem in the United States. <sup>[1]</sup> Therefore, more patients with opioid use disorder are receiving opioid replacement therapy with methadone or buprenorphine. As a result, physicians will more frequently encounter patients receiving opioid replacement therapy who develop acutely painful conditions, requiring effective treatment strategies. <sup>[2]</sup> This presents clinicians with greater challenges than those faced when treating the opioid-naïve. Treatment aims include effective relief of acute pain, prevention of drug withdrawal, assistance with any related social, psychiatric and behavioral issues, and ensuring continuity of long-term care. <sup>[3]</sup>

**Benefits and Harms for Consideration:**

*Benefits of continuing use of Buprenorphine-containing drugs in the perioperative period:* To reassure patients with a history of opioid use disorders that their pain will be adequately managed. Additionally, patients who continue buprenorphine use have a lower risk of relapse. <sup>[2]</sup>

*Harms of stopping use of Buprenorphine-containing drugs in the perioperative period:* Unsuccessful or under treatment of acute pain in patients receiving long-term opioid replacement therapy. <sup>[2]</sup> Discontinuation of buprenorphine -- whether outside of care or under a clinician's guidance -- is highly associated with relapse, with reported relapse rates as high as 90%. More importantly, both all cause and overdose mortality is more than double among patients who have discontinued buprenorphine when compared to mortality rates of patients who remain on the medication. <sup>[4-9]</sup>

**Definitions:**

Opioid Use Disorder: A problematic pattern of opioid use leading to clinically significant impairment or distress. It often includes a strong desire to use opioids, increased tolerance to opioids, and withdrawal syndrome when opioids are abruptly discontinued.

Mild Pain: Noticeable but tolerable, does not interfere with sleep or activities (able to cough, deep breath and ambulate)

Moderate Pain: Strong, deep, distressing, interferes with sleep and activities (coughing, deep breathing, ambulation)

Severe Pain: Very intense, dominates thought, prevents sleep and movement

IV: an apparatus used to administer a fluid (as of medication, blood, or nutrients) intravenously

PCA: Patient-controlled analgesia

NOTE: Buprenorphine is a partial opioid-agonist. Morphine equivalent dose is not easily translatable for buprenorphine, so buprenorphine is not subject to morphine milligram equivalents (MME/day) dose exclusion. Approximately 30 times as potent as morphine, buprenorphine produces effective analgesia at low receptor occupancy (5 to 10%). <sup>[9-13]</sup> It is a partial agonist at the  $\mu$  receptor and an antagonist at the  $\kappa$  and  $\Delta$  receptors, with a wide safety profile including less potential for abuse and respiratory depression compared with traditional opioids. <sup>[9, 14-18]</sup>

**Guideline Eligibility Criteria:**

- Surgical patients on buprenorphine-containing drugs
- Pregnant women on buprenorphine-containing drugs

**Guideline Exclusion Criteria:**

- None



**Evidence Summary:** (see accompanying evidence brief)

Currently, no consensus nationally or high-level evidence exists on optimal acute pain management strategies for patients receiving opioid replacement therapy. [9] There is a lack of consistency in the literature with one article recommending patients continuously use buprenorphine during the perioperative period, [19] while another recommends patients start short-acting opioid or be weaned off before surgery. [9] Therefore, an evidence review was conducted to evaluate the harms and benefits

of continuing buprenorphine for patients undergoing surgical procedures. Three case reports, four case series and one retrospective cohort study were identified, and appraised using the GRADE methodology. **Although the literature is of very low quality, it does support the continuation of buprenorphine for patients requiring surgery.** Additionally, one systematic review, one case series and one historical-cohort control study found **there is very low quality evidence to support the continuation of opioid replacement therapy through labor, delivery, and the post-partum period.**

**Clinical Practice Recommendations**

**Continuing Buprenorphine Use in Perioperative Period**

Continue buprenorphine use in the perioperative period for surgical patients on buprenorphine. [20-29]

- *Strong Recommendation; Very Low Quality Evidence*

**PRACTICE IMPLICATIONS FOR OHSU:**

The surgical team will be the first one identifying patients on buprenorphine and should communicate with Perioperative Medicine Clinic and anesthesia teams to coordinate care.

**Continuing Buprenorphine Use in Pregnant Women**

Continue buprenorphine use in pregnant women on buprenorphine through labor, delivery, and post-partum period. [30-32]

- *Strong Recommendation; Very Low Quality Evidence*

**WHEN POSTOPERATIVE PAIN IS EXPECTED TO BE MILD:**

<b>Recommendations for Mild Pain:</b>	
Pre-operative:	<ul style="list-style-type: none"> <li>• Patient should be informed pre-operatively about challenges in managing postoperative pain.</li> <li>• Continue use of previously prescribed pre-operative dose of non-opioids, unless contraindicated for surgical reasons</li> <li>• To optimize multimodal analgesia, consider adding preoperative non-opioid analgesics such as acetaminophen (APAP), nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentinoids.</li> </ul>



Intra-operative:	<ul style="list-style-type: none"> <li>• If possible, use local anesthesia during surgical procedure.</li> <li>• If an opioid is needed intraoperatively, use potent opioids, e.g., hydromorphone, fentanyl, or sufentanil.</li> </ul>
Post-operative:	<ul style="list-style-type: none"> <li>• Preferred method is to increase dose of buprenorphine as an analgesia option. Divide daily dose into an every 6-8 hour regimen. May use as needed dosing in addition to regularly scheduled dose. <sup>[33-34]</sup></li> <li>• Do not routinely prescribe supplemental opioids.</li> </ul>

**WHEN POSTOPERATIVE PAIN IS EXPECTED TO BE MODERATE TO SEVERE:**

<b>Recommendations for Moderate to Severe Pain:</b>	
Pre-operative:	<ul style="list-style-type: none"> <li>• Patient should be informed pre-operatively about challenges in managing postoperative pain.</li> <li>• Continue previously prescribed preoperative dose of above non-opioids, unless contraindicated for surgical reasons.</li> <li>• When postoperative pain is expected to be moderate to severe (i.e., anticipated use of postoperative opioids), consult preoperatively with Inpatient Adult Pain Service (APS) and Inpatient Addiction Medicine Service (IMPACT) to develop individual treatment plan.</li> <li>• Consider adding non-opioid analgesics such as acetaminophen (APAP), nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentinoids.</li> </ul>
Intra-operative:	<ul style="list-style-type: none"> <li>• Regional anesthesia (peripheral nerve blocks, epidural): consider continuous infusion catheters.</li> <li>• Unless contraindicated, use ketamine infusion post-operatively.                             <ul style="list-style-type: none"> <li>– IV lidocaine use outside the OR is restricted to APS.</li> <li>– IV ketamine use outside the OR can be used by ICU providers (ICU patients only), palliative medicine team and APS.</li> </ul> </li> <li>• Consider intra-operative intravenous (IV) lidocaine infusion (<a href="https://ohsu.ellucid.com/documents/view/5307">https://ohsu.ellucid.com/documents/view/5307</a>)</li> <li>• Consider intra-operative dexmedetomidine infusion. A post-operative infusion will require ICU stay.</li> </ul>
Post-operative:	<ul style="list-style-type: none"> <li>• Unless contraindicated, use ketamine infusion post-operatively.                             <ul style="list-style-type: none"> <li>– IV lidocaine use outside the OR is restricted to APS.</li> <li>– IV ketamine use outside the OR can be used by ICU providers (ICU patients only), palliative medicine team and APS.</li> </ul> </li> <li>• Consider post-operative intravenous (IV) lidocaine infusion (<a href="https://ohsu.ellucid.com/documents/view/5307">https://ohsu.ellucid.com/documents/view/5307</a>)</li> <li>• Consider close nursing respiratory monitoring in the postoperative period.                             <ul style="list-style-type: none"> <li>– Patients are at increased risk for respiratory depression. If patient is not in the ICU for other medical reasons, keep remote monitoring pulse oximetry.</li> </ul> </li> <li>• Prescribe IV hydromorphone or fentanyl PCA postoperatively.</li> <li>• At discharge, continue inpatient pain management regimen and coordinate follow-up with outpatient buprenorphine prescribing provider for supplemental opioid wean.</li> </ul>

**BUPRENORPHINE SUPPLY:**

Plain buprenorphine	Combined with naloxone (buprenorphine/naloxone)
Preparations include: <ul style="list-style-type: none"> <li>• Buccal film</li> <li>• Sublingual tablet*</li> <li>• IV injection*</li> <li>• Extended Release: transdermal patch, intradermal implant, and subcutaneous injection</li> </ul>	Preparations include: <ul style="list-style-type: none"> <li>• Sublingual tablet* (available in 2 mg-0.5 mg; 8 mg-2 mg)</li> <li>• Sublingual film</li> <li>• Buccal film</li> </ul>

\*Available on OHSU inpatient formulary

**Quality Measures:****Process**

- Continuation of buprenorphine use in perioperative patients on buprenorphine
- Continuation of buprenorphine use in pregnant women on buprenorphine
- Utilization of preoperative non-opioid analgesics in patients on buprenorphine
- Use of potent opioids intraoperatively in patients on buprenorphine
- Supplemental opioids prescribed in patients on buprenorphine
- Referrals to outpatient buprenorphine prescribing provider

**Outcome**

- Decrease opioid misuse relapse rate of perioperative patients
- Decrease opioid misuse relapse rate of pregnant women through labor, delivery, and post-partum period

### References

1. Welsh, C., & Valadez-Meltzer, A. (2005). Buprenorphine: a (relatively) new treatment for opioid dependence. *Psychiatry (Edgmont)*, 2(12), 29-39.
2. Alford, D. P., Compton, P., & Samet, J. H. (2006). Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy. *Annals of Internal Medicine*, 144(2), 127-134.
3. Huxtable, C. A., Roberts, L. J., Somogyi, A. A., & MacIntyre, P. E. (2011). Acute pain management in opioid-tolerant patients: a growing challenge. *Anaesthesia & Intensive Care*, 39(5), 804-823.
4. Fiellin, D. A., Schottenfeld, R. S., Cutter, C. J., Moore, B. A., Barry, D. T., & O'Connor, P. G. (2014). Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Intern Med*, 174(12), 1947-1954. doi:10.1001/jamainternmed.2014.5302
5. Ling, W., Hillhouse, M., Domier, C., Doraimani, G., Hunter, J., Thomas, C., . . . Bilangi, R. (2009). Buprenorphine tapering schedule and illicit opioid use. *Addiction*, 104(2), 256-265. doi:10.1111/j.1360-0443.2008.02455.x
6. Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., . . . Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*, 357. doi:10.1136/bmj.j1550
7. Weiss, R. D., Potter, J. S., Fiellin, D. A., Byrne, M., Connery, H. S., Dickinson, W., . . . Ling, W. (2011). Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Archives of General Psychiatry*, 68(12), 1238-1246. doi:10.1001/archgenpsychiatry.2011.121
8. Briand, L. A., & Blendy, J. A. (2010). Molecular and Genetic Substrates Linking Stress and Addiction. *Brain Research*, 1314C, 219. doi:10.1016/j.brainres.2009.11.002
9. Anderson, T. A., Quaye, A. N. A., Ward, E. N., Wilens, T. E., Hilliard, P. E., & Brummett, C. M. (2017). To Stop or Not, That Is the Question: Acute Pain Management for the Patient on Chronic Buprenorphine. *Anesthesiology*, 126(6), 1180-1186. doi:10.1097/aln.0000000000001633
10. Heit, HA, Gourlay, DL . Buprenorphine: new tricks with an old molecule for pain management. *Clin J Pain* 2008; 24:93–7.
11. Johnson, RE, Fudala, PJ, Payne, R . Buprenorphine: considerations for pain management. *J Pain Symptom Manage* 2005; 29:297–326.
12. Tigerstedt, I, Tammisto, T . Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain. *Acta Anaesthesiol Scand* 1980; 24:462–8.
13. Tyers, MB . A classification of opiate receptors that mediate antinociception in animals. *Br J Pharmacol* 1980; 69:503–12.
14. Walsh, SL, June, HL, Schuh, KJ, Preston, KL, Bigelow, GE, Stitzer, ML . Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology (Berl)* 1995; 119:268–76.
15. Walsh, SL, Preston, KL, Stitzer, ML, Cone, EJ, Bigelow, GE . Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 1994; 55:569–80.
16. Cicero, TJ, Inciardi, JA, Surratt, H . Trends in the use and abuse of branded and generic extended release oxycodone and fentanyl products in the United States. *Drug Alcohol Depend* 2007; 91:115–20.
17. Cicero, TJ, Surratt, H, Inciardi, JA, Munoz, A . Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States. *Pharmacoepidemiol Drug Saf* 2007; 16:827–40.
18. Cicero, TJ, Surratt, HL, Inciardi, J . Use and misuse of buprenorphine in the management of opioid addiction. *J Opioid Manag* 2007; 3:302–8.
19. Lembke, A., Ottestad, E., & Schmiesing, C. (2018). Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Medicine*, pny019-pny019. doi:10.1093/pm/pny019

20. Book, S. W., Myrick, H., Malcolm, R., & Strain, E. C. (2007). Buprenorphine for postoperative pain following general surgery in a buprenorphine-maintained patient. *American Journal of Psychiatry*, 164(6), 979. doi:10.1176/ajp.2007.164.6.979
21. Bryson, E. O. (2014). The perioperative management of patients maintained on medications used to manage opioid addiction. *Current Opinion in Anaesthesiology*, 27(3), 359-364. doi:10.1097/aco.0000000000000052
22. Curatolo, C., & Trinh, M. (2014). Challenges in the perioperative management of the patient receiving extended-release naltrexone. *A & A Case Reports*, 3(11), 142-144. doi:10.1213/xa.0000000000000069
23. Huang, A., Katznelson, R., de Perrot, M., & Clarke, H. (2014). Perioperative management of a patient undergoing Clagett window closure stabilized on Suboxone(R) for chronic pain: a case report. *Canadian Journal of Anaesthesia*, 61(9), 826-831. doi:10.1007/s12630-014-0193-y
24. Israel, J. S., & Poore, S. O. (2013). The clinical conundrum of perioperative pain management in patients with opioid dependence: lessons from two cases. *Plastic & Reconstructive Surgery*, 131(4), 657e-658e. doi:10.1097/PRS.0b013e31828277bd
25. Khelemsky, Y., Schauer, J., & Loo, N. (2015). Effect of buprenorphine on total intravenous anesthetic requirements during spine surgery. *Pain Physician*, 18(2), E261-264.
26. Kornfeld, H., & Manfredi, L. (2010). Effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery: a case series. *American Journal of Therapeutics*, 17(5), 523-528. doi:10.1097/MJT.0b013e3181be0804
27. Macintyre, P. E., Russell, R. A., Usher, K. A., Gaughwin, M., & Huxtable, C. A. (2013). Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesthesia & Intensive Care*, 41(2), 222-230.
28. Salama-Hanna, J., & Chen, G. (2013). Patients with Chronic Pain. *Medical Clinics of North America*, 97(6), 1201-1215. doi:https://doi.org/10.1016/j.mcna.2013.07.005
29. Silva, M. J., & Rubinstein, A. (2016). Continuous Perioperative Sublingual Buprenorphine. *J Pain Palliat Care Pharmacother*, 30(4), 289-293. doi:10.1080/15360288.2016.1231734
30. Buckley, D. N., & Ibrahim, M. (2014). Brief review: Obstetric care and perioperative analgesic management of the addicted patient. *Canadian Journal of Anaesthesia*, 61(2), 154-163. doi:https://dx.doi.org/10.1007/s12630-013-0084-7
31. Jones, H. E., Johnson, R. E., & Milio, L. (2006). Post-cesarean pain management of patients maintained on methadone or buprenorphine. *American Journal on Addictions*, 15(3), 258-259. doi:https://dx.doi.org/10.1080/10550490600626721
32. Meyer, M., Paranya, G., Keefer Norris, A., & Howard, D. (2010). Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. *European Journal of Pain*, 14(9), 939-943. doi:https://dx.doi.org/10.1016/j.ejpain.2010.03.002
33. Dahan, A., Yassen, A., Romberg, R., Sarton, E., Teppema, L., Olofsen, E., & Danhof, M. (2006). Buprenorphine induces ceiling in respiratory depression but not in analgesia. *British Journal of Anaesthesia*, 96(5), 627-632. doi:10.1093/bja/ael051
34. Khanna, I. K., & Pillarsetti, S. (2015). Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res*, 8, 859-870. doi:10.2147/jpr.s85951

### **Guideline Preparation**

This guideline was prepared by the Office of Clinical Integration (CI) and Evidence-Based Practice (EBP) in collaboration with content experts at Oregon Health and Science University.

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### **Development Process**

This guideline was developed using the process outlined in the CI and EBP Manual (2016). The review summary documents the following steps:

1. Review Preparation
  - PICO questions established
  - Evidence search confirmed with content experts
2. Review of Existing Internal and External Guidelines
  - Literature Review of Relevant Evidence
3. Critically Analyze the Evidence
4. Summarize the Evidence by preparing the guideline, and order sets
  - Materials used in the development of the guidelines, review summaries and content expert team meeting minutes are maintained in a Continuing Buprenorphine or Naltrexone-Containing Drugs in Peri-Operative Patients EB review manual with the Office of CI and EBP.

### **Evaluating the Quality of the Evidence**

Published clinical guidelines were evaluated for this review using the **University of Pennsylvania's Trustworthy Guideline Rating Scale**. The summary of these guidelines are included in the evidence summary. The rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains. This scale evaluates a guideline's transparency, conflict of interest, development group, systematic review, supporting evidence, recommendations, external review and currency and updates. The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guideline does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated).

The **GRADE (Grading of Recommendations, Assessment, Development and Evaluation)** criteria were utilized to evaluate the body of evidence used to make clinical recommendations. The table below defines how the quality of the evidence is rated and how a strong versus conditional recommendation is established. The evidence summary reflects the critical points of evidence.

Recommendation	
<b>STRONG</b>	Desirable effects clearly outweigh undesirable effects or vice versa
<b>CONDITIONAL</b>	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
<b>High</b>	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
<b>Moderate</b>	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
<b>Low</b>	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
<b>Very Low</b>	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

### Recommendations

Recommendations for the guidelines were directed by the existing evidence, content experts, and consensus. Patient and family preference were included when possible. When evidence is lacking, options in care are provided in the guideline and the order sets that accompany the guideline.

### Approval Process

Guidelines are reviewed and approved by the Content Expert Team, Office of CI and EBP, Knowledge Management and Therapeutics Committee, Professional Board, and other appropriate hospital committees as deemed appropriate for the guideline's intended use. Guidelines are reviewed and updated as necessary every 2 to 3 years within the Office of CI and EBP at OHSU. Content Expert Teams will be involved with every review and update.

### Conflict of Interest

None of the content expert team members has any affiliations or financial involvement that conflicts with the material presented in this guideline.

### Disclaimer

Guideline recommendations are made from the best evidence, clinical expertise and consensus, in addition to thoughtful consideration for the patients and families cared for within the Integrated Delivery System. When evidence was lacking or inconclusive, content experts made recommendations based on consensus. Expert consensus is implied when a reference is not otherwise indicated.

The guideline is not intended to impose standards of care preventing selective variation in practice that is necessary to meet the unique needs of individual patients. The physician must consider each patient and family's circumstance to make the ultimate judgment regarding best care.