

Perioperative Continuation of Buprenorphine at Low–Moderate Doses Was Associated with Lower Postoperative Pain Scores and Decreased Outpatient Opioid Dispensing Compared with Buprenorphine Discontinuation

Aurora Quaye, MD,^{*,†} Kevin Potter, PhD,^{*} Sarah Roth,^{*} Gregory Acampora, MD,^{*} Jianren Mao, MD, PhD,^{*} and Yi Zhang, MD, PhD^{*}

^{*}Massachusetts General Hospital, Boston, Massachusetts; [†]Maine Medical Center, Portland, Maine, USA

Correspondence to: Yi Zhang, MD, PhD, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA. Tel: 617-643-9308; Fax: 617-726-7536; E-mail: yzhang20@partners.org.

Funding sources: None.

Conflicts of interest: None.

Abstract

Objective. An increasing number of individuals are prescribed buprenorphine as medication-assisted treatment for opioid use disorder. Our institution developed guidelines for perioperative buprenorphine continuation with an algorithm for dose reduction based upon the surgical procedure and patient's maintenance dose. The objective of this study was to compare the effects of buprenorphine continuation with those of discontinuation on postoperative pain scores and outpatient opioid dispensing. **Design.** Retrospective observational study. **Subjects.** Surgical patients on buprenorphine from March 2018 to October 2018. Patients on buprenorphine for chronic pain and those with minor procedures were excluded from analysis. **Methods.** We compared postoperative outpatient opioid dispensing and postanesthesia care unit (PACU) pain scores in patients where buprenorphine was continued compared with held perioperatively, collecting single surgical subspecialty prescriber data on outpatient full mu-opioid agonist prescriptions dispensed, converted into mean morphine equivalents. Buprenorphine formulations were not included in our morphine milligram equivalents (MME) total. **Results.** There were 55 patients total (38 cont. vs 17 held). There was no difference in postoperative buprenorphine treatment adherence (91% cont. vs 88% held, $P=0.324$). The number of opioid prescriptions dispensed was significantly higher with buprenorphine discontinuation (53% cont. vs 82% held, $P=0.011$), as was MME dispensed (mean of 229 cont. vs mean of 521 held, $P=0.033$). PACU pain scores were higher with buprenorphine discontinuation (mean 2.9 cont. vs mean 7.6 held, $P<0.001$). **Conclusions.** There was a significant reduction in opioid prescriptions filled, MME dispensed, and PACU pain scores in patients where buprenorphine was continued vs held perioperatively. We provide evidence to support that buprenorphine can be continued perioperatively and that continuation is associated with decreased postoperative pain and decreased outpatient opioid dispensing. These results contribute to the existing literature supporting the perioperative continuation of buprenorphine.

Key Words: Buprenorphine; Postoperative Pain; Opioid Use Disorder

Introduction

The United States is in the midst of an opioid epidemic. More than two million Americans have become dependent on prescription and nonprescription opioid

medications [1,2]. The consequences of opioid misuse are deadly, and there has been an exponential increase in the number of deaths nationwide due to overdose. In 2017, opioids were responsible for >49,000 deaths—a rise of 10% from 2016—eclipsing lethal overdose rates

sustained at the height of the heroin epidemic in the late 70s [2,3]. This rise has fueled a decline in life expectancy for the third year in a row—a national trend not seen since the influenza pandemic of 1918 [4–6]. In response to the opioid crisis, policies have been implemented to decrease the production and consumption of opioid medications, in tandem with increasing availability of treatment options for opioid use disorder (OUD) [7–9].

Buprenorphine is a partial mu opioid receptor agonist and kappa opioid receptor antagonist that is effective as medication-assisted treatment (MAT) for OUD. Buprenorphine has a higher affinity to the mu receptor, is 30 times more potent than morphine, and its kappa receptor antagonism has been implicated in the treatment of depressive symptoms [10–13]. As more adults are being maintained on buprenorphine, it will be critical to establish standard-of-care perioperative pain management guidelines for these patients. Currently, there is no unified practice. Some providers recommend buprenorphine discontinuation when acute pain management is anticipated, suggesting that its pharmacokinetic profile interferes with the analgesic efficacy of opioids used for pain control [14–16]. However, there is growing acceptance that buprenorphine can be continued without deleterious consequences to pain management [13,17,18]. Furthermore, buprenorphine continuation can potentially be advantageous in preventing opioid misuse, as premature discontinuation of MAT is known to lead to relapse of opioid use disorder [19,20].

In January 2018, an expert panel was convened at Massachusetts General Hospital to develop institutional guidelines for the perioperative management of patients on buprenorphine. Patients are continued on their buprenorphine maintenance regimen when minimal postoperative pain is anticipated, and when moderate to significant postoperative pain is expected, patients on >16 mg daily of buprenorphine are tapered to 16 mg the day before surgery and continued perioperatively at 8 mg daily until surgical pain subsides and their previous buprenorphine dose can be resumed. The rationale and implementation of our management algorithm has been described previously [13]. Before these guidelines, the practice at our institution was to withhold buprenorphine 72 hours before surgery, with opioid agonist supplementation to prevent withdrawal.

The objective of our study was to determine the difference in postoperative pain and outpatient opioid dispensing in patients where buprenorphine was held perioperatively compared with continued following the implementation of our buprenorphine guidelines.

Overall, we found a statistically significant reduction in outpatient opioid prescriptions filled and morphine milligram equivalents dispensed for patients where buprenorphine was continued. Additionally, postanesthesia care unit (PACU) pain scores were significantly higher in patients where buprenorphine was held perioperatively. These results contribute to the existing literature

supporting the perioperative continuation of buprenorphine.

Methods

After institutional review board approval, we performed an electronic medical record review of patients on buprenorphine maintenance therapy for OUD who had surgery from March 2018 to October 2018 at the Massachusetts General Hospital. Minor procedures, such as endoscopies and colonoscopies, were excluded from our analysis. Patients on transdermal buprenorphine patches and those on buprenorphine for chronic pain management were also excluded from our analysis. In order to limit our study to subjects who could either reduce their buprenorphine according to our guidelines or discontinue buprenorphine preoperatively, those who underwent emergent surgery were excluded.

To obtain information on outpatient opioid utilization, we accessed each patient's Massachusetts Prescription Awareness Tool (MassPAT) record, the monitoring program that tracks all schedule II-V medications prescribed in Massachusetts, Maine, and Rhode Island. We collected single surgical subspecialty prescriber data up to 60 days after the surgical date. We examined surgical prescriber data because at our institution postoperative opioid analgesics are managed by the subspecialty team that performed the surgery, and all provider-prescribed morphine milligram equivalents (MME) are less reflective of postsurgical pain and could represent drug-seeking behavior. We collected data on the number of full mu opioid agonist prescriptions filled and the total amount of opioids dispensed, converted into mean morphine equivalents using the National Center for Injury Prevention and Control morphine equivalent conversion table [21]. Buprenorphine formulations were not included in our MME total.

To determine postoperative buprenorphine treatment adherence, we also collected data on the number of buprenorphine prescriptions filled 60 days after the surgical date. To obtain information on postoperative pain levels, we recorded pain scores that were obtained in the PACU after surgery. The pain scores in the PACU were a cumulative average of the measurements recorded from PACU nursing assessment notes. A numeric rating scale (NRS) score ranging from 0 to 10 was used to measure the degree of postoperative pain. Patients who reported pain control as adequate and were discharged directly from the PACU, however, did not provide a numeric pain score and were assigned pain scores of <3 for our analysis. All other patients had numerical pain scores that were recorded and collected.

Statistical Analysis

Subjects' demographic and clinical characteristics were summarized via means and percentages. Variability in

Table 1. Demographics and characteristics of study subjects

Variable	Continued (N = 38)	Held (N = 17)	P Value
% female	37	24	
BUP dose, mean (95% CI)	17.7 (15.3–20.1)	15.1 (12.5–17.9)	0.499
Age, mean (95% CI), y	50.3 (46.9–53.5)	51.1 (44.9–57.1)	0.498
Surgical type			
% orthopedic	50	53	0.499
% orofacial	8	0	0.475
% cardiothoracic	11	12	0.49
% abdominal	21	18	0.471
% neurology	3	0	0.261
% urology/gynecology	8	18	0.489

Demographics of patients. There was no difference between the two groups of patients in age, gender, dose of buprenorphine, or surgical types. BUP = buprenorphine; CI = confidence interval.

the sample was summarized via 95% confidence intervals (CIs). To avoid any potential issues due to skewed and/or bounded data, univariate comparisons were based on a nonparametric test, specifically a bootstrapped difference of means (using 1,000,000 samples for accuracy up to three decimal places). Statistical tests were conducted using the software R (version 3.4.3; R Core Team, Vienna, Austria) [22]. For all tests, a *P* value of <0.05 was deemed statistically significant.

Results

Our electronic medical record search yielded a total of 55 patients. Of these, 38 continued buprenorphine perioperatively and 17 had their buprenorphine held, resulting in 69% adherence to our guidelines of buprenorphine continuation. There was no significant difference in age, gender, or preoperative buprenorphine dose in the buprenorphine continued vs held group (Table 1). Both groups had similar types of surgeries, and the majority of patients had either an abdominal or orthopedic procedure performed. There was no difference in postoperative buprenorphine treatment adherence; the majority of patients continued buprenorphine postoperatively (91% cont. vs 88% held, *P* = 0.324) (Figure 1). Patients were significantly more likely to have an opioid prescription dispensed as an outpatient when buprenorphine was held perioperatively (53% cont. vs 82% held, *P* = 0.011) (Table 2). MMEs of full mu opioid agonists dispensed were significantly higher in the buprenorphine discontinuation group (mean of 229 cont. vs mean of 521 held, *P* = 0.033) (Figure 2A). PACU pain scores were significantly higher in the buprenorphine discontinuation group (mean of 2.9 cont. vs mean of 7.6 held, *P* < 0.001) (Figure 2B).

Discussion

There is growing evidence that buprenorphine can be continued without untoward effects on acute pain management [13,17,18]. Here, we demonstrate that not only can buprenorphine be continued at a moderate dose

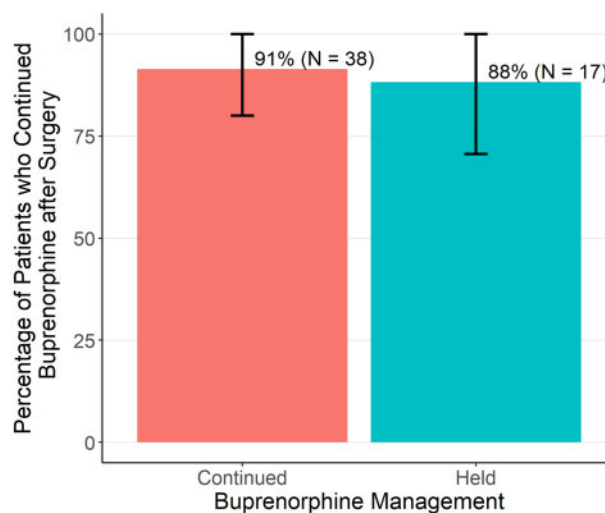


Figure 1. Bar plot of percentage of patients who continued BUP postoperatively based on whether BUP was continued or held perioperatively. BUP=buprenorphine.

perioperatively with effective pain control, but also that continuation leads to improved pain management and decreased outpatient opioid utilization.

These findings are important for several reasons. Foremost, buprenorphine continuation can potentially mitigate the risk of perioperative OUD relapse and misuse. Although the consequences of perioperative buprenorphine discontinuation are unknown, there is clear evidence that premature discontinuation of buprenorphine leads to relapse of opioid use disorder [9,19,20]. Furthermore—particularly during the preoperative discontinuation of buprenorphine days before hospitalization for the procedure and postdischarge if re-induction is needed—there is vulnerability for OUD relapse [13]. Buprenorphine continuation at a lowered dose can potentially mitigate both of these concerns. It may obviate the need for preoperative opioid prescribing and can help facilitate the return to a patient's maintenance buprenorphine dose without going through a withdrawal period.

In the sample studied, there were high rates of postoperative buprenorphine treatment adherence in both

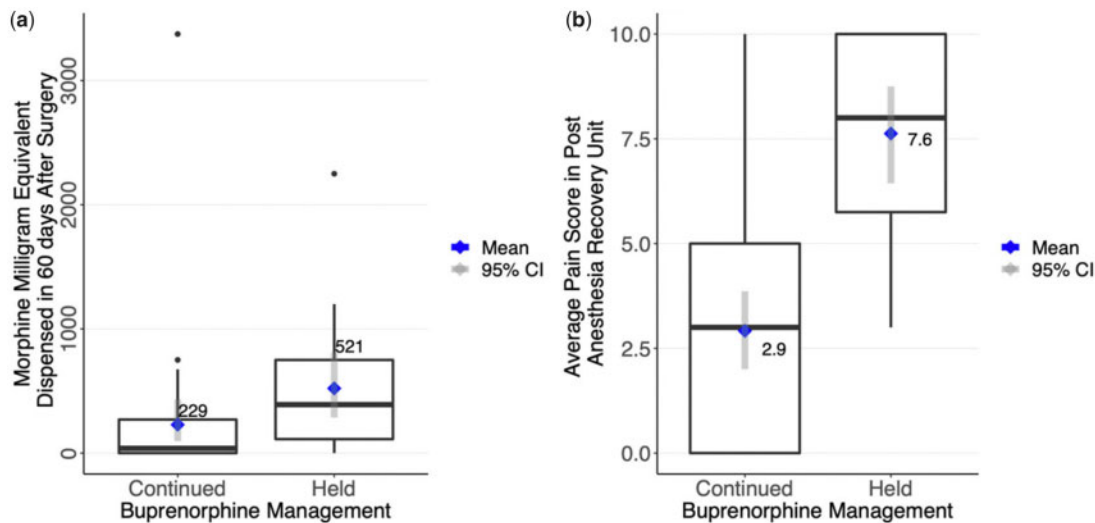


Figure 2. A) Boxplot of full mu agonists dispensed, converted to MME over a 60-day period when BUP was continued vs held. B) Boxplot of PACU pain scores when BUP was continued vs held. For both panels, means are marked with a blue diamond, and 95% confidence intervals are denoted by gray bars. BUP=buprenorphine; MME=morphine milligram equivalents; PACU=postanesthesia care unit.

Table 2. Percentage of patients receiving opioid prescription at discharge

Buprenorphine Management	Opioids Prescribed	No Opioids Prescribed	Percentage
Continued	20	18	53
Held	14	3	82

At discharge after surgery, a significantly higher percentage of patients received an opioid prescription when buprenorphine was held perioperatively (53% continued vs 82% held, $P = 0.011$).

$P = 0.011$.

groups—defined by consecutive buprenorphine prescriptions dispensed 60 days after the surgical date (Figure 1). Notably, the majority of patients in both groups were on buprenorphine therapy for >12 months. It is possible that the rates of buprenorphine adherence detected were, in part, due to the fact that duration of MAT is associated with increased treatment adherence [23]. Future study should investigate if similar trends in treatment adherence are present in cohorts on shorter buprenorphine treatment durations before surgery.

Remarkably, although there was no between-group difference in buprenorphine treatment retention, there was a significant difference in outpatient opioid dispensing, with the buprenorphine continuation group obtaining significantly less opioids than the discontinuation group. Notably, our MME analysis solely included full mu agonists, and the 1:30 conversion of buprenorphine to morphine was not included in the MME calculation. Over a 60-day period, the buprenorphine continuation group obtained a mean total of 229 MME—roughly equivalent to 30 oxycodone tablets (5 mg each)—while the buprenorphine discontinuation group obtained a mean total of 521 MME—roughly 70 oxycodone tablets

(5 mg each). This novel finding challenges what was previously understood about the clinical consequence of buprenorphine pharmacology interfering with opioid-based pain management. It also has substantial public health implications, as establishing treatment plans where patients are provided with less opioids as outpatients diminishes opioid availability in the community, decreasing the opportunity for diversion.

There are limitations to our observational study worth mentioning. In our sample, buprenorphine discontinuation vs continuation was not randomized but rather reflected the clinical practice at our institution. Each patient seen through our preoperative clinic was advised to continue buprenorphine, as per our new guidelines. Adherence to our recommendations, overall, was high; however, the patient, the buprenorphine provider, and the surgeon all had influence over the final decision regarding management.

In this study, buprenorphine was discontinued preoperatively in 31% of patients. There were various patient and provider factors that influenced this decision, and it is possible that this could contribute to selection bias in our results. There were patients who elected to stop buprenorphine because they were fearful of the ability to control postoperative pain, and there were patients who had previously undergone surgeries where they had been instructed to hold buprenorphine and so they were reluctant to now continue buprenorphine. Also, there were patients whose providers had advised them to discontinue buprenorphine as they were either unaware of our guidelines or thought that pain control was not achievable with continuation. It is possible that these patients could have inherently more difficult-to-control pain requiring greater amounts of opioid administration than

the continuation group, confounding the results of our study.

Although continuation vs discontinuation was not random, we contend that it occurred in part due to provider and patient perceptions of buprenorphine management as opposed to surgical severity, as the types of surgeries were similar in both groups. However, it is feasible that there were also surgical factors that could have influenced a provider's decision to have the patient discontinue buprenorphine. Regardless, in this study the majority of subjects continued buprenorphine, reflecting strong adherence to our guidelines. To overcome this limitation, a prospective trial where patients are randomized to continue or stop buprenorphine should be conducted in the future.

The buprenorphine continuation group had significantly lower pain scores than the discontinuation group postoperatively. However, another study limitation is that we examined PACU pain scores as opposed to postoperative day 1 (POD1) pain scores. It is worth mentioning that our analysis of outpatient opioid dispensing data aligns with the finding of superior postoperative pain control, as patients who were continued on buprenorphine also filled significantly fewer opioid prescriptions. Similarly, another limitation is that we looked at all surgical cases and not just a specific surgical type. However, there was no difference in surgical severity, as surgeries that are considered to have significant postoperative pain were similar between groups (Table 1). Another consideration is that we did not account for the presence or absence of a regional anesthetic in this study. As we investigated all surgical cases and not a particular surgical type, there was a significant number of cases in both groups who were not amenable to a regional anesthetic. Although including regional anesthesia utilization would drastically influence PACU pain scores, it would have a less profound impact on opioid prescriptions and MME dispensed in the outpatient setting, which was the primary outcome of our study. Along these lines, as the intraoperative anesthetic and analgesic management strategies were not standardized, we did not quantify PACU opioid administration. To control for the influence of regional anesthesia on PACU pain scores and opioid administration, future studies should be designed to study a single surgical type with a standardized anesthetic management protocol. Ultimately, the population of patients who use buprenorphine for OUD is heterogeneous and is not isolated to a particular surgical subtype, and so our finding of buprenorphine continuation being associated with adequate pain control across surgical types has true practice generalizability.

Here, we excluded subjects who underwent emergent surgery, as these patients represented a different category of buprenorphine management, as dose reduction or discontinuation would not be able to occur until after surgery. The results from our study are not applicable to this surgical population, and pain management outcomes

from continuing, stopping, or reducing buprenorphine immediately postoperation remain unclear.

In our study, there are assumptions made related to the retrospective design. As we looked at MassPAT data on opioids dispensed, we are assuming that patients used the medications they obtained as prescribed. It is possible that these medications were diverted or misused in non-prescribed patterns. Also, we make the assumption that filling a buprenorphine prescription represents buprenorphine treatment adherence. It is possible that patients engaged in illicit, nonprescription opioid use even if they continued buprenorphine maintenance, or that they diverted their buprenorphine. We assume that buprenorphine dispensing is a reasonably dependable correlate to buprenorphine retention because refilling a buprenorphine prescription would require an evaluation from a buprenorphine provider that would make assessments on the patient's candidacy for remaining in treatment. To resolve the inherent drawbacks of our retrospective design, a definitive prospective trial utilizing patient self-reports of opioid use and urine-verifiable toxicology screens should be conducted in the future.

Although not evaluated in this study, it is worth mentioning that patients on transdermal and buccal formulations of buprenorphine for chronic pain management may also benefit from continuation of their medications during the perioperative period. Our rationale is that these pain management products deliver buprenorphine in significantly lower doses than the sublingual formulations used for OUD treatment when administered in Food and Drug Administration–approved dosing regimens. Sublingual buprenorphine used for OUD is prescribed in doses ranging from 8 to 32 mg per day, whereas Belbuca buccal film is dispensed in 75–900- μ g concentrations, or 0.075–0.9 mg of buprenorphine per 12 hours. Similarly, Butrans transdermal patches are dispensed in concentrations of 5–20 μ g, or 0.005–0.020 mg of buprenorphine, one hour per seven days. In healthy subjects, serum concentrations average 0.224 ng/mL for 10- μ g/h butrans patches and 0.47 ng/mL for 300-mcg Belbuca. Serum concentrations for 8 mg/2 mg of sublingual buprenorphine/naloxone are higher, at 3.37 ng/mL [24–27]. Based on the receptor availability studies mentioned previously, it is unlikely that buprenorphine would have a significant antagonizing effect on mu receptors at these doses. However, definitive studies are needed to validate our approach, supporting perioperative continuation of buprenorphine in patients using formulations used to treat chronic pain.

This study adds to new data showing that pain control is better with low–moderate-dose buprenorphine simultaneous with administration of full opioid agonists when compared with buprenorphine discontinuation. It remains unclear if continuation of buprenorphine at a full dose would lead to similar findings. As we discussed previously, there is growing preclinical and clinical evidence to support that simultaneous administration of

buprenorphine with full opioid agonists within their respective analgesic dose ranges results in an additive analgesic response [13]. Further investigation will need to be conducted to determine the significance and the mechanism of this finding.

In conclusion, we identified that the implementation of our guidelines for perioperative buprenorphine management led to decreased outpatient opioid outpatient utilization and postoperative pain control. Our institution will continue to manage patients with low-dose buprenorphine perioperatively. Broad guidelines that recommend buprenorphine discontinuation should be reconsidered, as there may be no added benefit to pain control and it may pose greater potential for opioid misuse and relapse of opioid use disorder.

References

- Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med* 2017;167(5):293–301.
- SAMHSA. An Update on the Opioid Crisis. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2018. Available at: https://www.samhsa.gov/sites/default/files/aatod_2018_final.pdf (accessed October 2019).
- NIDA. Overdose death rates. 2018. Available at: <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates> (accessed October 2019).
- CDC. Health in the United States, 2017, with special feature on mortality. 2017. Available at: <https://www.cdc.gov/nchs/data/abus/abus17.pdf> (accessed October 2019).
- CDC. CDC Features. Remembering the 1918 influenza pandemic. 2018. Available at: <https://www.cdc.gov/features/1918-flu-pandemic/index.html> (accessed October 2019).
- Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. NCHS Data Brief. 2018. Available at: <https://www.cdc.gov/nchs/data/databriefs/db328-h.pdf> (accessed October 2019).
- SAMHSA. Medications for Opioid Use Disorder: For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. Rockville, MD: Substance Abuse and Mental Health Services Administration (US); 2018. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK535275/> (accessed October 2019).
- Manchikanti L, Sanapati J, Benyamin RM, Atluri S, Kaye AD, Hirsch JA. Reframing the prevention strategies of the opioid crisis: Focusing on prescription opioids, fentanyl, and heroin epidemic. *Pain Physician* 2018;21(4):309–26.
- National Academies of Sciences, Engineering, and Medicine. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. Washington, DC: The National Academies Press; 2017.
- Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Int Med* 2006;144(2):127–34.
- Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003;349(10):949–58.
- Johnson RE, Fudala PJ, Payne R. Buprenorphine: Considerations for pain management. *J Pain Symptom Manage* 2005;29(3):297–326.
- Quaye AN, Zhang Y. Perioperative management of buprenorphine: Solving the conundrum. *Pain Med* 2019;20(7):1395–408.
- Bryson EO. The perioperative management of patients maintained on medications used to manage opioid addiction. *Curr Opin Anaesthesiol* 2014;27(3):359–64.
- Jonan AB, Kaye AD, Urman RD. Buprenorphine formulations: Clinical best practice strategies recommendations for perioperative management of patients undergoing surgical or interventional pain procedures. *Pain Physician* 2018;21(1):E1–12.
- Wachholtz A, Gonzalez G. Co-morbid pain and opioid addiction: Long term effect of opioid maintenance on acute pain. *Drug Alcohol Depend* 2014;145:143–9.
- Goel A, Azargive S, Lamba W, et al. The perioperative patient on buprenorphine: A systematic review of perioperative management strategies and patient outcomes. *Can J Anaesth* 2019;66(2):201–17.
- Lembke A, Ottestad E, Schmiesing C. Patients maintained on buprenorphine for opioid use disorder should continue buprenorphine through the perioperative period. *Pain Med* 2019;20(3):425–8.
- Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *BMJ* 2017;357:j1550.
- Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. *Arch Gen Psychiatry* 2011;68(12):1238–46.
- CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors. 2018 Available at: <https://www.cdc.gov/drugoverdose/resources/data.html> (accessed October 2019).
- R: A Language and Environment for Statistical Computing Vienna: R Foundation for Statistical Computing; 2017. Available at: <https://www.R-project.org/> (accessed October 2019).
- Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction* 2016;111(4):695–705.
- L.P. PP. Butrans package insert. 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021306s015s019lbl.pdf (accessed June 2014).
- Pharmaceuticals E. Belbuca package insert. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207932s000lbl.pdf (accessed October 2015).
- RBP, Inc. Suboxone package insert. 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf (accessed August 2010).
- Kuhlman JJ Jr, Levine B, Johnson RE, Fudala PJ, Cone EJ. Relationship of plasma buprenorphine and norbuprenorphine to withdrawal symptoms during dose induction, maintenance and withdrawal from sublingual buprenorphine. *Addiction* 1998;93(4):549–59.