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REVIEW ARTICLE/BRIEF REVIEW

The perioperative patient on buprenorphine: a systematic review of perioperative management strategies and patient outcomes

Le patient en période périopératoire sous buprénorphine : revue systématique des stratégies de gestion périopératoire et de l'évolution des patients

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Abstract

Background *An increasing number of patients with opioid use disorder (OUD) are treated with opioid agonist-antagonists such as buprenorphine/naloxone. Perioperative management of patients on buprenorphine/naloxone is inconsistent and remains a controversial topic with mismanagement posing a significant risk to the long-term health of these patients.*

Methods *We performed a systematic literature search involving Medline, Medline In-Process, Embase, Cochrane Central, Cochrane Database of Systematic Reviews, PsycINFO, Web of Science (Clarivate), Scopus (Elsevier), CINAHL (EbscoHosst), and PubMed (NLM).*

Results *Eighteen studies were included in the final sample, including one controlled study and four observational studies . Neither the controlled study nor the observational studies assessed addiction treatment retention, harm reduction, or long-term mortality rates as primary or secondary outcomes. Of the observational studies, authors showed equivalent peri- and postoperative*

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pain control among buprenorphine continued patients. All but one authors described adequate analgesia among the case reports in which buprenorphine ≤ 16 mg sublingually (SL) daily was continued during the perioperative period. Long-term harm reduction was not reported with only three case reports including any long-term abstinence or relapse rates.

Conclusions *The current understanding of the risks and benefits of continuing or stopping buprenorphine perioperatively is limited by a lack of high-quality evidence. Observational studies and case reports indicate no evidence against continuing buprenorphine perioperatively, especially when the dose is < 16 mg SL daily. In patients with significant potential for relapse, such as those with a recent history of OUD, the discontinuation of buprenorphine should have a strong rationale supported by patient and surgical preferences. Future studies require standardized reporting of median doses, details on the route of delivery, dosing schedules and any dosing changes, and rates of addiction relapse, including long-term morbidity and mortality where possible.*

Résumé

Contexte *Un nombre croissant de patients présentant un trouble d'utilisation des opioïdes (TUO) sont traités avec des agonistes/antagonistes des opioïdes, tels que la buprénorphine et la naloxone. La gestion périopératoire des patients sous buprénorphine/naloxone n'est pas constante et reste un sujet de controverses; de plus une mauvaise gestion pose un risque significatif pour la santé à long terme de ces patients.*

Méthodes *Nous avons effectué une recherche systématique de la littérature dans les bases de données suivantes : Medline, Medline In-Process, Embase, Cochrane Central, Cochrane Database of Systematic Reviews, PsycINFO, Web of Science (Clarivate), Scopus (Elsevier), CINAHL (EbscoHosst) et PubMed (NLM).*

Résultats *Dix-huit études ont été incluses dans l'échantillon final, y compris une étude contrôlée et quatre études observationnelles. Ni l'étude contrôlée ni les études observationnelles n'ont évalué la continuation du traitement de l'addiction, la réduction des préjudices infligés ou les taux de mortalité à long terme parmi les critères d'évaluation principaux ou secondaires. Dans les études observationnelles, les auteurs ont montré qu'il y avait un contrôle équivalent de la douleur en péri- et postopératoire chez les patients continuant à recevoir de la buprénorphine. Tous les auteurs sauf un ont décrit une analgésie satisfaisante dans les rapports de cas où la buprénorphine sublinguale avec une dose ≤ 16 mg par jour était maintenue pendant la période périopératoire. La réduction des préjudices à long terme n'était pas décrite; seulement trois rapports de cas indiquaient le taux d'abstinence à long terme ou les taux de rechute.*

Conclusions *Les connaissances actuelles des risques et avantages de la poursuite ou de l'arrêt de la buprénorphine en période périopératoire sont limitées par le manque de données probantes de grande qualité. Les études observationnelles et les rapports de cas ne fournissent pas de données probantes à l'encontre de la poursuite de la buprénorphine dans la période périopératoire, en particulier quand la dose journalière par voie sublinguale est < 16 mg. Chez les patients présentant un risque significatif de rechute, comme ceux ayant des antécédents récents de TUO, l'arrêt de la buprénorphine devrait être solidement justifié avec le soutien des préférences des patients et des équipes chirurgicales. Les futures études nécessitent une normalisation du rapport des doses médianes, des détails sur les voies d'administration, de la posologie et de sa modification et des taux de rechute, en incluant aussi, chaque fois que possible, les taux de morbidité et mortalité à long terme.*

Buprenorphine has been used for opioid detoxification, addiction therapy, as well as acute and chronic pain management since 2002.[1] It has unique properties that make it a distinct option in chronic pain and opioid-replacement therapy. It is a partial Mu agonist with high Mu receptor affinity, slow dissociation from the Mu receptor, and demonstrates kappa antagonist properties.[2] Buprenorphine exhibits 25-50 times the potency and a partition coefficient 1,000 times that of morphine.[3] In human and animal models, buprenorphine has been shown to produce full analgesic effect depending on the intensity of the stimulus.[4] Intravenous buprenorphine (0.2 $mg \cdot kg^{-1}$ and 0.4 $mg \cdot kg^{-1}$) reduced experimental pain with a ceiling effect on ventilation.[5] Dahan explained this by suggesting that buprenorphine acts as a partial agonist at the Mu opioid receptors involved in respiratory depression while simultaneously acting as a full agonist at opioid receptors in analgesic pathways. Other theories have suggested the partial agonist effect on respiratory depression due to a predominantly spinal mechanism of action.[5]

Suboxone® (Indivior Inc., Richmond, NJ, USA) is an abuse-deterrent sublingual formulation of buprenorphine

and naloxone indicated for the treatment of opioid use disorder (OUD) and used off-label for management of chronic pain and opioid withdrawal. Buprenorphine's wide safety profile and purported full agonist effects for analgesia have made it increasingly prescribed in patients with chronic pain and addiction, with wide-ranging reported success.[3] Table 1 describes the different formulations of buprenorphine available in Canada.

Budd[6] demonstrated the analgesic efficacy of intravenous buprenorphine in 50 patients recovering from elective Cesarean delivery under general anesthetic. All patients were demonstrated to receive complete analgesia with 0.4-7 mg of buprenorphine. All of these factors make buprenorphine an important alternative in the management of pain among patients with complex pain and addiction history.

Indeed, one of the toughest challenges in pain medicine given the advent of the new Centers for Disease Control and Canadian Opioid Guidelines is the management of patients with opioid doses well beyond the suggested safe dose of 90 mg·day^{-1} of daily morphine equivalents. Suboxone has been used to rotate these patients off high-dose and misuse-prone opioids with a reduction in their pain symptoms as well as excellent success rates in the context of a behavioural support program (acceptance and commitment therapy).[7] Additional formulations (Table 1) of buprenorphine indicated for the management of addiction are due to be released in Canada, substantiating the need for more research on this topic.

Several narrative reviews have summarized existing literature and include expert recommendations for perioperative management of patients taking buprenorphine.[1,3,8-12] We conducted a systematic review to summarize the following features regarding the perioperative management of buprenorphine: 1) the indication for buprenorphine use; 2) the preparation and preoperative dose of buprenorphine; 3) whether buprenorphine therapy was continued perioperatively; 4) analgesic outcomes; 5) adverse events; and 6) success of deterrence against opioid use.

Methods

A literature search was performed (by M.E.) involving Medline (1946–June Week #1 2017), Medline In-Process/ePubs (June 13, 2017), Embase (1947–June 13, 2017), Cochrane Central (April 2017), Cochrane Database of Systematic Reviews (2005–June 9, 2017), PsycINFO (1806–June Week #1, 2017) (all via the Ovid search interface), Web of Science (1900–June 13, 2017) (Clarivate), Scopus (1960–June 2017) (Elsevier), CINAHL (1982–June 2017) (EbscoHost), and PubMed (1946–June 14, 2017, excluding Medline records) (NLM), to identify studies in which patients using buprenorphine and undergoing a surgical procedure were studied in the perioperative period. Searching was completed on June 14, 2017. Search terminology included blocks of terms for (surgery or perioperative or preoperative or postoperative terms) + (buprenorphine) + (drug use or chronic pain). The search strategies were not limited by study type. We supplemented the results with searches for book chapters, theses/dissertations, and ongoing clinical trials. Searches were limited to human studies. The retrieved citations were imported to Endnote™ (Clarivate Analytics) and checked for duplicates. The search strategy is further outlined in Appendix 1.

Eligibility criteria, study selection, and data extraction

We used the following inclusion criteria in our review:

Types of studies

All relevant studies, including randomized controlled trials (RCTs), observational studies including case control studies and cohort studies, as well as case series and case reports (CR). Conference proceedings were removed from the search strategy.

Participants

All human participants with no age restrictions, being administered buprenorphine prior to surgery for either chronic pain or addiction management.

Intervention

All reports involving the perioperative management of patients taking buprenorphine in the preoperative period to manage addiction or pain were included. Reports where patients were administered buprenorphine solely in the intraoperative or solely in the postoperative period were excluded. Any cases in which buprenorphine was continued beyond 12 hr postoperatively were considered to be in the buprenorphine "continued" category. Other information about descriptors of management was collected where possible, including: 1) rationale for preoperative buprenorphine use; 2) maintenance dose and preparation of buprenorphine; and 3) mode of continuation or discontinuation depending on management strategy suggested by the author.

Table 1 Buprenorphine: formulations available and pending distribution in Canada

Formulation and brand name	Dosage	Indication	Time to peak plasma concentration (hr)	Mean half life
Buccal film Belbucca	75, 150, 300, 450, 600, 750, 900 μg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate	2.5-3	16-39 hr
Sublingual tablet (buprenorphine) Subutex	2 mg 4 mg 8 mg 12 mg	For the treatment of opioid dependence and as part of a complete treatment plan including counselling and psychosocial support	1.3-1.8	31-35 hr
Buccal, sublingual film (buprenorphine/naloxone) Suboxone	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	For the treatment of opioid dependence and as part of a complete treatment plan including counselling and psychosocial support	0.5-1	24-42 hr
Transdermal system Butrans	5 10 15 20 $\mu g \cdot hr^{-1}$	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate	72	26 hr
Subcutaneous injection Sublocade (Availability TBD)	100 300 mg	For the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine containing product followed by dose adjustment for a minimum of seven days	24	43-60 days

Adapted, in part, from Sen *et al.*[8] and Jonan *et al.*[3]

TBD = to be determined

Outcomes

The review did not aim to pool data, hence the outcomes are reported in Table 2 and important results are summarized. Relative effectiveness of either continuing buprenorphine or stopping buprenorphine in the perioperative period was reported as either proportion of patients with successful outcomes, or as mean scores with standard deviation. Successful outcomes included cases in which the authors did not highlight any complications (i.e., respiratory depression, apnea). Complications were noted to either be surgically related or due to other factors, including management of pain. Pain parameters and other patient reported outcomes were noted when available. Long-term follow-up, including information about opioid relapse and chronic pain information was noted when available.

Data analysis and interpretation of findings

Studies were grouped into RCTs and/or controlled studies (CS), observational comparator-controlled studies, and CR. In individual groups, the extracted data were organized in tabular form. Data extracted for the various pre-specified outcomes were collated, interpreted, and summarized into a narrative format. Standardized forms like the one shown in Appendix 1 were used to collect data. This was performed by two persons (A.G. and S.A.) in duplicate, and data were compared to ensure uniformity. Conflicts were assessed by the supervising expert (H.C.).

Results

The literature search yielded 3,630 results; after removal of duplicates, 2,632 articles were identified by two independent reviewers (A.G. and S.A.). After undergoing initial screening, and subsequent screening to remove previously unidentified duplicates and studies that did not meet our inclusion criteria, 18 papers were finally included, shown in the PRISMA flow diagram (Figure). The kappa agreement score between the investigators was 0.9. A majority, 72% (13/18), were CRs or case series (Table 2).[13-25] Only one true case series was identified, with five of the CRs including single patients who underwent two surgeries at different time points. A total of 17 patients were included in the CRs and case series, five of whom underwent two procedures at different time

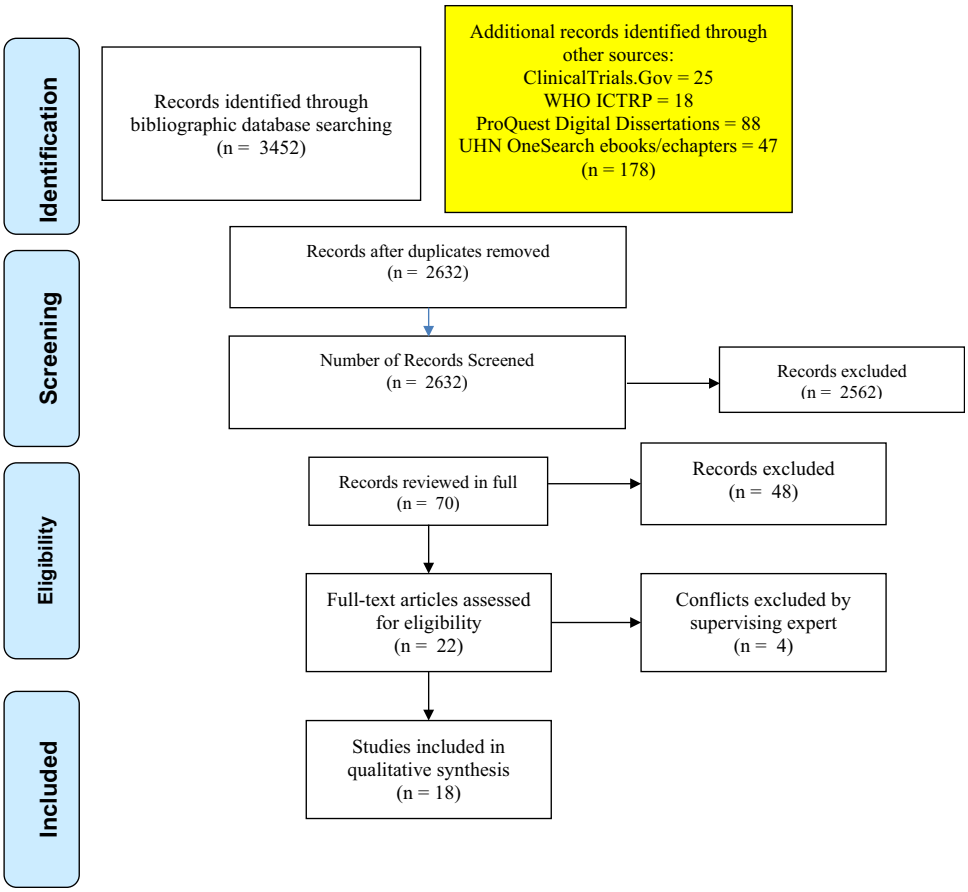

Figure PRISMA search diagram: *outline of the search strategy for final included studies*

points. The remaining five studies consisted of four observational studies and one CS that did not differentiate between buprenorphine and methadone in their controlled randomization (Table 2).[26-30] Of the four observational studies, only two had sample sizes greater than 50, while the CS studied 19 Cesarean patients.[30]

Buprenorphine management

Of the 12 single surgery cases, six of the patients (50%) were continued on buprenorphine throughout the perioperative period. Of the five CRs with patients undergoing surgery at two different time points, three CRs (60%) described opposite management strategies (continued *vs* stopped). When buprenorphine was stopped, the stop date ranged from several months preoperatively to 12 hr after surgery. Gupta *et al.*[26] and Meyer *et al.*[28] described outcomes in patients who continued buprenorphine in the obstetrical patient population while Macintyre *et al.*[27] and Hansen *et al.*[29] described observational studies in which 50% of the study patients were continued on buprenorphine. The CS[29] similarly compared opioid-replacement therapy in 37 study patients (three of which had two pregnancies) with 80 controls. The opioid-replacement therapy group included buprenorphine and methadone as one group (37 patients in the study group were randomized to buprenorphine or methadone), limiting conclusions regarding the causal relationship between buprenorphine and the main outcomes.

Buprenorphine indication

Preoperative buprenorphine use was characterized into OUD, chronic pain (CP), and postoperative analgesia (PA). In certain cases, there were multiple indications. The CS and observational studies quoted OUD as the indication for buprenorphine therapy in their respective cohorts with one observational study indicating both OUD and CP, and one that did not report the indication. Of the 17 patients described in the case series, buprenorphine was prescribed for OUD in five patients (29%), and CP alone in ten patients (59%). Buprenorphine was prescribed for both OUD and CP in one out of these 17 patients. One study had both OUD and PA as the indication.

Postoperative analgesic requirements

Controlled observational studies

One CS by Hoflich *et al.*[30] compared parturients on opioid-replacement therapy with controls but did not stratify their results by buprenorphine or methadone use for this outcome. As a group, females on an opioid-replacement therapy using methadone (mean daily dose 63.89 mg) or buprenorphine (mean daily dose 15.33 mg) received significantly less opioid analgesics and significantly more non-steroidal anti-inflammatory drug therapy following Cesarean delivery compared with controls. Of note, this study also showed that the rates of Cesarean delivery were higher in methadone continued patients (68.4%) compared with buprenorphine continued patients (31.8%) although this result was not statistically significant.[30] Pain scores and relapse rates were not reported.

Observational studies

Among the observational studies, Hansen *et al.*[29] performed a prospective matched cohort study from a total joint arthroplasty database of patients receiving opioid-replacement therapy (patients receiving buprenorphine or methadone were pooled into one group and not differentiated in the analysis or results). When patients who were continuing opioid-replacement therapy (n = 17) were compared with matched counterparts who discontinued opioid-replacement therapy perioperatively (n = 34), one-year postoperative pain scores were not statistically different. Nevertheless, the study group had a mean increase in postoperative morphine use (793 mg·day^{-1}) compared with the control group (109 mg·day^{-1}). Relapse rates and route of delivery were not reported.

Meyer *et al.*[28] compared parturients (44 vaginal and 19 Cesarean delivery) taking buprenorphine to controls in a case control study. This observational study demonstrated that females who continued buprenorphine perioperatively had similar pain and analgesic requirements during labour, but experienced more post-partum pain (pain scores 5.1 *vs* 3.3 in age matched controls not taking buprenorphine) and required 47% more analgesic following Cesarean delivery. Relapse rates and indication for buprenorphine were not reported.

Macintyre *et al.*[27] studied buprenorphine/naloxone and methadone in a retrospective cohort study. They showed no difference in patient-controlled analgesia (PCA) morphine equivalents or pain scores when comparing perioperative continuation *vs* cessation of buprenorphine. There was no significant difference in days requiring acute pain service or PCA. They did show higher rates of sedation in buprenorphine continued patients, but this did not correlate with lower respiratory rates. Nevertheless, continuation of buprenorphine in this study was inconsistent with 14/22 (64%) continuing on day of surgery and 11/22 (50%) continuing on postoperative day (POD) 1. Relapse rates were not reported.

Case reports

Buprenorphine Continued Patients

Kornfeld *et al.*[23] reported five cases, four of which were successfully managed on buprenorphine maintenance therapy ($\leq$ 24 mg daily) in the perioperative setting with increased PA requirements and well controlled pain levels. Relapse rates were not reported.

Silva and Rubinstin[15] report the case of a patient (24 mg buprenorphine sublingually [SL] daily) who underwent two total knee replacements (TKR) over a two-year period with well controlled pain. This same patient required higher doses of morphine (150 mg daily) to manage his postoperative pain when buprenorphine was discontinued for his second surgery. This patient relapsed into hydrocodone misuse at an unreported postoperative date after his second procedure.

Chern *et al.*[16] and Huang *et al.*[13] reported unsuccessful management of postoperative pain after a vaginal mesh removal and a Clagett window closure, with the former taking 24 mg buprenorphine SL daily and the latter taking 32 mg buprenorphine SL daily during a 41-day hospital stay. The same patient in Chern *et al.*[16] discontinued buprenorphine in a follow-up procedure (addressed in the next section). Huang *et al.* only reported continued abstinence from opioids at a three-week follow-up and *Chern et al.* did not report this outcome.at any time period.

Book *et al.*[14] reported the successful management of postoperative pain after removal of breast implants using supplemental buprenorphine alone in a patient continued on 24 mg SL daily.

Jones *et al.* (18 mg buprenorphine SL daily)[18] describes a Cesarean delivery in which good pain control was achieved with daily morphine doses of 48 mg and 180 mg respectively. McCormick *et al.*[21] described an emergent bilateral thigh and calf fasciotomy for compartment syndrome where a daily dose of 24 mg buprenorphine SL was continued until 12 hr postoperatively. Pain scores were reported as being well controlled. Book *et al.*,[14] Jones *et al.*,[18] and McCormick *et al.*[21] did not report relapse rates.

Buprenorphine discontinued patients

Kornfeld *et al.*[23] included two cases of five where 2 mg buprenorphine SL daily was discontinued and pain was

Table 2 Results: summary of randomized-controlled trials, observational studies, and case reports where patients taking buprenorphine were managed in the perioperative setting

Study	Sample size	Design	Population	Indication	Formulation	Dose reported (/day)	Continued perioperatively	Analgesia success	Relapse rates
Hoflich 2012	37 + 80 controls; (three females had a second child and switched to the opposite group, totaling 40 cases)	Matched cohort within larger (CS)	Vaginal (n = 21) and Cesarean (n = 19) delivery, Bup (n = 19, 13 vaginal) or Met (n = 21, eight vaginal)	OUD	NR	Mean (SD) = 12.77 (5.32) mg (vaginal) and 15.33 (7.86) mg (Cesarean)	Yes	NR	NR
Hansen 2016	17 + 34 controls	Matched cohort	Total hip (n = 8) and knee (n = 9) arthroplasty, continuing Bup/naloxone or Met (data pooled and not differentiated)	OUD	NR	Median (range) = 870 MEq mg (150-3000), Bup or Met (data pooled and not differentiated)	Yes	Well controlled; No significant difference between groups	NR
Meyer 2010	63 + 63 controls	Case control	Vaginal (n = 44) and Cesarean (n = 19) delivery taking Bup	NR	NR	Mean (SD) = 13.7 (6.2) mg	Yes	Well controlled; Significantly higher pain scores in study group *vs* controls postpartum	NR
Macintyre 2013	51	Retrospective cohort	Any surgery, taking Bup/naloxone (n = 22) or Met (n = 29)	OUD CP	NR	Mean (SD) = 13.7 (6.6) mg	Partial; Bup/naloxone continued POD 0 in 14/22 patients (64%) and POD 1 in 11/22 patients (50%)	Well controlled; No significant difference between groups or between continuation *vs* stopping	NR
Gupta 2013	19	Retrospective cohort	Vaginal (n = 10) and Cesarean (n = 9) delivery	NR	SL, PO, IV, IM	NR	Yes	NR	NR
Kornfeld 2010	5; (two patients had two procedures, totaling seven cases)	CR	60M; Rt Colectomy	CP	SL	24 mg (32 mg postoperatively)	Yes; Increased dose	Well controlled; Not available POD 1	NR
			43M; Rt TKR	CP	SL	12 mg (16 mg postoperatively)	Yes; Increased dose	Well controlled	NR
			43M; Lt TKR; two years post Rt TKR	CP	SL	12 mg	No; Restarted at discharge	Well controlled	NR
			60M; Small bowel resection	CP	Gelatin Troche	2 mg	No; Restarted POD 3	Well controlled	NR
			42F; B/L Mastectomy and reconstruction	CP	SL	8 mg (2 mg at post-admission)	Partial; Reduced dose; preoperative dose restarted at discharge	Well controlled	NR

Table 2 continued

Study	Sample size	Design	Population	Indication	Formulation	Dose reported (/day)	Continued perioperatively	Analgesia success	Relapse rates
			42F; Breast reconstruction two years post mastectomy	CP	SL	6 mg (4 mg on day of surgery, 2 mg on POD 1)	Partial; Reduced dose; preoperative dose restarted at discharge	Well controlled	NR
			58M; X-Stop removal, lumbar spine	CP	SL	16 mg (3 mg postoperatively)	Yes	Well controlled	NR
Khelemsky 2015	1; (two procedures)	CR	44F; Anterior cervical corpectomy	OUD	SL	24 mg	Yes	NR	NR
			44F; Anterior cervical fusion	OUD	SL	24 mg	No	NR	NR
Silva 2016	1; (two procedures)	CR	53M; Rt TKA	CP	SL	24 mg	Yes	Well controlled	NR
			53M; Lt TKA	CP	SL	0 mg (weaned two years prior)	N/A	Poorly controlled	Relapsed with hydrocodone
Chern 2013	1; (two procedures)	CR	37F; Vaginal mesh removal and cystoscopy	CP	SL	24 mg	Yes	Poorly controlled	NR
			37F; Vaginal mesh removal	CP	SL	24 mg	No; Switched to HM 4 mg q4-6h five days before surgery	Poorly controlled; "unbearable" 7-8/10	NR
Book 2007	1	CR	32F; Breast implant removal	OUD PA	SL	24 mg (72 mg postoperatively, 24 mg on POD 11)	Yes; Increased dose postoperatively; Preoperative dose restarted on POD 11	Well controlled	NR
Brummett 2009	1	CR	41M; Posterior lumbar spinal fusion	CP	SL	16 mg	No; D/C day of surgery	Poorly controlled	NR
Hassamal 2017	1	CR	25F; Tricuspid and Aortic valve repair	CP	NR	12 mg	NR; D/C and restarted postoperatively; timing of changes not reported	Well controlled	Abstinent at six months follow-up
Huang 2014	1	CR	47F; Clagett window closure	CP	SL	32 mg	Yes; Decreased by 50% postoperatively, with subsequent tapering to 0 mg before discharge	Poorly controlled; Improved after postoperative decrease	Abstinent at three week follow-up (two months postoperatively)
Israel 2013	1	CR	37F; B/L Mastectomy	OUD	SL	NR	No	Poorly controlled	NR
Jones 2006	1	CR	32F; Cesarean delivery	OUD	SL	18 mg	Yes	Well controlled	NR

Table 2 continued

Study	Sample size	Design	Population	Indication	Formulation	Dose reported (/day)	Continued perioperatively	Analgesia success	Relapse rates
Marcucci 2009	1	CR	47M; THA	OUD	SL	1 tablet q4h	No; Discontinued day of surgery	Poorly controlled	NR
McCormick 2013	1	CR	50M; Emergency B/L thigh and calf fasciotomy	OUD CP	SL	NR	Yes; Discontinued 12 hr postoperatively	Well controlled	NR; Restarted Bup/ naloxone therapy at two month follow-up
Rodgman 2012	1	CR	29F; Heart transplant	OUD	SL	24 mg	No; Discontinued 12 hr preoperatively	Poorly controlled	NR

Bup = buprenorphine; B/L = bilateral; CP = chronic pain; CR = case report; D/C = discontinued; HM = hydromorphone;; Lt = left; MEq = morphine equivalents; Met = methadone; N/A = not available; NR = not reported; OUD = opioid use disorder; PA = postoperative analgesia; PO = by mouth; POD = postoperative day; Rt = right; SD = standard deviation; SL = sublingual; THA = total hip arthroplasty; TKA = total knee arthroplasty; TKR = total knee replacement. Note: Gupta *et al.*[26] reported pre-admission quantities of buprenorphine but these quantities were subdivided by exposure (or not) to neuraxial opioids. Measures of central tendency and dispersion were not clearly identified

well controlled. The first patient had two procedures with buprenorphine continued in the first and discontinued in the second. Pain was well controlled for both procedures. In the second patient, buprenorphine was restarted at POD 3 and their admission was uncomplicated and their pain was well controlled. The relapse rate was not reported.

Chern *et al.*[16] reported the case of a 37-yr-old female (24 mg buprenorphine SL daily) who underwent two procedures for vaginal mesh removal and buprenorphine was discontinued for the second procedure, switched to hydromorphone five days before surgery. Intraoperatively, doses up to 1000 μg of fentanyl were required in the induction period when buprenorphine was discontinued. This patient reported poorly controlled pain after both procedures and noted the postoperative pain during the second case (when buprenorphine was discontinued) to be "unbearable". This patient required an additional 100 μg of fentanyl with several adjunctive analgesics to manage postoperative pain in this instance.

Brummett *et al.* (16 mg buprenorphine SL daily)[25] reported a case of posterior lumbar spinal fusion with buprenorphine discontinued on the day of surgery. The authors administered a dexmedetomidine infusion to improve their patient's symptoms after failure to manage pain with a hydromorphone PCA in the intensive care unit. The relapse rate was not reported.

Israel *et al.*[17] reported the case of a 37-yr-old female who presented for bilateral mastectomy and was transitioned from buprenorphine to a fentanyl patch three days preoperatively; this patient subsequently required up to 480 MEq·day$^{-,1}$ adjuncts, and an APS consultation. Dose and relapse rates were not reported.

Marcucci *et al.*[19] described the case of a patient with OUD who used illicitly obtained buprenorphine as part of a self-guided "crash detoxification program" three days before surgery to obliterate detectable cocaine levels in a urine test that was to be performed preoperatively. Buprenorphine was discontinued on the day of surgery and pain levels were poorly controlled. The dose was only reported as one tablet q4h and the relapse rate was not reported.

Rodgman and Pletsch[22] reported the case of a 29-yr-old heart transplant patient (24 mg buprenorphine SL daily) who had their buprenorphine stopped in the preoperative setting; this patient required 90 MEq·day^{-1} and had high pain scores on re-induction of buprenorphine. The relapse rate was not reported.

Buprenorphine change or pain levels not reported

Hassamal *et al.*[24] included a case of a 25-yr-old woman who underwent a tricuspid and aortic valve repair. She was taking 12 mg buprenorphine by an unreported route daily

for CP. Buprenorphine was discontinued and restarted but the authors failed to report the timing of these changes, whether the discontinuation was preoperative or postoperative. Nevertheless, this was the only study to properly report the relapse rate with the patient remaining abstinent at a six-month follow-up.

Khelemsky *et al.*[20] did not report pain levels in their case of a 44-yr-old woman who underwent two procedures. She was continued on 24 mg buprenorphine SL daily for an anterior cervical corpectomy but had her buprenorphine discontinued for an anterior cervical fusion four days later. The authors reported increased movement during surgery and higher anesthetic requirements when the buprenorphine was continued. Relapse rates were not reported. In a retrospective cohort study, Gupta[26] compared vaginal and Cesarean deliveries. Daily peri-partum rescue analgesics in buprenorphine continued patients did not change with peri-partum neuraxial intervention. This study was underpowered to assess this outcome, lacking a control group and not reporting pain levels, rate of relapse, or indication of buprenorphine.

Discussion

The quality of evidence regarding perioperative management of patients on buprenorphine is weak. The number of studies is limited, and few directly evaluate the question of continuation versus discontinuation of buprenorphine. Among the studies that address this question, controls are scant with none being randomized. Of the observational studies (matched cohort, prospective cohort, retrospective cohort) that included patients on buprenorphine as part of their outcomes, four met our inclusion criteria and only two studied the effects of buprenorphine as a main outcome. The only CS combined patients taking buprenorphine and methadone into one group. This limits this study's applicability to this systematic review to the level of an observation study as the lack of differentiation between methadone and buprenorphine makes the controlled randomization ineffectual. Thirteen CRs and a case series were identified. Many of these publications reported variables such as pain levels, buprenorphine dose, and perioperative buprenorphine continuation. Only three studies—all CRs—included relapse rates with one extending beyond the three-week time point.

There is insufficient evidence to support the decision to discontinue buprenorphine perioperatively. The main impetus for discontinuation, i.e., inadequate pain management, may be based on expert opinion and not on the existing evidence, as other authors have noted.[19,20] The evidence does support the receptor occupancy theory described by Volpe *et al.*,[31] which suggests near-maximal receptor occupancy at buprenorphine (SL) doses of 16 mg daily. Interestingly, in CRs with complete reporting (eight articles, 16 cases in total), every patient whose buprenorphine was discontinued and experienced poorly controlled pain was taking 16 mg SL daily or greater preoperatively.[16,22,25] In fact, pain was successfully controlled in all but one of the patients taking 16 mg buprenorphine SL daily or greater who continued buprenorphine.[13-16,18,23] Clinically correlated pharmacokinetic studies are required to confirm this cut-off, especially in the context of high inter-patient variability.

The existing evidence does suggest that the traditionally conservative approach of discontinuing and reducing opioids perioperatively may not be the most effective way to manage this complex patient population. Some evidence suggests that continuation with supplemental doses may offer the most effective analgesia while maintaining opioid-replacement therapy.[14,15,23] Silva and Rubinstein directly address this theory with their observation that pain control was "easier to achieve" with greater functional recovery when buprenorphine was "continued throughout the perioperative period".[15]

In addition to problematic pain management, discontinuation may hinder harm reduction with respect to addiction. Some expert opinions suggest improved treatment retention and lower misuse rates with discontinuation but do not acknowledge the greater risk of destabilizing a pre-existing CP condition or OUD when opioid-replacement therapy is stopped. According to the reviewed literature, there is no evidence to suggest that discontinuation of buprenorphine is the preferred method of preventing OUD relapse. Relapse rates are poorly defined in the reviewed literature, a surprising result given the importance of addiction management in this population. Also concerning is the lack of reporting the indication for buprenorphine use. The majority of reviewed studies report CP as the main indication *vs* OUD (ten *vs* five). This failure to report the indication for buprenorphine therapy in the existing literature may reflect the lack of awareness surrounding addiction therapy among perioperative physicians. If patient well-being beyond the operative room is to be factored into the decision-making process, current guidelines seem insufficient in addressing this matter.

Existing guidelines are largely driven by expert opinion with little reference to peer-reviewed primary evidence (Table 3). Potential weaknesses in the existing guidelines include the recommendation to transition patients to short-acting opioids before surgery.[32] Evidence to the contrary shows lower relapse rates in the OUD patient population that are maintained on buprenorphine.[9] Other guidelines

Table 3 Summary of major existing guidelines for perioperative management of buprenorphine

Title	Date	Major perioperative recommendations
Anderson *et al.*[1]	2017	1. Where moderate to severe pain is expected, cancel surgery such that buprenorphine is weaned off before surgery and short-acting opioids are used to replace it
		2. A plan for follow-up and reinstitution of therapy should be established
		3. Anticipate patient's opioids requirements will be similar to an opioid-tolerant patient
		4. Consider adjuncts - NSAIDs, membrane stabilizers, acetaminophen, local anesthetics, regional anesthetic techniques
		5. Ensure appropriate outpatient follow-up with buprenorphine provider
Sen *et al.*[8]	2016	1. Discontinue buprenorphine 72 hr before operative procedure, or replace buprenorphine with methadone
		2. Expect additional opioid doses for acute pain control
		3. Discharge on pure opioid induction protocol of buprenorphine in conjunction with primary provider
Jonan *et al.*[3]	2018	1. Utilize non-opioid adjuncts, regional anesthesia, and local anesthetic infiltration by surgeon where possible.
		2. Where low post operative pain is expected, continue buprenorphine perioperatively without taper
		3. Where intermediate pain is expected, discontinue buprenorphine 3 days prior to procedure, consider high dose PCA, and consider ICU admission for respiratory monitoring
		4. Where High pain is expected, discontinue buprenorphine 3-5 days prior to procedure, consider pure opioid agonist to manage withdrawal, and consider ICU for respiratory monitoring
Childers and Arnold[9]	2012	1. Adjuvant analgesics and interventional procedures should be provided if available
		2. Hold buprenorphine and start short acting opioid agonists if expecting moderate to severe pain
		3. Re-initiate buprenorphine in the postoperative period with the buprenorphine provider
		4. Where mild to moderate pain is expected, consider treating pain with buprenorphine alone, or use short-acting opioid agonists at higher doses
		5. Consider replacing buprenorphine with methadone for opioid addiction where ongoing pain management is expected
Bryson[10]	2014	1. Ideally, buprenorphine should be discontinued 72 hr before surgery, then restarted once patient no longer has acute pain requiring narcotic analgesics
		2. If the plan is to continue buprenorphine, use short-acting opioid analgesics to achieve pain control, expecting higher than normal effective doses. Divide buprenorphine maintenance dose and administer every 6-8 hr
		3. If the plan is to stop the buprenorphine, use standard opioids for analgesia, conduct a slow taper over 2 weeks or an abrupt taper over 3 days, remaining buprenorphine free for 72 hr before surgery
		4. If the relapse rate is too high, replace maintenance dose of buprenorphine with methadone before surgery, and use another short-acting opioid and analgesic for breakthrough pain
Berry *et al.* (Vermont Guidelines)[11]	2015	1. Reduce buprenorphine dose to 8 mg SL on the day of surgery
		2. Use oxycodone or other full agonists to make up opiate debt + typical post operative course management
		3. Expect longer than normal pain management regimen in the postoperative period
		4. Buprenorphine doses above 10 mg daily will block opioid analgesics for pain
Lembke *et al.* (Editorial)[33]	2018	1. Continue buprenorphine in the perioperative period for patients taking 12 mg SL or less
		2. Taper buprenorphine to 12 mg SL 2-3 days preoperatively
		3. Multimodal analgesia, Regional techniques where possible
		4. Higher than normal doses of opioids to treat pain for 2-4 days postoperatively

ICU = intensive care unit; NSAIDs = non-steroidal anti-inflammatory drugs; PCA = patient-controlled analgesia; SL = sublingually

disagree with this practice and do not recommend replacing buprenorphine with full mu agonists in the perioperative period.[10] Lembke *et al*. most recently editorialized their support of perioperative buprenorphine continuation with evidence from CRs and series.[33]

Other flaws in the existing guidelines include recommendations to prescribe full mu agonists at discharge for patients who had their buprenorphine discontinued.[32] Some authors point to "opioid debt" i.e., (an insufficient opioid dose) as a potential complicating factor of this strategy.[30] A CR by Rodgman and Pletsch indicate poor outcomes with this strategy[22] with another by Khelemsky *et al.* reporting severe opioid withdrawal, apparently the most cited

Table 4 Potential risk factors for opioid use disorder exacerbation in the perioperative setting

Risk factor for OUD exacerbation*
Discontinuation of buprenorphine prior to surgery
Introduction of a full mu agonist in place of buprenorphine prior to surgery
Duration of buprenorphine therapy for OUD < 20 months
Positive urine drug screen in the last 20 months
Post-surgical discharge without maintenance of some buprenorphine dose
Insufficient and/or delayed perioperative communication with outpatient buprenorphine provider

*Note: These risk factors have not been validated and are suggested risk factors based on the literature review herein. OUD = opioid use disorder

reason patients have OUD relapse while on opioid-replacement therapy.[20]

Overall, the current evidence to continue or discontinue buprenorphine perioperatively is limited. This gap in the literature represents an important area of research for those hoping to understand and appropriately manage the iatrogenic causes of the current opioid crisis. To better manage these patients, physicians caring for patients on buprenorphine in the perioperative setting need to incorporate harm reduction into their goals and decisions. In every case, connecting with outpatient primary care physicians and addiction specialists during the preoperative period is advised to ensure proper follow-up for these patients. During preoperative assessment, attention should be paid to each patient's buprenorphine dose, indication, and risk for relapse (Table 4). There is a paucity of circumstances where the benefits of buprenorphine discontinuation (which could lead to relapse) outweigh the risks of continuation. Discontinuation is not benign and may impact relapse and result in poor acute pain management. The authors herein reinforce perioperative continuation of buprenorphine to be safe.

Conflicts of interest Joel Bordman declares a conflict of interest with Purdue, Indivior, and Paladin Labs.

Editorial responsibility This submission was handled by Dr. Gregory L. Bryson, Deputy Editor-in-Chief, *Canadian Journal of Anesthesia.*

Author contributions *Akash Goel*, *Saam Azargive, Marina Englisakis*, and *Hance Clarke* formulated and devised the systematic review protocol. *Akash Goel*, *Saam Azargive*, *John Hanlon*, *Harsha Shanthanna*, *Karim Ladha*, and *Wiplove Lamba* assisted in writing the manuscript. *Joel Bordman*, *Sanjho Srikandarajah*, *Scott Duggan*, *Tania Di Renna,* and *Philip Peng* assisted in reviewing and editing the manuscript.

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Appendix 1

Medline - Search strategy summarized in PRISMA diagram outlined in the Figure

Ovid MEDLINE(R) <1946 to June Week 1 2017>

#	Searches	Results
1	exp Surgical Procedures, Operative/	2827360
2	exp Specialties, Surgical/	186108
3	exp Surgeons/	3869
4	su.fs. ["Surgery" floating subheading]	1808252
5	exp Anesthesia Recovery Period/	4869
6	exp Perioperative care/	138411
7	exp Intraoperative care/	15674
8	exp Postoperative care/	56528
9	exp Preoperative care/	64754
10	exp Perioperative Period/	71533
11	exp Perioperative Nursing/	13243
12	(before adj2 operat????).mp,kw.	14163
13	(before adj2 surgery).mp,kw.	34665
14	(before adj3 procedur*).mp,kw.	8132
15	(prior adj2 operat????).mp,kw.	2055
16	(prior adj2 surgery).mp,kw.	12106
17	(prior adj3 procedur*).mp,kw.	3182
18	(surgery or surgeries or surgeon? or surgical*).mp,kw.	1742136
19	intraop*.mp,kw.	142094
20	intra-op*.mp,kw.	10610
21	operation?.mp,kw.	344725
22	operative*.mp,kw.	272481
23	perioperat*.mp,kw.	75999
24	peri-operat*.mp,kw.	5031
25	periprocedur*.mp,kw.	3579
26	peri-procedur*.mp,kw.	684
27	peroperat*.mp,kw.	4405
28	peroperat*.mp,kw.	4405

Appendix continued

#	Searches	Results
29	post-intervention*.mp,kw.	7868
30	postop*.mp,kw.	692328
31	post-op*.mp,kw.	53969
32	postproced*.mp,kw.	5082
33	post-proced*.mp,kw.	3807
34	preintervention*.mp,kw.	2525
35	pre-intervention*.mp,kw.	2520
36	preop*.mp,kw.	261461
37	pre-op*.mp,kw.	24563
38	preprocedur*.mp,kw.	2495
39	pre-procedur*.mp,kw.	1317
40	reoperat*.mp,kw.	92806
41	re-operat*.mp,kw.	4296
42	Re-resect*.mp,kw.	513
43	Resect*.mp,kw.	267828
44	or/1-43 [Surgery or Periop or Preop or Postop]	4145213
45	exp Buprenorphine/	4603
46	Buprenorphine, Naloxone Drug Combination/	197
47	40D3SCR4GZ.mp,kw,rn.	4556
48	52485-79-7.mp,kw,rn.	0
49	53152-21-9.mp,kw,rn.	0
50	"6029 m".mp,kw.	0
51	6029m.mp,kw.	0
52	Addnok??.mp,kw.	2
53	anorfin??.mp,kw.	0
54	Belbuca??.mp,kw.	2
55	bunavail??.mp,kw.	3
56	Buprel??.mp,kw.	0
57	Buprenex??.mp,kw.	4
58	Buprenexreg??.mp,kw.	0
59	Buprenophine??.mp,kw.	12
60	Buprenorfina??.mp,kw.	83
61	buprenorfine??.mp,kw.	4
62	buprenorphine??.mp,kw.	5637
63	Buprenorphinum??.mp,kw.	0
64	Buprigesic??.mp,kw.	0
65	buprine??.mp,kw.	0
66	Butrans??.mp,kw.	14
67	"cl 112,302".mp,kw.	0
68	"cl 112302".mp,kw.	0
69	"cl112,302".mp,kw.	0
70	"cl112302".mp,kw.	0
71	finibron??.mp,kw.	0
72	lepetan??.mp,kw.	1
73	Morgesic??.mp,kw.	0

Appendix continued

#	Searches	Results
74	"nih 8805".mp,kw.	0
75	"nih8805".mp,kw.	0
76	Norphin??.mp,kw.	4
77	Norspan??.mp,kw.	4
78	pentorel??.mp,kw.	0
79	prefin??.mp,kw.	63
80	Probuphenine??.mp,kw.	0
81	Probuphine??.mp,kw.	2
82	"rx 6029 m".mp,kw.	0
83	"rx 6029m".mp,kw.	0
84	rx6029m.mp,kw.	0
85	Suboxone??.mp,kw.	95
86	Subutex??.mp,kw.	94
87	Temgesic??.mp,kw.	53
88	Temgesicreg??.mp,kw.	0
89	Tidigesic??.mp,kw.	1
90	transtec??.mp,kw.	16
91	"um 952".mp,kw.	0
92	"um952".mp,kw.	0
93	zubsolv??.mp,kw.	10
94	or/45-93 [Buprenorphine]	5721
95	44 and 94 [(Surgery or Periop or Preop or Postop) + Buprenorphine]	1045
96	Drug Users/	2194
97	substance-related disorders/ or drug overdose/ or opioid-related disorders/ or heroin dependence/ or morphine dependence/ or substance abuse, intravenous/ or substance withdrawal syndrome/	141497
98	Opiate Substitution Treatment/	1928
99	(substance? adj6 abus*).mp,kw.	48370
100	(substance? adj6 depend*).mp,kw.	6284
101	(substance? adj6 disorder*).mp,kw.	95908
102	(drug? adj2 abus*).mp,kw.	25130
103	(drug? adj2 addict*).mp,kw.	11699
104	(drug? adj4 depen*).mp,kw.	17296
105	(drug? adj2 user?).mp,kw.	15942
106	((drug? or opiate? or substance?) and (maintenance adj2 therap*)).mp,kw.	5805
107	addict*.mp,kw.	50405
108	or/96-107 [Drug use]	215876
109	95 and 108 [(Surgery or Periop or Preop or Postop) + Buprenorphine + Drug Use]	88
110	Chronic Pain/ [MeSH term since 2012]	8587
111	Causalgia/	675
112	exp Arthralgia/	10747
113	exp Back Pain/	34326

Appendix continued

#	Searches	Results
114	exp Central Nervous System/ and exp *"Wounds and Injuries"/	32795
115	exp Central Nervous System/ and exp Pain/	21998
116	exp Central Nervous System/in [Injuries]	8740
117	exp Chronic Illness/ and exp Pain/ [Historical search for chronic pain]	21638
118	exp Complex Regional Pain Syndromes/	5234
119	exp Diabetic Neuropathies/	20227
120	exp Headache Disorders/	32459
121	exp Herpes Zoster/	10995
122	exp Hyperalgesia/	9726
123	exp Mononeuropathies/	18221
124	exp Nerve Compression Syndromes/	20588
125	exp Neuralgia/	17341
126	exp Neurons, Afferent/	128029
127	exp Nociceptors/	10771
128	exp Pain/ and exp Chronic Diseases/ [Historical]	21638
129	exp Palliative Care/	49314
130	exp Pelvic Pain/	8060
131	exp Peripheral Nervous System/ and exp *"Wounds and Injuries"/	17814
132	exp Peripheral Nervous System/ and exp Pain/	22279
133	exp Peripheral Nervous System/in [Injuries]	12807
134	exp Polyneuropathies/	25087
135	Glossalgia/	284
136	Mastodynia/	123
137	Metatarsalgia/	227
138	Piriformis Muscle Syndrome/	87
139	Reflex Sympathetic Dystrophy/	3554
140	(afferent adj2 neuron?).mp,kw.	25756
141	(back? adj2 pain*).mp,kw.	46810
142	(chronic* adj2 headache?).mp,kw.	3282
143	(chronic* adj2 head-ache?).mp,kw.	1
144	(chronic* adj2 migrain*).mp,kw.	1581
145	(chronic* adj3 pain*).mp,kw.	46218
146	(deafferentation adj2 pain*).mp,kw.	289
147	(deafferentation adj2 pain*).mp,kw.	289
148	(dysa?sthetic adj2 pain*).mp,kw.	7
149	(maladapt* adj2 pain*).mp,kw.	84
150	(mal-adapt* adj2 pain*).mp,kw.	1
151	(mononeurit* adj1 multiple*).mp,kw.	579
152	(mono-neurit* adj1 multiple*).mp,kw.	1
153	(nerve? adj12 pals???).mp,kw.	12610
154	(nerve? adj2 damag*).mp,kw.	6059
155	(nerve? adj2 injur*).mp,kw.	27230
156	(nerve? adj2 injur*).mp,kw.	27230
157	(nerve? adj2 sensitiv*).mp,kw.	1127

Appendix continued

#	Searches	Results
158	(nerve? adj3 entrap*).mp,kw.	1817
159	(neural adj2 damag*).mp,kw.	1394
160	(neural adj2 injur*).mp,kw.	1331
161	(neural adj3 entrap*).mp,kw.	33
162	(neural adj3 sensitiv*).mp,kw.	816
163	(neuro* adj2 pain*).mp,kw.	19143
164	(neuro* adj2 pain*).mp,kw.	19143
165	(neuro* adj2 sensitiv*).mp,kw.	6431
166	(neuropath* adj2 pain*).mp,kw.	15053
167	(pain adj2 low?? adj2 back?).mp,kw.	26427
168	(pain adj5 multiple scleros*).mp,kw.	602
169	(pain or pains or pained or painful*).mp,kw.	565431
170	(pain* adj3 syndrom*).mp,kw.	17158
171	(pelvic adj5 pain*).mp,kw.	9711
172	(peripheral* adj1 mononeurit*).mp,kw.	6
173	(peripheral* adj1 mono-neurit*).mp,kw.	0
174	(peripheral* adj1 neurit*).mp,kw.	249
175	(peripheral* adj1 polyneurit*).mp,kw.	47
176	(peripheral* adj1 poly-neurit*).mp,kw.	0
177	allodynia*.mp,kw.	6309
178	arthralgi*.mp,kw.	12413
179	causalgi*.mp,kw.	912
180	cephalalgi*.mp,kw.	678
181	cephalgi*.mp,kw.	340
182	chronic noncancer* pain?.mp,kw.	441
183	chronic non-cancer* pain?.mp,kw.	345
184	chronic nonmalignan* pain?.mp,kw.	323
185	chronic non-malignan* pain?.mp,kw.	214
186	colic.mp,kw.	9145
187	dysaesthesi*.mp,kw.	338
188	dysesthesi*.mp,kw.	1631
189	dysmenorrhea*.mp,kw.	5161
190	dysmenorrhoea*.mp,kw.	931
191	earache?.mp,kw.	986
192	ear-ache?.mp,kw.	32
193	failed back?.mp,kw.	792
194	glossalgi*.mp,kw.	287
195	Herpes Zoster.mp,kw.	12722
196	hyper?esthesi*.mp,kw.	1448
197	hyperalges*.mp,kw.	14671
198	hyperpathi*.mp,kw.	166
199	hypo?esthesi*.mp,kw.	1137
200	mastodyni*.mp,kw.	297
201	metatarsalgi*.mp,kw.	732
202	migrain*.mp,kw.	33170
203	mononeuropath???.mp,kw.	1619

Appendix continued

#	Searches	Results
204	mono-neuropath???.mp,kw.	12
205	neuralgi*.mp,kw.	21859
206	neuropath*.mp,kw.	113404
207	neuropathic.mp,kw.	19908
208	neuropathies.mp,kw.	26655
209	neuropathy.mp,kw.	57981
210	nocicept*.mp,kw.	32775
211	palliat*.mp,kw.	77021
212	paraesthesi*.mp,kw.	1637
213	paresthesi*.mp,kw.	10193
214	phantom limb?.mp,kw.	1997
215	piriformis muscle syndrome?.mp,kw.	109
216	polyneuropath???.mp,kw.	14355
217	poly-neuropath???.mp,kw.	16
218	reflex sympathetic dystroph*.mp,kw.	3980
219	sciatic??.mp,kw.	31919
220	shingles.mp,kw.	994
221	somatosensory.mp,kw.	34204
222	toothache?.mp,kw.	3120
223	tooth-ache?.mp,kw.	30
224	or/110-223 [Chronic Pain Hedge - updated June 13 2017]	1076164
225	95 and 224 [(Surgery or Periop or Preop or Postop) + Buprenorphine + Chronic Pain]	701
226	109 or 225 [(Surgery or Periop or Preop or Postop) + Buprenorphine + (Drug Use or Chronic Pain)]	741
227	exp animals/ not (exp animals/ and humans/)	4413504
228	226 not 227	547
229	limit 226 to human	546
230	228 or 229	547
231	remove duplicates from 230	532

Appendix 2

Systematic review of preoperative use of buprenorphine in human participants

Data collection form

1. **Reference Manager ID**

2. **Journal**

3. **Year of publication**

4. **First author**

5. **Country**

6. **Single or multi-centre**
Mark only one oval.

- ◯ Single-centre
- ◯ Multi-centre

7. **Report classification**
Mark only one oval.

- ◯ Case report/series
- ◯ Observational (case control/cohort)
- ◯ RCT

8. **Ethics board approval**
Mark only one oval.

- ◯ Yes
- ◯ No
- ◯ Not stated

9. **Sample size calculation provided (mark one oval only)**

- ◯ Provided
- ◯ Not provided
- ◯ Not stated

Part 2: Study assessment (for all study types)

10. **Number of patients**

11. **Buprenorphine intention**
Check all that apply.

- ☐ Postoperative analgesia
- ☐ Intraoperative analgesia
- ☐ Chronic pain
- ☐ Addiction/maintenance

12. **Formulation**
Check all that apply.

- ☐ Sublingual
- ☐ Patch
- ☐ Other:

13. **Rate/dosing regimen (preoperative)**

14. **Remarks (re: rate/dosing, if necessary)**

15. **Type of surgical intervention (list)**

16. Outcome of surgery

- Successful management
- Highlighting a complication

17. **Technique**
Mark only one oval.

- Buprenorphine maintained *Skip to question 21.*
- Buprenorphine tapered *Skip to question 18.*
- Buprenorphine stopped *Skip to question 20.*

Skip to question 21.

Part 2: Continued (buprenorphine tapered)

18. **Rationale**

19. **Type of taper**
Mark only one oval.

- Rapid taper preoperatively
- Slow taper preoperatively

Skip to question 21.

Part 2: Continued (buprenorphine stopped)

20. **Time of stop**
Mark only one oval.

- Stopped preoperatively
- Stopped postoperatively

Skip to question 21.

Part 3A: Observational/RCT study assessment
Leave empty if case report/series

21. **Comparator (placebo, etc.)**

22. **Outcome (quantitative)**

23. **Time of outcome measurement**

Part 3B: RCT study risk of bias assessment
Leave empty if case report/series or observational

24. **Randomized**
Mark only one oval.

- Yes
- No
- Not stated

25. **Method of randomization**

26. **Blinding**
Mark only one oval per row.

	Yes	No	Not stated
Patient			
Physician			
Assessor			
Data analyst			

27. **Allocation concealment**
Mark only one oval.

- Yes
- No
- Not stated

28. **Method of allocation concealment**

29. **Sequence generation**
Mark only one oval.

- Yes
- No
- Not stated

30. **Method of sequence generation**

31. **Loss to follow-up or incomplete outcome data**

- Yes (skip to question 32)
- No (skip to question 34)
- Not started (skip to question 34)

32. Were there measures to incorporate loss to follow-up or incomplete outcome data onto the analysis?

- Yes
- No
- Not started

RCT = randomized-controlled trial.

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