DATE: October 2017

OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary

Continuing Buprenorphine or Naltrexone-Containing Drugs in Peri-Operative Patients

Prepared for: Julio Gonzalez-Sotomayor, MD
Authors: Elizabeth Crabtree, PhD, MPH; Andrew Hamilton, MLIS, MS

BACKGROUND

More patients with opioid substance use disorders are receiving opioid replacement therapy with methadone and buprenorphine. As a result, physicians will more frequently encounter patients receiving opioid replacement therapy who develop acutely painful conditions, requiring effective treatment strategies (Alford, Compton, & Samet, 2006). This presents clinicians with greater challenges than those faced when treating the opioid-naive. Treatment aims include effective relief of acute pain, prevention of drug withdrawal, assistance with any related social, psychiatric and behavioural issues, and ensuring continuity of long-term care (Huxtable, Roberts, Somogyi, & MacIntyre, 2011).

Undertreatment of acute pain is suboptimal medical treatment, and patients receiving long-term opioid replacement therapy are at particular risk (Alford, Compton, & Samet, 2006). Pharmacological approaches incorporate the continuation of usual medications (or equivalent), short-term use of sometimes much higher than average doses of additional opioid, and prescription of non-opioid and adjuvant drugs, aiming to improve pain relief and attenuate opioid tolerance and/or opioid-induced hyperalgesia (Huxtable, Roberts, Somogyi, & MacIntyre, 2011).

Limited data exist on optimal acute pain management strategies for these patients. Therefore, suggestions are generally made based on case reports and provider opinion. Currently, no consensus or high-level evidence exists on optimal acute pain management strategies for patients receiving opioid replacement therapy (Anderson et al., 2017).

ASK THE QUESTION

Question 1: In surgical patients taking buprenorphine or naltrexone-containing drugs, is continuing use of these drugs during the peri-operative period associated with harms (i.e., unsuccessful pain control) and/or benefits (i.e., lower risk for relapse in patients with substance use disorders)?

DATE: October 2017

SEARCH FOR EVIDENCE

Databases included Ovid MEDLINE, Cochrane Database of Systematic Reviews, National Guideline Clearinghouse

Search Strategy see Appendix C

Filters/limits included articles in the English language published from 1996 – August 2017

CRITICALLY ANALYZE THE EVIDENCE

Primary Literature

Acute Pain Management for Surgical, Non-Pregnant Patients Maintained on Buprenorphine or Naltrexone-Containing Drugs

Three case reports (Book, Myrick, Malcolm, & Strain, 2007; Curatolo & Trinh, 2014; Huang, Katznelson, de Perrot, & Clarke, 2014), four case series (Israel & Poore, 2013a; Khelemsky, Schauer, & Loo, 2015; Kornfeld & Manfredi, 2010; Silva & Rubinstein, 2016), and one retrospective cohort study (Macintyre, Russell, Usher, Gaughwin, & Huxtable, 2013) were found evaluating the harms and benefits of continuing opioid agonist therapy for patients undergoing surgical procedures. The overall level of evidence is very low, due to risk of bias, imprecision and inconsistency across studies.

A case report of a buprenorphine-maintained patient using supplemental doses of sublingual buprenorphine for pain management undergoing surgical removal of breast implants noted the patient had adequate pain control, with total daily doses of up to 72/18 mg following surgery that typically may require 60 mg per day of oxycodone. Furthermore, because no other respiratory depressants were used, this high dose of buprenorphine could safely be used as an outpatient dose. The patient was able to successfully and comfortably taper her dose by postoperative day 11 to her baseline dose of 24/6 mg. The patient did not report taking other analgesics, including non-steroidals (Book et al., 2007).

A second report presented a case of a 22-year-old woman receiving XR naltrexone for a history of heroin abuse undergoing a thyroidectomy and neck dissection. The patient last received XR naltrexone approximately 3½ weeks before her scheduled procedure and was due for her next dose in a few days. Anesthesia consisting of nitrous oxide along with infusions of propofol, ketamine, and remifentanil was given. The patient's pain level score in the postanesthesia care unit was 0 of 10 on a Visual Analog Scale. Overnight, the patient experienced a 4 of 10 pain score at the surgical site and received acetaminophen 650 mg by mouth for two doses six hours apart with good relief (1 of 10 pain score). Additionally, she complained of a 6 of 10 odynophagia score for which

she received benzocaine-menthol 15-3.6 mg lozenges and thereafter reported a 1 of 10 pain score. The patient was discharged home the next day (postoperative day one) with minimal pain (2 of 10) at the surgical site. The patient did not require and did not take any pain medications after discharge. The patient has remained abstinent and continued maintenance with XR naltrexone at the time the study was written (Curatolo & Trinh, 2014).

A case series of five patients maintained on buprenorphine undergoing seven major surgical procedures was conducted to evaluate surgical outcomes and pain assessments. The patients were maintained on stable doses of sublingual buprenorphine. Postoperative pain was adequately controlled using full agonist opioids according to self-report and physician assessment (Kornfeld & Manfredi, 2010).

A second case series compared two different outcomes for the same surgical course performed at two different times on the same chronic pain patient. Pain control was easier to achieve, and functional recovery was greater when buprenorphine was maintained throughout the perioperative period when compared with using a full mu agonist opioid for chronic pain preoperatively. The authors noted these differences may be attributable to the variable of buprenorphine being present for one perioperative course and not the other (Silva & Rubinstein, 2016).

A retrospective cohort study was conducted comparing pain relief and opioid requirements in the first 24 hours after surgery in 22 patients maintained on buprenorphine and in 29 patients maintained on methadone prescribed patient-controlled analgesia. There were no significant differences in pain scores (rest and movement), incidence of nausea or vomiting requiring treatment, or sedation between the buprenorphine and methadone patient groups overall, or between those patients within each of these groups who had and had not received their methadone or buprenorphine the day after surgery. There were also no significant differences in patient-controlled analgesia requirements between buprenorphine and methadone patient groups overall, or between patients who did or did not receive methadone on the day after surgery. Buprenorphine patients who were not given their usual buprenorphine the day after surgery used significantly more patient-controlled analgesia opioid ($P=0.02$) compared with those who had received their dose (Macintyre et al., 2013).

A case series reported on a 27-year-old man who had undergone mastectomy for gynecomastia on an outpatient basis and was receiving monthly doses of intramuscular extended-release naltrexone for opioid dependence. Despite the patient's significant preoperative anxiety, his postoperative pain was well controlled with tramadol 50 mg, one to two tablets every six hours. The naltrexone was resumed two weeks later. The patient in the second case was a 37-year-old woman who had undergone bilateral mastectomies and was taking oral buprenorphine-naloxone for opioid dependence. On the advice of her psychiatrist, the patient discontinued the buprenorphine-naloxone and applied a fentanyl patch three days before surgery. On postoperative day one, her pain was inadequately

controlled with the fentanyl patch, ketorolac 15 mg every six hours, and a fentanyl patient-controlled analgesia pump. An Acute Pain Service consultation recommended discontinuing the patient-controlled analgesia, continuing the patch, and adding oxycodone 10 to 30 mg every three hours plus acetaminophen 1000 mg every 8 hours. The patient did well and was discharged on postoperative day two with acetaminophen and oxycodone (Israel & Poore, 2013b).

The final case report in this brief presents conflicting results from what was reported above. A 47-yr-old female with a history of a Clagett window procedure for pulmonary aspergillosis and subsequent chronic pain presented for a window closure procedure. Preoperatively, her pain regimen included buprenorphine-naloxone 16 mg bid, which was continued perioperatively. Postoperatively, her course was complicated by suboptimal pain at the surgical site requiring in excess of 70 mg/24 hr of intravenous hydromorphone. Liberal addition of long-acting oral opioids was ineffective in improving pain management. Eventually, concern was raised regarding opioid receptor blockade by her long-acting buprenorphine-naloxone, and the decision was made to taper her buprenorphine-naloxone. Following this, her pain control improved dramatically and her opioid requirements were markedly reduced (Huang et al., 2014).

The last case series contrasts the anesthetic requirements of a patient undergoing emergency cervical spine surgery while taking buprenorphine with anesthetic requirements of the same patient undergoing a similar procedure after weaning of buprenorphine. Use of intraoperative neurophysiological monitoring prevented use of paralytics and inhalational anesthetics during both cases, therefore total intravenous anesthesia was maintained with propofol and remifentanil infusions. During the initial surgery, intraoperative patient movement could not be controlled with very high doses of propofol and remifentanil. The patient stopped moving in response to surgical stimulation only after the addition of a ketamine. Buprenorphine-naloxone was discontinued postoperatively. Five days later the patient underwent a similar cervical spine surgery. She had drastically reduced anesthetic requirements during this case, suggesting buprenorphine's profound effect on anesthetic dosing. The authors concluded that discontinuation of buprenorphine is likely warranted for patients who present for major spine surgery, which necessitates the avoidance of volatile anesthetic and paralytic agents (Khelemsky et al., 2015).

None of the studies evaluated the outcome of relapse in patients with substance use disorders, although one case report noted that a woman maintained on naltrexone during the peri-operative period was still abstinent at the time the report was written (Curatolo & Trinh, 2014).

Conclusion: There is **very low quality evidence** to support the continuation of buprenorphine and naltrexone-containing drugs for patients requiring surgery.

Acute Pain Management in Pregnant Women on Buprenorphine or Naltrexone-Containing Drugs

Three relevant studies were found assessing the harms and benefits of continuing opioid replacement therapy in the management of acute pain in pregnant women (Buckley & Ibrahim, 2014; Huang et al., 2014; Khelemsky et al., 2015). The overall level of evidence is very low, due to risk of bias, imprecision and inconsistency across studies.

A systematic review did not find any studies meeting inclusion criteria, and noted there are few controlled trials on addiction care in obstetrical management, and controlled trials are lacking in obstetrical analgesia and addiction and in perioperative analgesia and addiction (Buckley & Ibrahim, 2014). The focus of the limited number of publications in the obstetrical population is on addiction management during pregnancy and does not address analgesic requirements. The review authors stated that protocols for management of patients receiving opioid replacement therapy for opioid addiction are well described, but that evaluations of these protocols are lacking in clinical trials, and the impact of addiction on perioperative outcomes is unknown (Buckley & Ibrahim, 2014).

A case series study examining pain management in two post-partum patients stabilized on opioid agonist medications noted that buprenorphine and methadone can be safely continued without interruption through labor, delivery, and post-partum. The two women in the study were treated daily with either buprenorphine (18 mg) or methadone (80 mg) and had adequate pain control post-partum with the use of other opioids in combination with acetaminophen and an NSAID (for methadone) (Jones, Johnson, & Milio, 2006).

An historical-cohort control study to determine whether buprenorphine maintenance alters intrapartum or postpartum pain or medication requirements was conducted (n=63), and found no differences in intrapartum pain or analgesia (Meyer, Paranya, Keefer Norris, & Howard, 2010). Following vaginal birth, buprenorphine maintained women had increased pain (buprenorphine 2.7 (1.7, 4.0); control 2.1 (1.2, 3.0), p = 0.006) but no increase in opioid utilization (buprenorphine: 11.8 ± 24.8; control 5.4 ± 10.4 mg/24 h, p = 0.10); following cesarean delivery both pain (buprenorphine: 5.1 (4.1, 6.1); control: 3.3 (2.5, 4.1), p = 0.009) and opioid utilization (buprenorphine: 89.3 ± 38.0, control: 60.9 ± 13.1 mg/24 h, p = 0.004) were increased (Meyer et al., 2010). The study noted that buprenorphine maintained women have similar intrapartum pain and analgesic needs during labor, but experience more postpartum pain and require 47% more opioid analgesic following cesarean delivery (Meyer et al., 2010).

None of the studies evaluated the outcome of relapse in patients with substance use disorders.

Conclusion: There is **very low quality evidence** to support the continuation of opioid replacement therapy through labor, delivery, and the post-partum period.

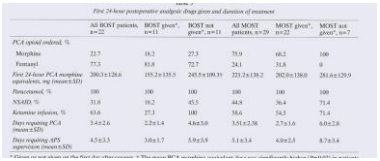
PICO Question: In surgical patients taking buprenorphine or naltrexone-containing drugs, is continuing use of these drugs during the peri-operative period associated with harms (i.e., unsuccessful pain control) and/or benefits (i.e., lower risk for relapse in patients with substance use disorders)?	Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across*
Population: surgical management unrelated to pregnancy	

Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations (Risk of Bias)*	*studies, populations, interventions, or outcomes varied)*
Total # of Studies: Click here to enter text. **# of Systematic Reviews:** Click here to enter text. **# of RCTs:** Click here to enter text. **# of Non-Randomized Studies:** Click here to enter text. **# of Diagnostic Studies:** Click here to enter text.						
Book et al, 2007, Am J Psychiatry	Present a case of postoperative pain control in a buprenorphine-maintained patient, using supplemental doses of sublingual buprenorphine for pain management	Case Report	32-year-old woman with opioid dependence who had been successfully maintained on sublingual buprenorphine/naloxone 24/6 mg daily for 6 months, up to and including the day she underwent surgical removal of breast implants under general anesthesia	The patient was seen in an outpatient addiction treatment clinic and prescribed buprenorphine/naloxone 2/0.5 mg tablets for postoperative pain control, with instructions to take one to two sublingual tablets every 4 to 6 hours for pain. On her first and second postoperative days at home, she reported taking 12/3 mg every 6 hours to relieve pain, in addition to her 24/6 mg per day baseline dose, for a total daily dose of 72/18 mg of buprenorphine/naloxone. She was able to successfully and comfortably taper her dose by postoperative day 11 to her baseline dose of 24/6 mg. The patient did not report taking other analgesics, including nonsteroidals.	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* <u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☐ Low ☒ Very Low
Curatolo & Trinh, 2014, *Anesthesia*	To discuss the intraoperative and postoperative anesthetic and analgesic planning required, as well as solutions to some of the challenges posed by patients receiving extended-release naltrexone undergoing surgery	Case report	22-year-old woman receiving XR naltrexone for a history of heroin abuse undergoing a thyroidectomy and neck dissection	Patient last received XR naltrexone approximately 3½ weeks before her scheduled procedure and was due for her next dose in a few days. General anesthesia was induced with propofol (150 mg), succinylcholine (100 mg), and remifentanil (150 mg). Further muscle relaxation was not used because neuromonitoring was performed throughout the case. The patient received 8 mg of dexamethasone before surgical incision, and anesthesia was maintained with 60% nitrous oxide along with infusions of ketamine (2 mg/kg/h), propofol (30–40 mcg/kg/min), and remifentanil (0.2–0.25 mcg/kg/min) for the duration of the surgery (approximately 4 hours). Before emergence from anesthesia, an	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

				ultrasound-guided unilateral superficial cervical plexus block using 15 mL of 0.25% bupivacaine was performed, and 1 g of acetaminophen was given intravenous (IV). The remifentanil infusion was stopped approximately 10 minutes before emergence. **After emergence from anesthesia, the trachea was extubated without incident, and her pain level score in the postanesthesia care unit was 0 of 10 on a Visual Analog Scale. Overnight, the patient experienced a 4 of 10 pain score at the surgical site and received acetaminophen 650 mg by mouth for 2 doses 6 hours apart with good relief (1 of 10 pain score). Additionally, she complained of a 6 of 10 odynophagia score for which she received benzocaine-menthol 15-3.6 mg lozenges and thereafter reported a 1 of 10 pain score. The patient was discharged home the next day (postoperative day 1) with minimal pain (2 of 10) at the surgical site. The patient did not require and did not take any pain medications after discharge**. Although the patient could have received her next dose of XR naltrexone soon after discharge, she made a personal decision to attempt abstinence without her medication. However, at the recommendation of her outpatient physicians and family, she did reinstitute XR naltrexone 3 months after her surgery and **has remained abstinent and continues maintenance with XR naltrexone at the time of this writing.**		
Huang et al, 2014, *Can J Anesth/J Can Anesth*	Present experience with a chronic pain patient on	Case report	47-yr-old female with a history of a Clagett window procedure for pulmonary aspergillosis and subsequent chronic pain	Preoperatively, her pain regimen included Suboxone 16 mg bid, which was continued perioperatively. Postoperatively, her course was	Study Limitations = ☐ None ***Non-Randomized Studies***	

	buprenorphine presenting for thoracic surgery		presenting for a window closure procedure	complicated by suboptimal pain at the surgical site requiring in excess of 70 mg/24 hr of intravenous hydromorphone. Liberal addition of long-acting oral opioids was ineffective in improving pain management. Eventually, concern was raised regarding opioid receptor blockade by her long-acting Suboxone, and the decision was made to taper her Suboxone. Following this, her pain control improved dramatically and her opioid requirements were markedly reduced. By discharge, her Suboxone was discontinued and she was managed on oral hydromorphone.	☐ Failure to develop and apply appropriate eligibility criteria ☒ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Israel & Poore, 2013, *Plastic and Reconstructive Surgery*	To highlight challenges opioid dependence presents for perioperative pain management in plastic surgery	Case series	#1: 27-year-old man who had undergone mastectomy for gynecomastia on an outpatient basis and was receiving monthly doses of intramuscular extended-release naltrexone for opioid dependence #2: 37-year-old woman who had undergone bilateral mastectomies and was taking oral buprenorphine-naloxone for opioid dependence	#1: Despite the patient's significant preoperative anxiety, his postoperative pain was well controlled with tramadol 50 mg, one to two tablets every 6 hours. The naltrexone was resumed 2 weeks later. Authors noted lessons learned from this case include the importance of patient education with thorough preoperative discussion. #2: On the advice of her psychiatrist, the patient discontinued the buprenorphine-naloxone and applied a fentanyl patch 3 days before surgery. On postoperative day 1, her pain was inadequately controlled with the fentanyl patch, ketorolac 15 mg every 6 hours, and a fentanyl patient-controlled analgesia pump. An Acute Pain Service consultation recommended discontinuing the patient-controlled analgesia, continuing the patch, and adding oxycodone 10 to 30 mg every 3 hours plus acetaminophen 1000 mg every 8 hours. The patient did well and was discharged on postoperative day 2 with acetaminophen and oxycodone. Authors noted that lessons from this case highlight the importance of a multidisciplinary approach to perioperative pain.	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☒ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Khelemsky et al, 2015, *Pain*	To contrast the anesthetic	Case series	44-year-old woman presenting for emergency anterior cervical	*Intraoperative anesthetic management of decompression and stabilization of a*	Study Limitations = ☐ None	

Physician	requirements of a patient undergoing emergency cervical spine surgery while taking buprenorphine with anesthetic requirements of the same patient undergoing a similar procedure after weaning of buprenorphine		corpectomy C6-7 and anterior cervical fusion C5-T1 for treatment of a pathologic C6-7 fracture with spinal cord compression. The patient had a past medical history of HIV, hepatitis C virus related cirrhosis, and IV drug (heroin) abuse. Her medications included Suboxone (buprenorphine 8mg/naloxone 2 mg) 3 sublingual tablets daily, lactulose, zolpidem, dexamethasone, and pantoprazole. She was chronically stable on Suboxone for the treatment of history of opioid dependence	*pathologic C6-7 fracture while on buprenorphine:* After an uneventful induction of anesthesia and intubation with propofol 150 mg, fentanyl 250 mcg, and succinylcholine 100 mg, infusions of propofol 150 mcg/ kg/min and remifentanil 0.4 mcg/kg/min were started. About one hour into the procedure, the patient began to move her legs and over-breathe the ventilator. Propofol 50 mg, midazolam 2 mg, and remifentanil 100 mcg were bloused, and the IV line checked for infiltration. Propofol infusion was increased to 200 mcg/ kg/min; however, the patient continued to move with surgical stimulation. A motionless surgical field was achieved only after the administration of ketamine 50 mg and infusion at 100 mg/hour. The patient remained intubated following the case *Intraoperative anesthetic management of C5-T1 arthrodesis with posterior instrumentation while off buprenorphine:* Five days after the initial surgery, the patient returned to the operating room for arthrodesis of C5-T1, with posterior segmental instrumentation. She was maintained on short-acting opioids prior to this procedure. After an uneventful induction of anesthesia with propofol 150 mg, fentanyl 150 mcg, and succinylcholine 100mg, and intubation, anesthetic maintenance was achieved with propofol 125 mcg/kg/min and remifentanil 0.2 mcg/kg. No ketamine was required for the procedure. The patient was extubated at the end of the case.	***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Kornfeld & Manfredi, 2010, *American Journal of Therapeutics*	To describe the surgical outcomes and pain assessments for a series of	Case series	5 patients, 7 major surgeries	Table 1 Surgical Procedure / Length of stay (days) / Pain assessment at discharge / Preoperative buprenorphine (mg) Right-side colectomy / 9 / "Pain free" / 24 Knee replacement (R) / 4 / "Excellent pain management" / 12 Knee replacement (L) / 3 / "Excellent analgesia" / 12 Small bowel resection / 5 / "Good analgesia" / 2 Bilateral mastectomy w/ reconstruction / 4 / "Pain fluctuates . . . responds to hydromorphone" / 8 Breast reconstruction X-STEP removal / 2 / "Good pain control" / 6 3 / "Excellent pain control" / 16 The patients were maintained on stable	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate	

	patients maintained on buprenorphine who underwent seven major surgical procedures			doses of sublingual buprenorphine. Postoperative pain was adequately controlled using full agonist opioids according to self-report and physician assessment	eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Macintyre et al, 2013. *Anaesth Intensive Care*	To compare pain relief and opioid requirements in the first 24 hours after surgery in buprenorphine opioid substitution therapy program participants and methadone substitution therapy program patients prescribed patient-controlled analgesia	Retrospective cohort study	22 buprenorphine opioid substitution therapy program participants and 29 methadone substitution therapy program patients prescribed PCA	There were no significant differences in pain scores (rest and movement), incidence of nausea or vomiting requiring treatment, or sedation between the BOST and MOST patient groups overall, or between those patients within each of these groups who had and had not received their methadone or buprenorphine the day after surgery. There were also no significant differences in patient-controlled analgesia requirements between BOST and MOST patient groups overall, or between patients who did or did not receive MOST on the day after surgery. BOST patients who were not given their usual buprenorphine the day after surgery used significantly more patient-controlled analgesia opioid (p=0.02) compared with those who had received their dose 	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	
Silva & Rubinstein, 2016, *J Pain and Palliative Care Pharm*	To present a case comparing two different outcomes for the same surgical course performed at two	Case series	53-year-old male carpet layer with past medical history of axial low back pain and knee osteoarthritis, treated with methadone 5 mg four times daily, using 80 MME daily A plan was made to transition	Surgical course #1: Returned for TKA 2 years later. A decision was made to have him remain on his regular buprenorphine dose up to, and including, the day of surgery, and throughout the perioperative period. He took his morning dose of 8 mg buprenorphine, and the procedure was	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria	

	different times on the same chronic pain patient		him to sublingual buprenorphine/naloxone in an effort to give him better pain control, reduce side effects of methadone, and decrease time missed from work. He transitioned successfully and was stabilized on 24 mg buprenorphine, per day, in three divided doses	performed with spinal anesthesia with bupivacaine and supplemented with a femoral block for postoperative pain control. Sedation was achieved with intravenous infusion of propofol 50 µg/kg/min, ketamine 40 mg, and 100 µg fentanyl. Postoperative analgesia consisted of hydromorphone via patient-controlled analgesia (PCA) for 48 hours plus acetaminophen 650 mg every 6 hours. His buprenorphine was continued at 8 mg three to four times daily. He reported good pain control throughout his hospitalization The patient was discharged on hospital day 3 with 50 tablets of hydrocodone 10 mg with acetaminophen 325mg and was instructed to take this in addition to his 24 mg daily dose of buprenorphine. Pharmacy records indicate that he used 50 of those tablets per week for 13 weeks. This is approximately 75 mg morphine equivalents (ME) of a full mu agonist per day, and a total morphine equivalency of 6500 mg for the entire 13-week postoperative course. During this time, he continued taking buprenorphine, had adequate analgesia, and was able to participate fully in his knee rehabilitation therapy. Approximately 16 weeks after his surgery, he was seen in our office. He had self- discontinued his hydrocodone, and his knee pain was minimal. Surgical course #2: Approximately 2 years later, the patient was scheduled for a TKA and returned to the pain center to discuss perioperative pain management. Tt was revealed that he had not tapered from the previous 80 mg hydrocodone daily, as had been planned. Transitioning back to buprenorphine was discussed, but the patient declined. He underwent a left TKA performed by the same surgeon. The patient received the same operative anesthesia protocol as in the prior surgery, with the	☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

				exception of ketamine administration. Postoperatively, the same pain treatment plan was attempted, but PCA doses were deemed by the patient and nursing to be inadequate, and multiple boluses of intravenous hydromorphone were required for rescue medication. He was transitioned to oral opioids on postoperative day 3, hydrocodone was inadequate, so he was changed to oxycodone and required upwards of 150 mg per day for analgesia. He was discharged on hospital day 4 (1 day more than with his prior surgery) with 500 tablets of oxycodone 5 mg. Pharmacy refill records showed that he used 150 mg per day of oxycodone (225 mg ME) for 16 weeks. Despite the use of an increased morphine equivalency for analgesia, his pain was still poorly controlled. The patient was unable to participate in physical therapy due to pain, and his range of motion did not progress adequately. Overall, he utilized a total of 25,200 mg ME of oxycodone for his second postoperative course. He was then slowly tapered back down to 80 mg hydrocodone and again returned to his primary care physician to manage his now chronic hydrocodone use		

References:

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:https://dx.doi.org/10.1176/ajp.2007.164.6.979

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/xaa.0000000000000069

Huang, A., Katznelson, R., de Perrot, M., & Clarke, H. (2014). Perioperative management of a patient undergoing Clagett window closure stabilized on Suboxone for chronic pain: a case report. *Canadian Journal of Anaesthesia, 61*(9), 826-831. doi:https://dx.doi.org/10.1007/s12630-014-0193-y

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:https://dx.doi.org/10.1097/PRS.0b013e31828277bd

Khelemsky, Y., Schauer, J., & Loo, N. (2015). Effect of buprenorphine on total intravenous anesthetic requirements during spine surgery. *Pain Physician, 18*(2), E261-264.

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:https://dx.doi.org/10.1097/MJT.0b013e3181be0804

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.

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

PICO Question: In surgical patients taking buprenorphine or naltrexone-containing drugs, is continuing use of these drugs during the	Lower Quality Rating

peri-operative period associated with harms (i.e., unsuccessful pain control) and/or benefits (i.e., lower risk for relapse in patients with substance use disorders)?						
Population: pain management in pregnant women						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations (Risk of Bias)*	
Total # of Studies: 3. **# of Systematic Reviews:** 1 **# of RCTs:** 0 **# of Non-Randomized Studies:** 2. **# of Diagnostic Studies:** 0.						
Buckley & Ibrahim, 2013, *Can J Anesth/JCan Anesth*	To identify papers addressing the perioperative management of analgesia in addicted patients	Systematic Review	No reports of randomized controlled trials evaluating optimal treatment of addicted patients presenting for surgery	There are few controlled trials on addiction care in obstetrical management, and controlled trials are lacking in obstetrical analgesia and addiction and in perioperative analgesia and addiction. The focus of the limited number of publications in the obstetrical population is on addiction management during pregnancy and does not address analgesic requirements. There are principle-based discussions on factors affecting analgesic management in patients receiving chronic opioid therapy and multimodal analgesic therapy. This discourse includes consideration of the physiological and affective factors that impact perioperative management. A number of empirically derived protocols available for managing alcohol withdrawal are based on response to the physical manifestations of withdrawal. Protocols for management of patients receiving opioid replacement therapy for opioid addiction are also well described. Nevertheless, evaluations of these protocols are lacking in clinical trials, and the impact of addiction on perioperative outcomes is unknown.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Jones et al, 2006, *American Journal on Addictions*	To compare post-cesarean pain management of patients stabilized on	Case series	#1: opioid-dependent, 32-year-old, multiparous black woman undergoing a cesarean section following the failed induction of labor post-date. At delivery, she had been	#1: Epidural anesthesia (mepivacine 0.5 cc=fentanyl 100 mcg; total 15 cc) was administered and adequate for surgery, and a healthy vigorous infant was delivered. Post-partum pain was controlled for 24 hours using	Study Limitations = ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria	

if:
☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*

☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible

	either buprenorphine or methadone. The management of post-operative pain in a buprenorphine maintained opioid-dependent woman who delivered by cesarean section is presented and contrasted to methadone		receiving double-blind doses of buprenorphine (Subutex 1) and placebo methadone for 111 days. Her delivery dose was 18 mg daily #2: opioid-dependent, 35-year-old, primiparous black woman undergoing a cesarean section at term for failure to progress in labor. At delivery, she had been receiving double-blind doses of methadone and placebo buprenorphine for 127 days. Her delivery dose was 80 mg daily	intravenous patient-controlled analgesia (PCA) with morphine according to hospital protocol. The protocol was morphine sulfate 1 mg=ml=min with demand dose of 1.5 mg, lockout interval of seven minutes and a 30 mg four-hour dose limit. Before PCA pump initiation, pain assessments were 7 and 10 (maximum score = 10). She took all medication provided (ie, 180 mg=day) and scored 0 out of 10 on all six post-pain assessments. At hospital discharge three days after delivery, she was prescribed oral oxycodone 5 mg plus acetaminophen 500 mg, two tablets by mouth every 4–6 hours for pain control. Over the next nine days, the patient's pain was controlled with a maximum daily dose of 60 mg oxycodone and six grams of acetaminophen, and all 27 pain assessment scores ranged between 0 and 5. #2: Epidural anesthesia and 24-hr PCA post-partum pain control protocols were the same as for the patient listed previously. She also took the maximum PCA dosage allowed for the 24-hr period. Her pain assessment scores were 10 of 10 prior to the PCA, 7 immediately after the PCA pump (prior to first lock-out) and then 0 s in the following 24 hrs. At hospital discharge three days after delivery, she was prescribed the same dose of oxycodone 5 mg plus acetaminophen 500 mg. After twelve hours, she reported that oxycodone 60 mg plus acetaminophen six grams=day was not adequate in controlling her pain (score = 7). The nonsteroidal antiinflammatory (NSAID) ibuprofen 600 mg by mouth every eight hours for five days was also prescribed. The fifteen pain scores over these five days of oxycodone=acetaminophen and NSAID were between 0–5.	☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☐ Low ☒ Very Low

Meyer et al, 2010, *European Journal of Pain*	To determine whether buprenorphine maintenance alters intrapartum or postpartum pain or medication requirements	Historical cohort-control study; 63 patients treated with buprenorphine for opioid dependence during pregnancy (vaginal n = 44; cesarean n = 19) were matched retrospectively to control women. Analgesic medication and pain scores (0–10) were extracted from the medical record	63 patients treated with buprenorphine for opioid dependence during pregnancy (vaginal n = 44; cesarean n = 19)	There were no differences in intrapartum pain or analgesia. Following vaginal birth, buprenorphine maintained women had increased pain (buprenorphine 2.7 (1.7, 4.0); control 2.1 (1.2, 3.0), p = 0.006) but no increase in opioid utilization (buprenorphine: 11.8 ± 24.8; control 5.4 ± 10.4 mg/24 h, p = 0.10); following cesarean delivery both pain (buprenorphine: 5.1 (4.1, 6.1); control: 3.3 (2.5, 4.1), p = 0.009) and opioid utilization (buprenorphine: 89.3 ± 38.0, control: 60.9 ± 13.1 mg/24 h, p = 0.004) were increased Buprenorphine maintained women have similar intrapartum pain and analgesic needs during labor, but experience more postpartum pain and require 47% more opioid analgesic following cesarean delivery	Study Limitations = ☒ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up ☐ Differences in important prognostic factors at baseline	

References:

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

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

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

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

External Guidelines

Five review articles, and two health systems offer recommendations related to providing analgesia for patients with acute pain who are receiving opioid replacement therapy. None of the recommendations are based on a systematic review of the evidence. The recommendations, and the quality rating for each guideline are noted below.

DATE: October 2017

Guideline Ratings

Guideline Issuer and Date	Review article in Annals (Alford et al, 2006)	Review article in ACOG (Alto & O'Connor, 2011)	U of Michigan (2017)	Review article in Anesthesia (Bryson, 2014)	Boston Medical Center (2017)	Review article in AJOG (Jones et al, 2014)	Review article in Med Clin North Am (Salama, 2013)
1. Transparency	C	C	C	C	C	C	C
2. Conflict of interest	NR	NR	C	C	C	C	C
3. Development group	NR	NR	NR	NR	NR	NR	NR
4. Systematic Review	B	B	B	B	B	B	B
5. Supporting evidence	C	C	C	C	C	C	C
6. Recommendations	C	C	C	C	C	C	C
7. External Review	NR	NR	NR	NR	NR	NR	NR
8. Currency and updates	C	C	B	B	B	B	C

See appendix B for full description of the Trustworthy Guideline grading system.

A review article published in the *Annals of Internal Medicine* in 2006 gives the following recommendations for providing analgesia for patients with acute pain who are receiving opioid agonist therapy (Alford, Compton, & Samet, 2006):

Addiction treatment issues

Reassure patient that addiction history will not prevent adequate pain management.

Continue the usual dose (or equivalent) of OAT.

Methadone or buprenorphine maintenance doses should be verified by the patient's methadone maintenance clinic or prescribing physician.

Notify the addiction treatment program or prescribing physician regarding the patient's admission and discharge from the hospital and confirm the time and amount of last maintenance opioid dose.

Inform the addiction treatment maintenance program or prescribing physician of any medications, such as opioids and benzodiazepines, given to the patient during hospitalization because they may show up on routine urine drug screening.

Pain management issues

Relieve patient anxiety by discussing the plan for pain management in a nonjudgmental manner.

Use conventional analgesics, including opioids, to aggressively treat the painful condition.

Opioid cross-tolerance and patient's increased pain sensitivity will often necessitate higher opioid analgesic doses administered at shorter intervals.

Write continuous scheduled dosing orders rather than as-needed orders.

Avoid using mixed agonist and antagonist opioids because they may precipitate an acute withdrawal syndrome.

If the patient is receiving methadone maintenance therapy and requires opioid analgesics

Continue methadone maintenance dose. Use short-acting opioid analgesics.

If the patient is receiving buprenorphine maintenance therapy and requires opioid analgesics, 4 options are available and should be chosen on the basis of the anticipated duration of pain, treatment setting, and response to the chosen option

Continue buprenorphine maintenance therapy and titrate short-acting opioid analgesics (for pain of short duration only).

Divide buprenorphine dose to every 6–8 hours.

Discontinue buprenorphine maintenance therapy and use opioid analgesics. Convert back to buprenorphine therapy when acute pain no longer requires opioid analgesics.

If the patient is hospitalized, discontinue buprenorphine therapy, treat opioid dependence with methadone at 20–40 mg, and use short-acting opioid analgesics to treat pain. Have naloxone available at the bedside. Discontinue methadone therapy and convert back to buprenorphine therapy before hospital discharge (for inpatients only).

Levels of Evidence not provided

A review article in the *American Journal of Obstetrics and Gynecology* published in 2011 states the following in regard to managing labor and postpartum pain in patients treated with buprenorphine (Alto & O'Connor, 2011):

There are several options for the management of labor pain. In many instances, no additional analgesia is necessary. The maintenance dose of buprenorphine can be divided, giving 25% of the daily dose every 6 hours. This takes advantage of the analgesic effects of the drug. Nonpharmacological interventions such as showers or hot tubs and position changes should be offered as appropriate. Additional augmentation with a short-acting injectable opioid such as morphine or fentanyl 25-50 mg every 30-60 minutes should be added as necessary. A higher dose and more frequent administration will be required than in opiate-naïve subjects. The patient's symptoms provide the guide to dosage. The fetus will be similarly habituated to opiates and should not be depressed.

Nonopioid analgesics may be adequate for routine postpartum pain after a vaginal delivery, but opioid analgesia should be made available if required. An epidural catheter can be left in place postoperatively. Preloading the operative incision with a long-acting local anesthetic such as bupivacaine is useful. Injectable ketoralac can be given. When pain is more severe, patient controlled analgesia using morphine has been advocated while maintaining the regular buprenorphine schedule. Another option is to decrease the regular buprenorphine dose to 8 mg (if applicable) while offsetting the buprenorphine reduction with oxycodone (1 mg buprenorphine = 15 mg oxycodone) or morphine (1 mg = 30 mg oral) given in divided doses plus provide the regular amount of opiates routinely given for that procedure in a drug-naïve patient.

If more than a day or two of opiate pain medication will be needed, buprenorphine should be stopped. Pain should be treated with frequent administration of short-acting opiates. As buprenorphine clears the body over the next several days, the analgesic dose requirements will decrease. When the pain has decreased, buprenorphine may be restarted using an induction protocol. A physician with experience in buprenorphine induction should be consulted.
Levels of Evidence not provided

A review article published in *Anesthesia and Medical Disease* in 2014 gives the following recommendations to support perioperative pain management in individuals maintained on opioid replacement or agonist therapy (Bryson, 2014):

Perioperative management strategies for patients maintained on buprenorphine are as follows (In either case, use nonopioid medications and employ regional anesthetic blockade where possible.):
(1) If the plan is to continue the buprenorphine: (a) Use short-acting opioid analgesics such as fentanyl in addition to the once-daily maintenance dose of buprenorphine and titrate to achieve effective pain control. (Note: effective doses may be much higher.) (b) Instead of once-daily dosing, divide the total buprenorphine maintenance dose over the course of 24 h and administer every 6–8h (relying solely on the analgesic properties of buprenorphine is only effective for mild-to-moderate pain). (2) If the plan is to stop the buprenorphine: (a) Stop the buprenorphine 72 h before surgery and use standard opioids for analgesia. (b) Conduct a slow taper over 2 weeks or an abrupt taper over 3 days followed by 72 h completely free of buprenorphine prior to elective surgery. (c) If the risk for relapse is too high, replace the maintenance dose of buprenorphine with methadone before surgery and then use another short-acting opioid analgesic for breakthrough pain.

Perioperative transition from buprenorphine to methadone is as follows:
(1) Patients maintained on buprenorphine should receive 30–40mg methadone per day. (2) This dose of methadone will prevent acute withdrawal in most patients. (3) For persistent opioid withdrawal, increase daily methadone by 5–10mg each day. (4) When the acute pain resolves, discontinue methadone and resume ORT with buprenorphine using an induction protocol (patient should be in mild opioid withdrawal before restarting buprenorphine therapy to avoid precipitation of acute withdrawal).
Levels of Evidence not provided

A review article published in 2014 in the *American Journal of Obstetrics and Gynecology* provides the following recommendations for managing acute pain during labor and delivery for women who are opioid-agonist-maintained (Jones et al., 2014):

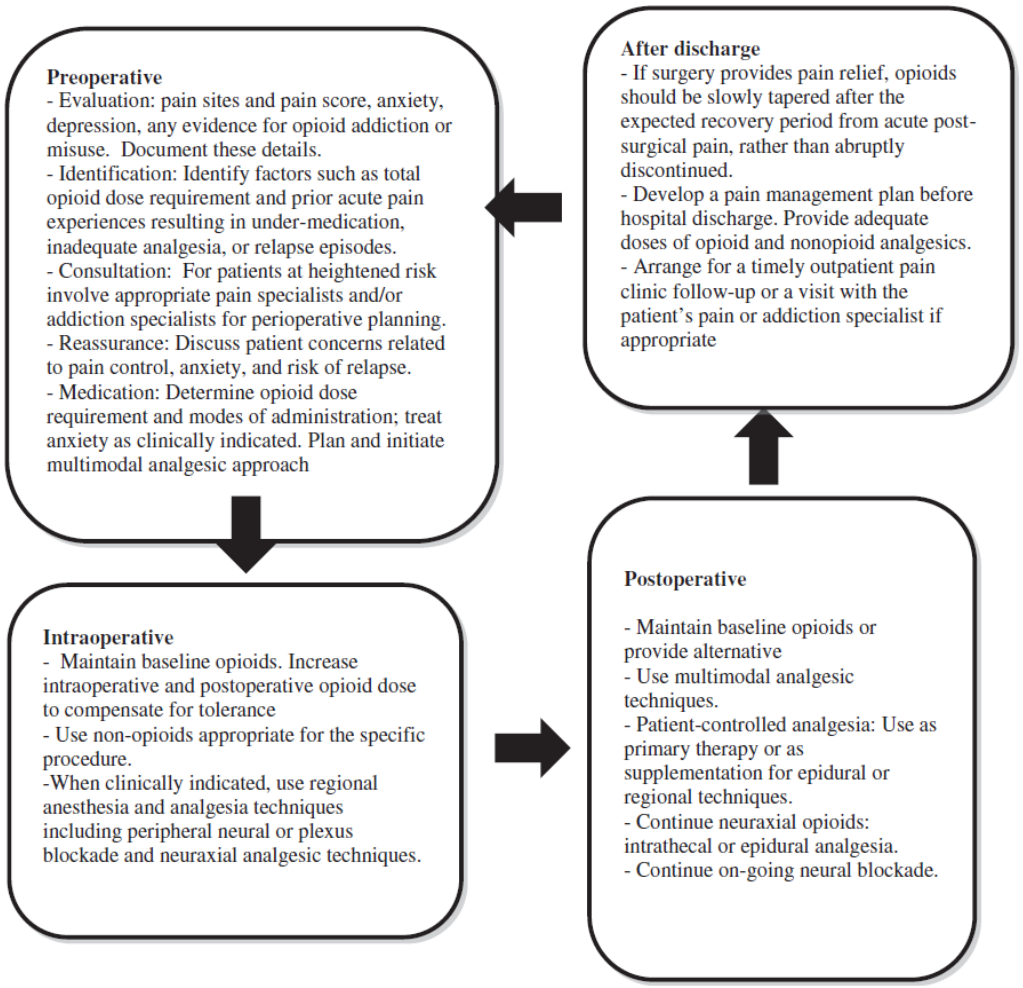
It is recommended to continue the established regimen and to augment pain management for the patient's acute needs. Once the type and dose of maintenance medication are verified, the patient's daily dose and number of doses per day of the agonist medication should not be changed unless medically necessary. Pain management during labor and delivery should be provided in the safest and

most effective manner possible, consistent with the patient's desire. Analgesic needs should be based on the clinical evaluation of the patient and not on the prescribed maintenance dose of opioid-agonist medication.

In this situation, higher opioid doses likely are needed for patients who are opioid-dependent. Long-term exposure to opioids produces both tolerance (ie, reduced opioid analgesic effectiveness) and hyperalgesia (ie, increased pain sensitivity). There are fewer appropriate intravenous pharmacologic choices to treat labor pain in patients who use opioids relative to patients who do not use opioids because of the need to avoid partial agonist/antagonists. Labor epidural or combined spinal/epidural analgesia typically works well. Initiating neuraxial (ie, spinal or epidural or combined spinal/epidural) analgesia early in labor may be particularly beneficial in attaining adequate pain relief in this population.
Levels of Evidence not provided

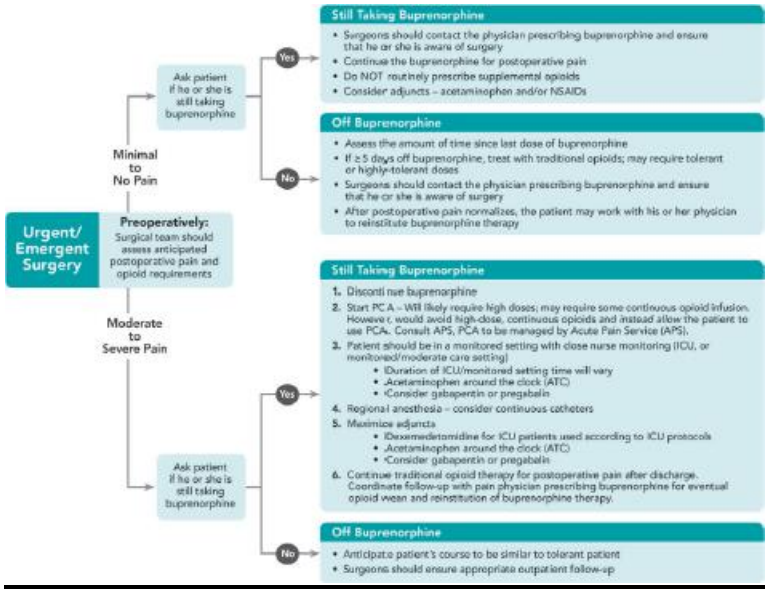
A review article by Salama-Hanna & Chen at OHUS published in *Medical Clinics of North America* in 2013 states the following (Salama-Hanna & Chen, 2013):

Formulating and communicating the plan for multidisciplinary preoperative treatment and multimodal perioperative pain control to patients and care teams help alleviate patient anxiety and improve care. Initiating treatment before surgical incision requires planning and is associated with the best outcomes.
Levels of Evidence not provided

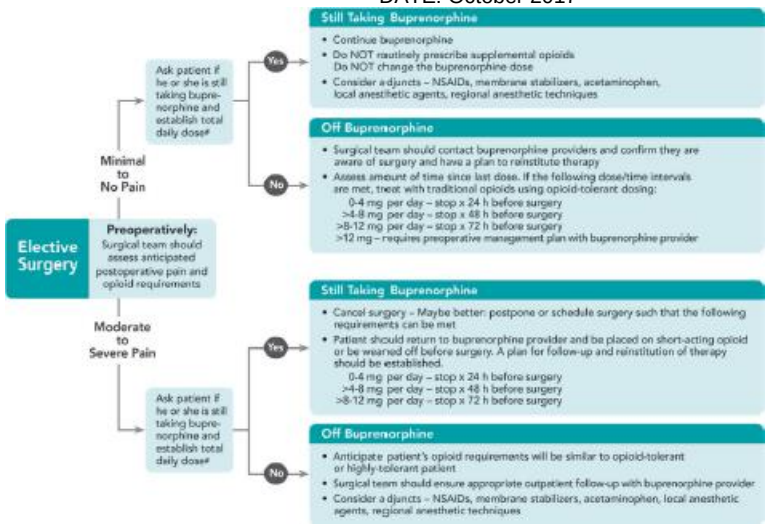


The University of Michigan Health System recommends the following for patients taking buprenorphine after surgery (Anderson et al., 2017):

Levels of Evidence not provided



DATE: October 2017



Boston Medical Center's 2012 guideline recommends the following for the perioperative management of non-pregnant patients on maintenance therapy for opioid dependence (Center, Feb 2017):

The appropriate treatment of acute pain in patients on buprenorphine and methadone maintenance includes continuing the patient's baseline opioid requirements to avoid increased pain sensitivity associated with opioid withdrawal. Thus, daily opioid maintenance treatment requirements must be met before attempting to achieve analgesia. These patients have also been shown to have increased pain sensitivity and cross-tolerance to opioid analgesics, therefore adequate pain control will often necessitate higher opioid doses at shorter dosing intervals. All patients on buprenorphine and methadone maintenance should be co-managed with their buprenorphine or methadone provider during the pre- and post-procedure period. Addiction medicine is available for consultation to assist with recommendations for opioid use disorder management in the postoperative period.
Levels of Evidence not provided

Table 1 from Boston Medical Center's Guideline

Opioid Dependence Patient Category	Pre-operative Pain Recommendations	Post-operative Pain Recommendations
Chronic Pain on Chronic Opioid Therapy **Inclusion:** Patient on chronic opioids > 2 weeks or with	Continue standing opioid dose the day of surgery. Hold any usual PRN breakthrough opioid doses the day of surgery.	Continue equivalent chronic opioid dose (IV if patient strict NPO) withhold parameters for sedation. For acute postoperative pain, utilize multimodal pain management with non-opioid medications (NSAID, acetaminophen, epidural/spinal analgesia, nerve blocks) as

other signs of physical dependence. Does not include patients taking occasional or prn opioids for breakthrough pain.		indicated. If opioids are required for breakthrough pain, patients with history of chronic opioid use may require higher than usual doses due to cross tolerance. PCA's may be considered if pain is not adequately captured. This may be utilized with or without a basal component.
Methadone Maintenance Therapy	Confirm methadone dose with patient's methadone maintenance treatment program (MMTP). Continue usual dose of methadone the day of surgery. The patient may need to arrange home doses of methadone ("medical take home doses") with his or her MMTP if they are unable to go to the MMTP on the day of surgery. If this is not possible, the patient should receive his or her usual confirmed methadone dose in the pre-operative area.	Continue usual daily methadone dose. If the patient is strict NPO, they should receive 50%-75% of their usual methadone dose given IV, divided into 2-4 doses/day (e.g. if usual dose is 60 mg PO daily, appropriate IV doses would be approximately 15 mg IV BID or 10 mg IV TID). For acute postoperative pain, utilize multimodal pain management with non-opioid medications (NSAID, acetaminophen, epidural/spinal analgesia, nerve blocks) as indicated. If opioids are required for breakthrough pain, patients with history of opioid use disorder may require higher than usual doses due to cross tolerance and increased pain sensitivity. PCA's without basal component may be considered in addition to patient's methadone if pain is not adequately captured. Remember to discontinue other oral PRN opioids. On discharge, the patient should be given a "last dose letter" addressed to the MMTP and whether any modifications have been made. The discharge case manager and patient may need to arrange for home doses of methadone ("medical take home doses") with his or her MMTP if he or she is unable to go to the MMTP on the days of after discharge.
Buprenorphine Maintenance Therapy	Take AM dose of buprenorphine on the day of the procedure.	Continue patient's home dose of buprenorphine post-operatively. Consider splitting patient's totally daily buprenorphine dose into q8h schedule for better pain coverage. For acute postoperative pain, utilize multimodal pain management with non-opioid medications (NSAID, acetaminophen, epidural/spinal analgesia, nerve blocks) as indicated. If opioids are required for breakthrough pain, patients with history of opioid use disorder may require higher than usual doses due to cross tolerance and increased pain sensitivity. PCA's without basal component may be considered in addition to patient's buprenorphine if pain is not adequately captured. Remember to discontinue other oral PRN opioids.
Naltrexone (oral or depot) Maintenance Therapy	Discontinue oral naltrexone 72 hours before surgery. Discontinue depot naltrexone 1 month prior to elective surgery, if possible.	Utilize multimodal pain management with non-opioid medications (NSAIDs, acetaminophen, epidural/spinal analgesia, nerve blocks) as indicated. If surgery performed emergently or naltrexone was not discontinued prior to surgery, naltrexone should be discontinued postoperatively. If this occurs, higher than usual doses of opioids may be attempted to overcome naltrexone's opioid antagonist effects. This must be done with close observation for respiratory depression.

REFERENCES

Alford, D. P., Compton, P., & Samet, J. H. (2006). Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med, 144*(2), 127-134.

Alto, W. A., & O'Connor, A. B. (2011). Management of women treated with buprenorphine during pregnancy. *American Journal of Obstetrics & Gynecology, 205*(4), 302-308. doi:10.1016/j.ajog.2011.04.001

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

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:https://dx.doi.org/10.1176/ajp.2007.164.6.979

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:https://dx.doi.org/10.1097/ACO.0000000000000052

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

Center, B. M. (Feb 2017). *Perioperative Management of Non-Pregnant Patients on Maintenance Therapy for Opioid Dependence*. Clinical Guideline. Boston Medical Center. Boston, MA.

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/xaa.0000000000000069

Huang, A., Katznelson, R., de Perrot, M., & Clarke, H. (2014). Perioperative management of a patient undergoing Clagett window closure stabilized on Suboxone for chronic pain: a case report. *Canadian Journal of Anaesthesia, 61*(9), 826-831. doi:https://dx.doi.org/10.1007/s12630-014-0193-y

Israel, J. S., & Poore, S. O. (2013a). The clinical conundrum of perioperative pain management in patients with opioid dependence: lessons from two cases. *Plastic & Reconstructive Surgery, 131*(4), 657e-658e. doi:https://dx.doi.org/10.1097/PRS.0b013e31828277bd

Israel, J. S., & Poore, S. O. (2013b). 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

Jones, H. E., Deppen, K., Hudak, M. L., Leffert, L., McClelland, C., Sahin, L., . . . Creanga, A. A. (2014). Clinical care for opioid-using pregnant and postpartum women: the role of obstetric providers. *American Journal of Obstetrics & Gynecology, 210*(4), 302-310. doi:https://dx.doi.org/10.1016/j.ajog.2013.10.010

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

Khelemsky, Y., Schauer, J., & Loo, N. (2015). Effect of buprenorphine on total intravenous anesthetic requirements during spine surgery. *Pain Physician, 18*(2), E261-264.

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:https://dx.doi.org/10.1097/MJT.0b013e3181be0804

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.

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

Salama-Hanna, J., & Chen, G. (2013). Patients with chronic pain. *Medical Clinics of North America, 97*(6), 1201-1215. doi:https://dx.doi.org/10.1016/j.mcna.2013.07.005

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

Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline 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.

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. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations
Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.
Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but

	the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated

Appendix C. Search Strategy in Ovid MEDLINE

1 exp Buprenorphine/ (3399)
2 exp Naloxone/ (9944)
3 Opiate Substitution Treatment/ (1798)
4 1 or 2 or 3 (13885)
5 exp Surgical Procedures, Operative/ (1696031)
6 su.fs. (1063366)
7 5 or 6 (1943882)
8 4 and 7 (742)
9 exp Postoperative Complications/ (292684)
10 exp Perioperative Care/ (76654)
11 9 or 10 (351470)
12 8 and 11 (270)
13 4 and 11 (453)
14 exp "Outcome and Process Assessment (Health Care)"/ (866266)
15 exp Mortality/ (260839)
16 exp Pain/ (229491)
17 exp Pain Measurement/ (67105)
18 exp Pain Management/ (17589)
19 exp anesthesia/ (74433)
20 exp anesthetics/ (102710)
21 16 or 17 or 18 or 19 or 20 (386583)
22 14 or 15 or 21 (1401866)
23 13 and 22 (336)
24 12 or 23 (366)
25 limit 24 to humans (238)
26 ((continu* or discontinu* or maintain* or mainten* or suspend* or suspension* or cancel* or withdraw* or (keep adj taking)) adj7 (buprenorphin* or nalox* or naltrex* or ((opiat* or opioid*) adj2 substitut*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2066)
27 7 or 11 (1994178)
28 26 and 27 (86)

29 ((continu* or discontinu* or maintain* or mainten* or suspend* or suspension* or cancel* or withdraw* or (keep adj taking)) adj7 (buprenorphin* or nalox* or naltrex* or ((opiat* or opioid*) adj2 substitut*)) adj10 (surger* or surgic* or operat*)).mp. (21)
30 ((drug* or substanc* or opioid* or opiat* or narcotic*) adj3 (addict* or dependen* or abus* or misus* or withdraw*)).mp. (82437)
31 24 and 30 (28)
32 28 or 29 or 31 (114)
33 limit 32 to humans (86)
34 ((surger* or surgic) adj5 (buprenorph* or naloxon* or naltrexon* or ((opioid* or opiat*) adj2 substitut*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (83)
35 limit 34 to humans (44)
36 25 or 35 (258)
37 36 not 33 (205)