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Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Excessive prescribing after surgery has contributed to a public health crisis of opioid addiction and overdose. However, the value of prescribing opioids to manage postoperative pain after surgical discharge remains unclear. We propose a systematic review and meta-analysis to assess the extent to which opioid analgesia impact postoperative pain intensity and adverse events in comparison to opioid-free analgesia in patients discharged after surgery.

Methods and analysis

Major electronic databases (MEDLINE, EMBASE, Cochrane Library, Scopus, Amed, Biosis, CINAHL and PsycINFO) will be searched for multi-dose randomized trials examining the comparative-effectiveness of opioid versus opioid-free analgesia after surgical discharge. Studies published from January 1990 will be targeted, with no language restrictions. We will consider studies involving patients undergoing minor surgery (in-office procedures) and major surgery (operating room procedures). Teams of reviewers will, independently and in duplicate, assess study eligibility, extract data, and evaluate risk of bias. Our main outcomes of interest are pain intensity and postoperative vomiting (adverse event). Study results will be pooled using random-effects models. When trials report outcomes for a common domain (e.g. pain intensity) using different scales, we will convert effect sizes to a common standard metric (e.g. visual analog scale). Minimally important clinical differences reported in previous literature will be considered when interpreting results. Sub-group analyses defined *a priori* will be conducted to explore heterogeneity among the pooled effect estimates. Risk of bias will be assessed according to the Cochrane Collaboration's Risk of Bias Tool 2.0. The quality of evidence for all outcomes will be evaluated using the GRADE rating system.

Ethics and dissemination

Ethical approval is not required since this is a systematic review based on published studies. Our results will be published in a peer-reviewed journal and presented at relevant conferences.

Strengths and limitations of this study

- This will be the first systematic review to synthesise the evidence on the comparative-effectiveness of opioid vs. opioid-free analgesia after postoperative discharge.
- This review will address a major knowledge gap that hinders the use of evidence-based prescribing as a strategy to mitigate postoperative opioid-related harms.
- We will use robust statistical methods to meta-analyse data from RCTs, but these methods are not free from limitations when outcome reporting is heterogeneous.
- The quality and strength of evidence will be evaluated using the Cochrane Collaboration's Risk of Bias Tool 2.0 and the GRADE framework.

INTRODUCTION

North America is facing a devastating opioid crisis exacerbated by excessive prescribing.[1,2] Surgery often serves as a gateway for opioid-naïve patients to obtain an opioid prescription,[3] and spiral into misuse and addiction.[4-8] Reports from Canada and the United States suggest that 6-14% of patients who are prescribed opioids after surgical discharge become persistent opioid users, i.e. they continue to take the drug for more than three months after surgery.[5, 9-12] Interestingly, rates of persistent opioid use are similar among patients undergoing major,[5, 10, 11] and minor surgeries.[12] Patients who do not become persistent users postoperatively may also contribute to the opioid crisis by diverting unused tablets for nonmedical use by others - up to 70% of all opioid tablets prescribed to surgical patients go unused and may become a source for diversion.[13] Given these factors, recent literature suggests that postoperative opioid prescribing should be judicious and based on the best available evidence regarding benefits and harms.[14, 15]

Studies have shown that postoperative pain management using only non-opioid drugs is common internationally but not in Canada nor in the United States, where opioid tablets are often prescribed instead of, or in addition to, non-opioid analgesics.[16-20] In countries such as the Netherlands,[21] China,[22] and Chile,[23] reported rates of opioid prescribing after surgical discharge range from 0% to 5%, while in North America, 80% to 95% of patients receive an opioid prescription to manage postoperative pain at home.[16-20] A recent study indicates that surgical patients in Canada and the United States fill opioid prescriptions at a rate that is seven times higher than those in Sweden.[24] Remarkably, in countries where opioids are not a mainstay for postoperative analgesia, pain-related outcomes (i.e. satisfaction with pain management) after surgery are often superior to North America.[16-18] This may, in part, reflect a potential therapeutic superiority of non-opioid drugs or increased opioid-related adverse events such as postoperative vomiting. Although these findings bring

into question the value of prescribing opioids to manage acute pain after surgical discharge, the decision to prescribe opioids must be informed by robust systematic reviews and meta-analyses focused on the comparative-effectiveness of opioid versus opioid-free postoperative analgesia. These, however, are currently non-existent in the literature.[25]

We therefore propose to undertake a systematic review and meta-analysis to summarize the evidence regarding the comparative-effectiveness of opioid versus opioid-free analgesia after discharge following surgery. Our study will follow the principles of the PICO framework,[26] and aims to respond to the following research questions: (1) in patients discharged after surgery, to what extent does opioid analgesia impact postoperative pain intensity in comparison to opioid-free analgesia? And (2) in patients discharged after surgery, to what extent does opioid analgesia impact the risk of postoperative vomiting in comparison to opioid-free analgesia?

METHODS AND ANALYSIS

Design

This protocol was designed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.[27] A draft protocol was circulated among our knowledge synthesis team [composed of synthesis leaders (JF, GB, and LF), synthesis managers (CEK and UD), a patient partner (AD), and collaborators] and adjustments were made according to their feedback. Any future amendments to this protocol and corresponding rationale will be tracked and dated.

Literature search

A comprehensive search of major electronic databases [MEDLINE (via Ovid), EMBASE (via Ovid), The Cochrane Library (via Wiley), Scopus (via Elsevier), Amed (via Ovid), Biosis (via Clarivate), CINAHL (via Ebsco) and PsycINFO (via Ovid)] will be conducted to identify relevant

studies. The main strategy (MEDLINE) was developed by an experienced medical librarian and information specialist (TL) with input from the synthesis team (Supplement 1). Subsequently, a second medical librarian peer-reviewed this search strategy according to Peer Review of Electronic Search Strategies (PRESS) standards,[28] and changes were made as required. The vocabulary and syntax of the MEDLINE strategy was tailored to allow adaptation and optimal electronic searching of the other databases. Searches will be limited to articles published after 1990, as earlier publications do not reflect current standards of surgical care with the widespread use of minimally invasive surgery and perioperative care pathways.[29-32] No language limitation will be applied. A combined library of the retrieved articles will be created using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; https://www.covidence.org/).[33] Duplicates will be excluded. To ensure literature saturation, we will also search trial registries (ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform), conference proceedings (identified via Scopus, Embase, Biosis, and Cochrane Library), articles cited by the included articles (identified via Scopus) and articles that cited the included articles (identified via Scopus). Furthermore, we will contact authors to obtain aggregated data from trials that were completed but not published.

Eligibility criteria

We will include studies that: (1) are parallel RCTs, (2) enrolled youth and/or adults patients (>15 years old) undergoing minor or major surgeries according to the WHO definition,[34, 35] (Table 1), (3) compared a post-discharge analgesia regimen including opioids (analgesic drugs that act on opioid receptors, such as codeine, oxycodone, hydromorphone, tramadol, and morphine) versus an analgesia regimen including only non-opioid drugs (such as acetaminophen, NSAIDs, gabapentinoids) and (4) involved a multiple-dose design focused on the overall effect of repeated

doses of the prescribed analgesics. Our age cut-off was chosen based on data showing fast-growing rates of opioid poisoning in youth over 15 years old.[36, 37] Studies involving any non-invasive route of analgesic administration (i.e. oral, transmucosal, transdermal and rectal) will be considered for inclusion. Studies where opioids were offered to the opioid-free group as rescue analgesia for breakthrough pain (i.e. pain that erupts while a patient is already medicated) will be included only if the opioid drugs were not readily available to patients (i.e. a new prescription was required via contact with a healthcare provider). Studies where patients received opioids while in the hospital or clinic will be included if the post-discharge analgesia was according to our inclusion criteria.

We will exclude single-dose trials as they do not reflect 'real-world' practices where analgesia regimens span several days postoperatively.[38] Besides, postoperative analgesia trials with a single-dose design have been extensively systematically reviewed in previous literature.[38, 39] We will also exclude: (1) placebo-controlled trials where no active analgesic drugs are offered to patients (they do not reflect standard practice), (2) studies where the postoperative analgesia regimen is not clearly described (e.g. placebo-controlled trials with unclear description of analgesics given in addition to placebo), (3) studies exclusively focused on children (≤15 years old), (4) studies with analgesic administration via invasive routes such as intravenous or epidural (rarely used after surgical discharge), and (5) studies evaluating analgesia for chronic postoperative pain (treatment starting beyond 2 months after surgery).[40]

Selection of studies

The titles/abstracts of the articles identified by our search strategy will be evaluated against the review's eligibility criteria by pairs of reviewers. Due to the anticipated large number of articles to be screened, eight reviewers (all with previous training in healthcare research) will be involved in the screening process. Screening will be conducted, independently and in duplicate, using the

Covidence software.[33] Two lead reviewers (JF and CEK) will pilot-test the eligibility criteria on the first 100 titles and abstracts identified by the search. To harmonize the rest of the screening process, reviewers will attend a training session and conduct a pilot screening of at least 20 titles/abstracts to prompt clarifications. A screening decision table was created to guide decision-making (Supplement 2). To ensure accuracy, all titles/abstracts will be screened by at least one lead member of the synthesis team (JF or CEK). Disagreements regarding eligibility will be resolved by consensus between the reviewers or by consulting an adjudicator (LF).

Articles that are clearly irrelevant will be excluded after examination of titles and abstracts; those that are potentially eligible will have their full-text versions retrieved and evaluated against the eligibility criteria. Publications in non-English language will be translated into English by an ISO certified translation company. Full-text screening will be conducted by two lead members of the synthesis team (JF and CEK) using the Covidence platform.[33] The extent of agreement between reviewers during full-text screening will be assessed using Kappa statistics (thresholds: <0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement and >0.80 almost perfect agreement).[41] Disagreements will be resolved by consensus or by consulting an adjudicator (LF).

Outcome measures

The primary outcome of interest in this review will be patient self-reported outcomes focused on postoperative pain intensity (i.e. self-perceived magnitude of pain at a given time postoperatively). The secondary *a priori* outcome of interest will be the risk of postoperative vomiting. These outcomes were chosen based on previous literature that showed good pain relief to be the most desirable outcome in perioperative care according to patient preference, while postoperative vomiting is the least desirable outcome.[42-44] If data are available in the eligible studies, we will

also explore the association of the interventions with other endpoints included in core outcome sets for research in perioperative care.[45, 46] These include: (1) drug adverse events (other than vomiting), (2) patient satisfaction with pain management, (3) participant disposition (i.e. withdrawal due to adverse events or ineffective treatment) (4) self-reported postoperative health status [overall and domain-based scores, i.e. vitality (i.e. fatigue), physical function, emotional function, social function, role function (i.e. work or other daily activities), sleep function], (5) emergency room visits and (6) hospital readmissions.

Data charting

A customized data extraction form was collectively developed by the synthesis team (Supplement 3). This form will be pilot tested by two independent reviewers (JF and CEK). Subsequently, a team meeting will take place to discuss potential issues and refine the form. Finally, the refined data extraction form will be integrated into the Covidence software.[33] Data extraction will be conducted, independently and in duplicate, by pairs of reviewers. The following data will be extracted from each study: author, publication date, study location, number of participating centres, funding source, inclusion and exclusion criteria, sample size (patients randomized and patients analysed in each group), patient characteristics (age, sex, clinical condition, type of surgery and proportion receiving preoperative opioids, if available), surgery classification (major vs. minor), type of anaesthesia, in-hospital analgesia interventions (if applicable), hospital length of stay (if applicable), characteristics of the post-discharge analgesia intervention [drugs, dosage (in morphine equivalents for opioids,[47]), frequency of administration and duration], outcome measures assessed, time points of assessment and duration of follow-up.

The number of reviewers involved in data extraction will depend on the number of RCTs fulfilling our eligibility criteria. To harmonize data extraction, reviewers will attend a training session,

conduct at least 2 pilot extractions, and receive a written 'data extraction guide' with detailed instructions. To ensure accuracy, at least one lead member of the synthesis team (JF or CEK) will extract data from each article. Data extracted in duplicate will be cross-checked by an independent third reviewer. Discrepancies in the extracted data will be resolved by consensus between the reviewers after revisiting the full-text article. If discrepancies remain, an adjudicator will be consulted (LF).

As this meta-analysis is focused on acute pain management after surgery, we will target outcome data collected up to 30 days postoperatively (from the day when the trial analgesia regimens were prescribed). Data regarding pain intensity (primary outcome) will be assessed as described in Table 2. Postoperative vomiting (secondary outcome) will be assessed as a dichotomous measure (presence of vomiting: yes/no). The assessment of other outcomes will be exploratory and will depend on whether data is available and how they are reported.

Methodological quality of individual studies

Risk of bias will be assessed independently and in duplicate by two lead members of the synthesis team (JF and CEK) using the Cochrane Collaboration's Risk of Bias Tool 2.0 for randomized trials (RoB 2.0).[48] Assessments will be conducted using an iterative form available online (www.riskofbias.info/). The RoB 2.0 appraises risk of bias across five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. The domain concerning missing outcome data will be assessed according to Akl,[49] and Ebrahim.[50] For each domain, risk of bias will be judged as 'low risk', 'some concerns', or 'high risk'. Studies are considered to have an overall 'high risk of bias' if at least one

domain is judged as 'high risk'. Disagreements regarding risk of bias will be resolved by consensus or by consulting an adjudicator (LF).

Quality of evidence (i.e. confidence in the effect estimates) will be assessed using the GRADE rating system.[51] Assessment will be conducted on an outcome-by-outcome basis by two lead members of the synthesis team (JF and CEK) working independently.[52] Specific guidelines will be followed to improve reliability.[53-74] Disagreements will be resolved by consensus or by consulting an adjudicator (LF). In the GRADE system, RCTs are initially rated as 'high confidence' evidence but may be rated down by one or more of five categories of limitations: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias.[51] After considering these categories, the confidence in estimates for each outcome will be categorized according to Table 3. Publication bias will be formally assessed by visual assessment of funnel plot asymmetry,[75] and by Begg's test,[76] when there are at least 10 studies available for meta-analysis. The final results will be summarized in an evidence profile.[51]

Data synthesis

For data synthesis, we will primarily assess the treatment effects of opioid versus opioid-free analgesia across all surgical procedures that are eligible for this review; however, we will also explore potential sources of heterogeneity between trials by assessing treatment effects across specific surgical contexts. Meta-analyses will be conducted using random-effects models, which are conservative in considering that the 'true' effect of an intervention may vary across different trials.[77] Weighted mean differences (WMDs) and 95% confidence intervals (95%CIs) will be calculated for pain intensity data reported by more than one RCT. The principle of 'weighting' by the inverse of the variance aims to attribute more weight to studies that provide more information about the treatment effect.[78] Methods described in the Cochrane Handbook will be used to

estimate the mean and standard deviation (SD) when median, range and sample size are reported, and to impute the SD if the standard error (SE) or SD for the differences are not reported.[79] Relative risks (RRs) with associated 95% CIs will be calculated for dichotomous data reported by more than one RCT (i.e. secondary outcome: vomiting). Analyses will follow the Hartung-Knapp-Sidik-Jonkman method as evidence supports that this approach outperforms traditional random-effects methods such as DerSimonian-Laird (known to lead to high type I error rates when the number of studies is small and there is moderate or substantial heterogeneity).[80] All analyses will be conducted using Stata statistical software version (Version 15.1, StataCorp, College Station, Texas, USA). Comparisons will be 2-tailed and use a threshold $p \leq 0.05$.

Interpreting effect estimates for pain intensity is challenging as this outcome can be assessed using different scales [e.g. visual analog scale (VAS), numerical rating scale (NRS), SF-36 bodily pain scale, or other scales]. To address this issue, we will follow specific guidelines to standardize this outcome into a standard metric.[81-83] We chose the 10cm Pain Intensity VAS (score range 0-10 cm; lower score represents less pain) as this is the pain intensity scale most commonly used in acute pain trials.[84-86] The process of standardization is described in Table 4. Once the WMD between opioid versus opioid-free analgesia is calculated for a given outcome, we will contextualize this value in relation to the corresponding minimally important difference (MID): the smallest change in score that patients perceive as important.[87] Reported MID in VAS pain scores for surgical patients, according to anchor-based methods, is 1/10cm.[88] As recommended by the OMERACT initiative,[81] we will use pain intensity WMD and MID data to determine the strength of the intervention effect, as described in Table 5.

When assessing pain intensity data, to further optimize the interpretation of meta-analyses results, we will also calculate the proportion of patients who reported adequate pain control (no more than

mild pain, as determined by a pain score <3/10cm VAS).[88, 89] By assuming a normal distribution of postoperative pain scores in both groups, differences in risk of reporting adequate pain control will be derived with its associated 95% CIs.[81-83]

If we identify more than one trial measuring the exploratory outcomes of interest in this knowledge synthesis (e.g. patient satisfaction, self-reported postoperative health status, readmissions), data will be meta-analysed and reported as WMDs (continuous measures) or RRs (dichotomous measures), as appropriate. Where relevant, outcome data using different metrics will be converted into a standard metric according to guideline recommendations.[81-83] Focused literature searches will be conducted to identify anchor-based MIDs.[87]

Heterogeneity between the RCTs included in the meta-analyses will be assessed using the χ^2 test and the I^2 test.[90] To explore potential sources of heterogeneity, we will test the *a priori* hypothesis that opioid analgesia has a larger effect in trials where patients are expected to feel more pain, such as those involving: (1) major surgery versus minor surgery,[5] (2) day surgery (i.e. with same-day discharge) versus in-patient surgery (i.e. at least one overnight stay in the hospital),[25] and (3) only women as participants [those reporting sex-specific data or involving sex-specific surgeries (e.g. gynaecological, breast)] versus men.[91-93] We also hypothesize that (4) trials with high risk of bias (versus lower risk of bias) will report larger effect sizes.[94, 95] Other clustering strategies for subgroup analyses [e.g. by surgical specialty (e.g. dental surgery, orthopaedic surgery), specific types of surgery (e.g. cholecystectomy, molar excision)] will be decided based on the characteristics of the trials identified, in consultation with clinicians (i.e. knowledge users) who care for the relevant surgical populations. These post-hoc subgroup analyses will be planned after data extraction, but prior to analyses of results. All subgroup analyses will be conducted regardless

of heterogeneity estimates if there are at least two trials in each subgroup. Tests of interaction will be performed to establish if subgroups differed significantly from one another.[96]

SIGNIFICANCE

North America is currently facing a major public-health crisis of opioid abuse. Opioid-based postoperative pain management is recognized as one of the driving forces behind this crisis. Given how commonly postoperative overprescription contributes to misuse, diversion, addiction and death, there is an urgent need to address this element of the opioid crisis. Alternatives to opioids are often overlooked, while they should be incorporated as the foundation of postoperative pain management whenever possible. This may prevent more people from becoming addicted in the future (it is impossible to become addicted without exposure) and, also importantly, reduce diversion of unused prescriptions. Our systematic review will provide key information to guide clinical decision-making regarding analgesia prescription after surgery. This work has the potential to contribute practice-changing evidence to inform future guidelines aimed to improve analgesia prescribing and mitigate postoperative opioid-related harms.

ETHICS AND DISSEMINATION

The results of this study will be published in an international peer-reviewed journal and presented at relevant conferences. This review will inform future guidelines on postoperative analgesia prescription. Ethical approval is not required since this is a systematic review based on published studies.

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AUTHORS' CONTRIBUTIONS

CEK, GB, LF, and JF contributed to the conception and the design of the study. CEK and JF wrote the first draft of the protocol. CEK, GO, MAC, AK, PNP, FR, UD, AD, TL, AAZ, RA, MM, GB, LF, and JF revised the protocol critically for important intellectual content. JF is the guarantor of this review. All authors have read and approved the final version of the manuscript to be published.

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COMPETING INTERESTS

JF has received grants from Merck and personal fees for consulting from Shionogi. LSF has received grants from Merck and Johnson & Johnson.

TABLES

Table 1. Definition of surgery (minor and major) according to the World Health Organization (WHO)

Surgery	Any intervention involving the incision, excision, manipulation or suturing of tissue and requiring regional or general anesthesia or sedation.
Minor surgery	A surgical intervention occurring in a physician's office or clinic (e.g. tooth extraction, cataract surgery, skin tumor excision).
Major surgery	A surgical intervention occurring in a hospital operating theatre (e.g. cesarean section, appendectomy, open fracture repair).

Table 2. Primary outcome data (pain intensity)

Pain assessment time points	• Multi-dose analgesia trials often involve the assessment of pain intensity at different time-points after surgery. • We will focus on the following time points: Day 0 (6-12 hours after prescription), Day 1 (13-24 hours), Day 2 (25-48 hours), Day 3 (49-72 hours), Day 4-7 (3-168 hours), Day 8-30 (169 to 720 hours). • These time points were the most commonly reported in the eligible trials identified by our scoping review and preliminary MEDLINE search. • We will consider for analysis the last measure obtained within the timepoint interval (i.e. the measure closest to the interval upper bound)
The primary time point of interest	• Our primary time point of interest will be Day 1 (13-24 hours), as evidence suggests that this is the period after surgery when patients report most severe pain.
Other important considerations	• We will prioritize reports of dynamic pain (during movement) over pain at rest if both are reported. Dynamic pain is deemed more relevant to the process of postoperative recovery. • We will also prioritize reports of 'worst pain' over 'average pain'. The latter is highly influenced by variations in instructions (e.g. should periods without any pain accounted for when pain is 'averaged'?).

Table 3. GRADE certainty ratings

Certainty	Interpretation
Very low	The true effect is probably markedly different from the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
High	The authors have a lot of confidence that the true effect is similar to the estimated effect.

Adapted from https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/

Table 4. Process of standardization (rescaling) of pain intensity measures into a common metric.

Step 1	• Non-VAS pain intensity scales will be initially converted into standardized mean differences (SMD), by dividing the between-group differences in means (in each trial), by the pooled SD of the two groups. • The SMD expresses the intervention effect in SD units, rather than the original units of measurement.
Step 2	• Standardization will be done by multiplying the SMD by the SD of the VAS scale. • The SD used here will be the pooled SD obtained from the largest trial where pain intensity was assessed via VAS.
Step 3	• Standardized data (now presented as a VAS score) will be meta-analyzed with data from other trials (i.e. those that used VAS or had pain data converted into VAS) to calculate a pooled WMD in VAS scores.

Table 5. Interpretation of weighed mean differences (WMDs) in relation to minimal important differences (MIDs)

Very large effect (most patients are likely to benefit)	**WMD equal or above 2 MIDs** (WMD $\geq$ 2MIDs)
Large effect (many patients may benefit)	**WMD equal or above 1 MID, but below 2 MIDs** (1 MID $\leq$ WMD < 2 MIDs)
Moderate effect (some patients may benefit)	**WMD above 0.5 MID, but below 1 MID** (0.5 MID < WMD < 1 MIDs)
Small effect (most patients are unlikely to benefit)	**WMD equal or below 0.5 MID** (0.5 MID $\leq$ WMD < 1 MIDs)

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Supplementary Material

Table of Contents

Supplement 1. Medline search strategy

#	Searches
1	Pain, Postoperative/
2	Postoperative Care/
3	Postoperative Period/
4	((after or following) adj3 (procedur* or resect* or surg*)).tw,kf.
5	(post-operat* or postoperat* or post-surg* or postsurg*).tw,kf.
6	or/2-5
7	(analgaes* or analges* or pain).tw,hw,kf.
8	6 and 7
9	1 or 8
10	Acetaminophen/
11	exp Adrenal Cortex Hormones/
12	Amitriptyline/
13	exp Analgesics, Non-Narcotic/
14	Anesthesia, Local/
15	exp Anesthetics, Local/
16	exp Anticonvulsants/
17	exp Anti-Inflammatory Agents, Non-Steroidal/
18	Aspirin/
19	Baclofen/
20	Bupivacaine/
21	Carbamazepine/
22	Celecoxib/
23	Clonidine/
24	exp Cyclooxygenase 2 Inhibitors/
25	Desipramine/
26	Dexamethasone/
27	Dexmedetomidine/
28	Diclofenac/
29	Diflunisal/
30	Dipyrone/
31	Duloxetine Hydrochloride/
32	Fenoprofen/
33	Flurbiprofen/
34	Gabapentin/
35	gamma-Aminobutyric Acid/
36	Ibuprofen/
37	Indomethacin/
38	Ketamine/
39	Ketoprofen/
40	Ketorolac/
41	Ketorolac Tromethamine/
42	Lidocaine/

43	Mefenamic Acid/
44	Mepivacaine/
45	Methocarbamol/
46	Methylprednisolone/
47	Methylprednisolone Hemisuccinate/
48	Naproxen/
49	exp Neuromuscular Agents/
50	Nortriptyline/
51	Phenytoin/
52	Piroxicam/
53	Prednisolone/
54	Prednisone/
55	Pregabalin/
56	Prilocaine/
57	Procaine/
58	Triamcinolone/
59	Triamcinolone Acetonide/
60	Venlafaxine Hydrochloride/
61	(a-methapred or artisone or besonia or dopomedrol or esametone or firmacort or lemod or medesone or medixon or medlone or medrate or m-predrol or medrol or medrone or mesopren or metastab or methyleneprednisolone or methylprednisolon* or metilbetasone or metilprednisolon* or metrisone or metrocort or moderin or nipypan or noretona or predni-n or prednisolone or prednol or promacortine or reactonol or sieropresol or solomet or solumedrol or summicort or suprametil or urbason* or wyacort).mp.
62	(acetaminophen or paracetamol or tylenol).mp.
63	(acetylsalicylic-acid or aspirin).mp.
64	(accufix or aeroseb-dex or ciprodex or cresophene or decaderm or decadron or decaspray or dexacen or dexacort or dexair or dexamethasone or dexasone or dexasporin or dexone or dexycu or encor-dec or endomethasone or hexadrol or maxidex or maxitrol or neodecadron or neomycin or ozurdex or septomixine or tobradex or tobramycin).mp.
65	(adasone or antocortone or betapar or bicortone or cartancyl or colisone or cortan or cortidelt or cotone or dacorten or dacortin or decortisyl or dellacort or delta-cortelan or delta-cortisone or delda-dome or delta-e or delta-some or deltacordene or deltacortisone or deltacortone or deltasone or deltison* or deltra or di-adreson or diadreson or econosone or encorton* or fernisone or fiasone or hostacortin or in-sone or incocortyl or juvason or lisacort or lodotra or lodtra or me-korti or metacortandracin or meticorten or metreton or nisona or nizon or novoprednisone or nurison or orasone or panafcort or panasol or paracort or parmenison or pehacort or prerdeltin or prednicen or prednicorm or prednicort or prednicot or prednidib or prednilonga or prednison* or prednitone or prednizon or prednovister or presone or pronison or rayos or rectodelt or retrocortine or servisone or sone or sterapred or supercortil or ultracorten* or winpred or wojtab or zenadrid).mp.
66	(addaprin or advil or caldolor or dyspel or europrofen or genpril or i-prin or IBU-200 or ibuprofen or motrin or neoProfen or novo-profen or provil).mp.
67	(adepril or amavil or amilit or amineurin or amiplin or amiprin or amitid or amitril or amitrip or amitriptyline or amyline or amyzole or anapsique or annoyltin or apo-peram or belpax or damilen-hydrochloride or daprimen or deprex or domical or elatrol or elatrolet or elavil or enafon or endep or etrafon or etravil or kyliran or laroxyl or larozyl or lentizol or levate or levazine or limbitrol or maxivalet or miketorin or mitaptyline or nornaln or novoprotect or novitriptyn or oasil-m or pinsanu or pinsaun or proavil or rantoron or redomex or saroten or sarotena or syneudon or teperin or

	trepiline or triavil or tridep or tripta or triptizol or triptyn or trynol or tryptacap-hydrochloride or tryptine or tryptizol or trytomer or vanatrip).mp.
68	(aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen).mp.
69	(aleviatin or auranile or causoin or cerebyx or comitoina or convul or danten or dantinal or dantoinal or dantoine or denyl or di-hydan or di-lan or di-phetine or difenilhidantoina or difenin or difetoin or difhydan or dihycon or dihydantoin or dilabid or dilantin* or dillantin or dintoin or dintoina or diphantoin or diphedal or diphedan or diphenin or diphenine or diphentyn or diphenylan or dyphenylhydantoin* or diphenylhydatanoin or ditoinate or ekko or elepsindon or enkelfel or epamin or epdantoin or epelin or epifenyl or epihydan or epilan-d or epilantin or epinat or epised or eptal or fenantoin or fenidantoin or fenitoina or fentoin or fenylepsin or fenytoin* or fosphenytoin-sodium or hidan or hidantal or hidantilo or hidantina or hidantomin or hydantal or hydantoinal or ictalis-simple or idantoil or iphenylhydantoin or kessodanten or labopal or lehydan or lepitoin or lepsin or mesantoin or minetoin or neosidantoina or novantoina or novophenytoin or oxylan or phanantin or phanatine or phenatine or phenatoine or phenhydanin or phentoin or phentytoin or phenytek or phenytex or phenytoin* or ritmenal or saceril or sanepil or silantin or sinergina or sodanthon or sodantoin or sodanton or solantin or sylantoic or thilophenyl or toin or tremytoine or zentropal or zentropil).mp.
70	(alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil).mp.
71	(algimabo or algirona or algopyrin or alnex or analgin or analgina or analgine or antalgin or antalgina or causalon or conmel or cornalgin or defin or di-shuang or dialgin or diprin or dolanet or dolemicin or dolgan or dolocalma or foragin or hexalgin or laper or magnopyrol or metamizol* or metazol or minalgin or natralgin or nolotil or novalcina or novalgin or novalgina or novalgine or optalgin or proalgin or promel or sinalgia or taxenil or telalgin or v-dalgin).mp.
72	(alphatrex or beta-val or betacort or betaderm or betagel or betaject or betamethasone or betamycin or betaprolene or betaprone or betatrex or beteflam or betnesol or betnovate or celestone or celestroderm or dermabet or diprogen or diprolene or diprosalic or diprosone or dovobet or ectosone or enstilar or lotriderm or lotrisone or luxiq or prevex-b or pro-sone or sernivo or taclonex or uticort or valisone or valnac).mp.
73	(amizepin* or bipotrol or biston or carbamazepen* or carbamazepin* or carbatrol or carbazepin* or carnexiv or epitol or equetro or finlepsin or karbamazepin or neurotol or stazepine or tegretal or tegretol or telesmin or teril or timonil).mp.
74	(amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*).mp.
75	(anti-inflammatory-analges* or antiinflammatory-analges*).tw,kf.
76	(arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia).mp.
77	(ariclaim or cymbalta or duloxetine or xeristar or yentreve).mp.
78	(aristospan or kenalog or triamcinolone or zilretta).mp.
79	(arthaxan or balmox or consolan or dolsinal or flambate or listran or mebutan or nabumeton* or prodac or relafen or relif or relifen or relifex or unimetone).mp.
80	(arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex).mp.
81	(ateven or avantyl or aventyl or demethylamitriptyline or demethylamitryptyline or desitriptilina or desmethylamitriptyline or lumbeck or noramitriptyline or noritren or nortroptilina or nortriptylin* or nortryptilin* or nortryptylin* or norventyl or pamelor or sensaval).mp.
82	(avetil or axacet or axisal or axum or delaxin or etroflex or forbaxin or lumirelax or methocal or methocarbamol* or methoxacet or methoxisal or metocarbamol* or metofenia or miolaxene or miorilas or miowas or myolaxene or neuraxin or parabaxin or perilax or reflexyn or relaxophen or relestrif or robax or robaxacet or robaximol or robaxin or robaxisal or robinax or romethocarb or spasmhalt or surquetil or tresortil).mp.
83	(baclofen* or gablofen* or kemstro or lioresal).mp.
84	(bupivacaine or exparel or marcaine or sensorcaine or vivacaine).mp.
85	(carbocaine or mepivacaine or polocaine or scandonest).mp.

86	(catapres or clonidine or clorpres or duraclon or kapvay).mp.
87	(celebrex or celecox*).mp.
88	(chloroprocaine or procaine).mp.
89	(corticoid* or corticosteroid* or cortico-steroid*).tw,kf.
90	(coxflam or coxicam or maxicam or melfax or melonex or meloxicam* or meloxivet or metacam or mobec or mobic or mobicox or movalis or movatec or revmoksikam or vivlodex).mp.
91	(daypro or deflam or oxaprozin*).mp.
92	(demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane).mp.
93	(desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*).mp.
94	(dexmedetomidine or precedex).mp.
95	diflunisal.mp.
96	(epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi).mp.
97	(feldene or piroxicam).mp.
98	(fenoprofen or nalfon).mp.
99	flurbiprofen.mp.
100	(frotek or ketoprofen).mp.
101	(gabapentin* or gralise or horizant or neurontin).mp.
102	(gabatril or gabitril or tiagabine).mp.
103	(indocin or indomethacin or novo-methacin or pro-indo or tivorbex).mp.
104	(ketalar or ketamine).mp.
105	(lidocaine or xylocaine or xylocard).mp.
106	(local-infiltration adj2 analgesia).tw,kf.
107	(lumiracoxib or prexige).mp.
108	(lyrica or pregabalin).mp.
109	(mefenamic-acid or ponstan or ponstel).mp.
110	(metassalone or metaxalon* or skelaxin or zorane).mp.
111	(narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid*).tw,kf.
112	(narop or naropin or noropine or ropivacain*).mp.
113	(nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid*).tw,kf.
114	(opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar*).tw,kf.
115	(oxcarbazepin* or oxtellar or timox or trileptal).mp.
116	parecoxib.mp.
117	(prialt or ziconotide).mp.
118	(sirdalud or ternelin or tizanidin* or zanaflex).mp.
119	or/10-118
120	9 and 119
121	Alfentanil/
122	exp Analgesics, Opioid/
123	Buprenorphine/
124	Butorphanol/
125	Codeine/
126	Dextropropoxyphene/
127	Fentanyl/

128	Hydrocodone/
129	Hydromorphone/
130	Meperidine/
131	Methadone/
132	Morphine/
133	Morphine Derivatives/
134	Nalbuphine/
135	Oxycodone/
136	Pentazocine/
137	Pirinitramide/
138	Remifentanil/
139	Sufentanil/
140	Tramadol/
141	(Abalgin or Adalgin or Algafan or Algaphan or Algodin or Antalvic or Daloxen or Darvocet or Darvon or Deprancol or Deprandol or Depromic or Depronal or Destropropossifene or Develin or Dextropropoxifeno or Dextropropoxyphen* or Dextroproxifeno or Dimeprotane-hydrochloride or Dolan or Dolene or Dolorphe or Doloxene or Doloxyne or Femadol or Kesso-gesic or Levitan or Leviton or Liberan or Piril or Pro-gesic or Prophene-65 or Propoxyphen* or Propoxyphine or Proxagesic or Proxyvon or Regredol or Tawasan).mp.
142	(Abstral or Actiq or Duragesic or Durogesic or Durotep or Epufen or Fentalis or Fentamyl or Fentane* or Fentanil* or Fentanyl* or Fentora or Innovar or Instanyl or Ionsys or Lazanda or Leptanal or Matrifen or Mezolar or Onsolis or PecFent or Phentanyl or Rapinyl or Recuvyra or Sentonil or Sublimase or Sublimaze or Subsys or Tanyl or Transfenta).mp.
143	(Acetazone or Ambenyl or Ardinex or Atasol or Bromanyl or Calmylin or Codein* or Codeprex or Codicaps or Codipertussin or Codrix or Codyl or Cotridin or Isocodeine or Mersyndol or Methylmorfine or Methylmorphine or Procet or Robaxacet or Robaxisal or Synalgos or Trezix or Trianal or Triatec).mp.
144	(Actiskenan or Algedol or Anafil or Arymo or Astramorph or Avinza or Contalgin or Depodur or Depomorphine or Dolcontin or Doloral or Duralmor or Duramorph or Embeda or Ethirfin or Graten or Infumorph or Kadian or Kapanol or Longphine or M-Ediat or Meslon or M-Eslon or Mitigo or Moraxen or Morcontin or Morficontin or Morphabond or Morphanton or Morphgesic or Morphia or Morphine* or Moscontin or MS-Contin or M-S-Contin or Noceptin or Oblioser or Oramorph or Rapi-ject or Relimal or Roxanol or Rylomine or Sevredol or Skenan or S-morphine or Statex or Vendal or Zomorph).mp.
145	(Adamon or Adolonta or Amadol or Analab or Analdol or Andalpha or Bellatram or Biodalgic or Biokanol or Biomadol or Calmol or Contramid or Contramal or Con-zip or Conzip or Dolana or Dolika or Dolmal or Dolotral or Dolzam or Dromadol or Durela or Eufindol or Exopen or Jutadol or Katrasic or Kontram or Labesfal or Mabron or Melanate or Mosepan or Newdorphin or Nobligan or Nonalges or Omnidol or Pengesic or Prontofort or Radol or Ralivia or Ranitidin or Rofy or Rybix or Ryzolt or Sefmal or Sensitram or Takadol or Tamolan or Tandol or Tarol or Theradol or Tiparol or Tiral or Topalgic or Trabar or Trabilan or Trabilin or Tradol* or Tradona or Tralgiol or Tralic or Tramabeta or Tramacet or Tramada or Tramadex or Trama-dorsch or Tramadi* or Tramado* or Tramadura or Tramagetic or Tramagit or Tramahexal or Tramake or Tramal or Tramaliv or Tramazac or Tramed or Tramex or Tramol or Tramundin or Trapidol or Trasedal or Trasik or Trexol or Tridol or Tridural or Trodon or Trondon or Ultracet or Ultram or Unitral or Urgendol or Zamadol or Zamudol or Zodol or Zumalgic or Zumatran or Zydol or Zytram).mp.
146	(Adanon or Algidon or Algolysin or Algovetin or Algoxale or Althose or Amidon* or Amidosan or Anadon or Biodone or Butalgin or Cophylac or Deamin or Depridol or Diaminon or Dianone or Dolafin or Dolamid or Dolesone or Dolmed or Dolophin* or Dorex or Dorexol or Eptadone or Fenadon or Gobbidona or Heptadon* or Heptanon or Ketalgin or Mecodin or Mepecton or

	Mephenon or Metadol or Metadon* or Metasedin or Methaddict or Methadon* or Methadose or Methaforte mix or Miadone or Moheptan or Pallidone or Phenadon* or Physepton* or Polamidon or Polamivet or Polamivit or Sedo-Rapide or Sinalgin or Symoron or Westadone).mp.
147	(Allay or Anexsia or Apadaz or Azdone or Bancap or Bekadid or Codamine or Codinovo or CO-GESIC or Dico or Dicodid or Dihydrocodeinone or Dihydrocodone or Duradyne-DHC or Flowtuss or Hidrocodona or Hycodan or Hycofenix or Hycon or Hydrocodeinonebitartrate or Hydrocodon* or Hydrocon* or Hydropane or Hy-Phen or Hysingla or Idrocodone or Lorcet-HD or Lortab or Multacodin or Norcet or Norco or Obredon or Reprexain or Rezira or Robidone or Tussicaps or Tussignon or Tussionex or Tycolet or Vantrela-ER or Vicodin or Vicoprin or Vicoprofen or Vituz or Xtrelus or Zohydro or Zutripro or Zydone).mp.
148	(Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen).mp.
149	(Algil or Alodan or Atropine or Centralgin* or Cluyer or Demero* or Dispadol or Dolanquifa or Dolantal or Dolantin* or Dolargan or Dolcontral or Dolestin* or Dolin or Dolocontral or Doloneurin or Doloneutrotat or Dolosal or Dolosan or Dolsin or Dolvanol or Endolate or Isonipecain* or Lidol or Lydol or Mefedina or Mepadin or Meperdol or Mepergan or Meperiden or Meperidin* or Meperidol or Mephedine or Mepiridine or Mialgin or Nemerol or Neomochin or Operidine or Opistan or Pantalgin or Petadin or Petantin* or Pethanol or Pethedine or Pethidin* or Petidin* or Petydyna or Phetidine or Pipersal or Piridosal or Sauteralgyl or Supplosal or Synlaudine).mp.
150	(Anorfin or Belbuca or Bunavail or Buprenex or Buprenorfin* or Buprenorphin* or Buprex or Buprine or Butrans or Cassipa or Finibron or Norphin or Pentorel or Prefin or Probuphenine or Probuphine or Somnena or Sublocade or Suboxone or Subutex or Temgesic or Transtec or Vetergesic or Zubsolv).mp.
151	(Avridi or Bionine or Bionone or Bolodorm or Broncodal or Bucodal or Cafacodal or Cardanon or Codeinone or Codenon or Codix-5 or Codoxy or Combunox or Dihydrohydroxycodeinone or Dihydrohydroxydodeinone or Dihydrone or Dihydroxycodeinone or Dinarkon or Diphydrone or Endine or Endone or Eubine or Eucodal* or Eudin or Eukdin or Eukodal or Eumorphal or Eurodamine or Eutagen or Hydrocodal or Hydroxycodein* or Ludonal or Medicodal or M-oxy or Narcobasin* or Narcosin or Nargenol or Narodal or Nucodan or Opton or Ossicodone or Oxanest or Oxaydo or Oxecta or Oxicodona or Oxicon or Oxicone or Oxicontin or Oxiconum or Oxikon or Oxy-ir or Oxycet or Oxycocet or Oxycod or Oxycodan or Oxycodeinon* or Oxycodon* or Oxycodyl or Oxycone or Oxycontin or Oxydose or Oxyfast or Oxygesic or OxyIR or Oxykon or OxyNEO or Oxynorm or Pancodine or Pancodone or Pavinal or Percobarb or Percocet or Percodan or Percolone or Pronarcin or Remoxy or Roxicet or Roxicodone or Roxilox or Roxiprin or Roxybond or Roxycodone or Sinthiodal or Stupenal or Supendol or Supeudol or Targin or Targiniq or Tebodal or Tekodin or Thecodin or Theocodin or Troxyca or Tylox or Xartemis or Xtampa or Xtampza).mp.
152	(Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol).mp.
153	(Biomorphyl or Cofalaudid or Dihydromorfinon or Dihydromorphinone or Dihydromorphone or Dilaudid or DiMo or Dimorphone or Dolonovag or Exalgo or Hidromorfona or Hydal or Hydromorfona or Hydromorph-Contin or Hydromorphinone-hydrochloride or Hydromorphon* or Hydrostat-ir or Hymorphan or Idromorfone or Jurnista or Laudacon* or Novolaudon or Opidol or Paliadon or Palladon* or Rexaphon or Semcox or Sophidone).mp.
154	(Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl).mp.
155	(Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide).mp.
156	(Dolapent or Fortal or Fortalgesic or Fortalin or Fortral or Fortraline or Fortwin or Lexir or Liticon or Peltazon or Pentacozine or Pentafen or Pentagin or Pentalgina or Pentazocin* or Pentozocine or Perutagin or Sosegon or Sosigon or TALACEN or Talioin or Talwin).mp.
157	(Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor).mp.
158	(Nicomorfin* or Nicomorphin* or Vilan).mp.

159	(Remifentanil or Remifentanyl or Ultiva).mp.
160	or/121-159
161	120 and 160
162	Animals/ not (Animals/ and Humans/)
163	Disease models, animal/ or Models, animal/
164	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.
165	or/162-164
166	161 not 165
167	(exp child/ or exp infant/) not (adolescent/ or exp adult/)
168	(baby or babies or boy* or child* or fetus or fetal or foet* or girl* or juvenile* or kid or kids or infan* or newborn* or new-born* or neonat* or neo-nat* or paediatr* or pediatr* or preadolesc* or prepubesc* or preteen* or pubescen* or toddler* or youth*).ti,jw.
169	167 or 168
170	166 not 169
171	Clinical trials as topic/
172	Controlled clinical trial/
173	Randomized controlled trial/
174	(placebo or randomized or randomly).tw.
175	trial.ti.
176	171 or 172 or 173 or 174 or 175
177	170 and 176

Following peer review, age filter was revised to retrieve articles from pediatric journals and studies including pediatric patients.

The queries at lines 167 and 168 of the original strategy were modified as follows:

167 (exp child/ or exp infant/) not (adolescent/ or exp adult/)

168 (baby or babies or boy* or fetus or fetal or foet* or girl* or kid or kids or infan* or newborn* or new-born* or neonat* or neo-nat* or preadolesc* or prepubesc* or preteen* or pubescen* or toddler*).ti,jw.

Supplement 2. Abstract screening decision tables

I. Any Study

Characteristics	Decision
Studies where the experimental design was **clearly** not a parallel randomized controlled trial (e.g. retrospective studies, historically controlled studies)	**Exclude**
Narrative review (commentaries, letters and editorials), systematic reviews, meta analyses	**Exclude**
Did not assess interventions for postoperative pain management	**Exclude**
Were conducted in animals	**Exclude**
Involved only pediatric patients	**Exclude**
Analgesia regimens compared were exclusively pre-operatory (e.g. preemptive gabapentin), with no indication that post-discharge analgesia was different between groups	**Exclude**
Analgesia regimens compared were exclusively intra-operatory (e.g. nerve blocks), with no indication that post-discharge analgesia was different between groups	**Exclude**
Analgesia regimen was offered exclusively during hospital stay (e.g. PCA, epidural), with no indication that post-discharge analgesia was different between groups	**Exclude**
Involved analgesia treatment exclusively for chronic postoperative pain (i.e. the intervention started over 2 two months after surgery)	**Exclude**

II. Randomized trials involving post-discharge analgesia

Primary analgesia regimen			Rescue analgesia requiring a new prescription	Decision
Analgesia intervention 1	**Analgesia intervention 2**	**Rescue analgesia readily available for patients (PRN prescription)**		
Non-opioid (or placebo)	Opioid	Non-opioid	Opioid OR Non-opioid OR Not used OR Unclear	**Verify full-text**
Non-opioid (or placebo)	Opioid	Not used	Opioid OR Non-opioid OR Not used OR Unclear	**Verify full-text**
Non-opioid (or placebo)	Opioid	Unclear	Opioid OR Non-opioid OR Not used OR Unclear	**Verify full-text**
Non-opioid (or placebo)	Opioid	Opioid	Opioid OR Non-opioid OR Not used OR Unclear	**Exclude**
Non-opioid	Non-opioid (or placebo)	Opioid OR Non-opioid OR Not used OR Unclear	Opioid OR Non-opioid OR Not used OR Unclear	**Exclude**
Opioid	Opioid	Opioid OR Non-opioid OR Not used OR Unclear	Opioid OR Non-opioid OR Not used OR Unclear	**Exclude**

Supplement 3. Data extraction form

A. STUDY IDENTIFICATION
STUDY DETAILS
1. Sponsorship source: **2. Country:** **3. Setting:** **4. Comments:**
AUTHORS
1. Author's name: **2. Institution:** **3. Email:** **4. Address:**
ADDITIONAL INFORMATION
1. Article title: **2. Journal, year, volume, number and page:** **3. Key findings:** **4. Publication source of study (peer reviewed or grey literature):** **5. Setting (university hospital, public hospital, private hospital database):** **6. Study aim(s)/research question(s):** **7. Year of publication:**

B. METHODS
1. Study design: **2. Describe methodology briefly:** **3. Primary outcome:** **4. Secondary outcomes:**
C. POPULATION
INCLUSION/ EXCLUSION CRITERIA
1. Inclusion criteria: **2. Exclusion criteria:** **3. Group differences:**
ADDITIONAL POPULATION DATA
1. Describe the sample size calculation **2. Were patients removed from the trial when they reported no improvement, no adherence to treatment and/or adverse events? (Yes/No)** **3. Was the study conducted in a single center or multiple centers?**
PATIENT CHARACTERISTICS
1. Group label (e.g. opioid-free/based): **2. Sample size:** **3. Number of patients randomized** **4. Number of patients analyzed** **5. Sex/gender (%F/%M):**

6. **Mean (or median) age:**
7. **ASA class:**
8. **Comorbidities and risk factors:**
9. **Preoperative diagnosis, including percentages (if available):**
10. **Surgery, including percentages (e.g. knee replacement, hysterectomy, colectomy):**
11. **Surgical approach, including percentages (e.g. open, laparoscopic, arthroscopic):**
12. **Hospital length of stay (if means or medians not reported, please specify the target length of stay or indicate 'day surgery'):**
13. **Other characteristics of enrolled subjects (relevant to the study):**
D. INTERVENTIONS
1. **Group label (e.g. opioid-free/based):**
2. **Analgesia intervention before surgery (pre-emptive analgesia intervention initiated in the preoperative period), if any:**
3. **Analgesia and anesthesia interventions in the operating room (e.g. systemic drugs, peripheral nerve blocks, epidural, spinal analgesia and/or local infiltrations):**
4. **Analgesia intervention after surgery (in hospital):**
5. **Analgesia intervention after surgery (after hospital discharge):**
6. **Other relevant characteristics of the intervention(s), or comments:**
E. OUTCOMES
1. **Outcome name**
2. **Outcome type (e.g. continuous, dichotomous)**

3. **Reported as [e.g. mean (± SD), percentage, etc.]**

4. **Outcome group (i.e. primary, secondary)**

5. **Outcome reported (e.g. fully reported, not reported)**

6. **Scale**

7. **Range**

8. **Unit of measurement**

9. **Direction (e.g. lower is better, higher is better)**

10. **Notes**

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	p.1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	p.1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	p. 16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p. 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p. 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	p. 7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	p. 6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	p. 9-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	p. 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	p. 10-11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	p. 9-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	p. 9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	p. 11-12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	p. 12-13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	p. 14-15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	p. 14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	p. 11-12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	p. 12 and Table 3

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Excessive prescribing after surgery has contributed to a public-health crisis of opioid addiction and overdose in North America. However, the value of prescribing opioids to manage postoperative pain after surgical-discharge remains unclear. We propose a systematic review and meta-analysis to assess the extent to which opioid analgesia impact postoperative pain-intensity and adverse events in comparison to opioid-free analgesia in patients discharged after surgery.

Methods and analysis

Major electronic databases (MEDLINE, EMBASE, Cochrane Library, Scopus, Amed, Biosis, CINAHL and PsycINFO) will be searched for multi-dose randomized-trials examining the comparative-effectiveness of opioid versus opioid-free analgesia after surgical-discharge. Studies published from January 1990 to July 2019 will be targeted, with no language restrictions. The search will be re-run before manuscript submission to include most recent literature. We will consider studies involving patients undergoing minor and major surgery. Teams of reviewers will, independently and in duplicate, assess eligibility, extract data, and evaluate risk of bias. Our main outcomes of interest are pain-intensity and postoperative vomiting. Study results will be pooled using random-effects models. When trials report outcomes for a common domain (e.g. pain-intensity) using different scales, we will convert effect sizes to a common standard metric (e.g. visual analogue scale). Minimally important clinical differences reported in previous literature will be considered when interpreting results. Sub-group analyses defined *a priori* will be conducted to explore heterogeneity. Risk of bias will be assessed according to the Cochrane Collaboration's Risk of Bias Tool 2.0. The quality of evidence for all outcomes will be evaluated using the GRADE rating system.

Ethics and dissemination

Ethical approval is not required since this is a systematic review of published studies. Our results will be published in a peer-reviewed journal and presented at relevant conferences. Further knowledge dissemination will be sought via public and patient-organizations focused on pain and opioid-related harms.

Strengths and limitations of this study

- This will be the first systematic review to synthesise the evidence on the comparative-effectiveness of opioid vs. opioid-free analgesia after postoperative discharge.
- This review will address a major knowledge gap that hinders the use of evidence-based prescribing as a strategy to mitigate postoperative opioid-related harms.
- We will use robust statistical methods to meta-analyse data from RCTs, but these methods are not free from limitations when outcome reporting is heterogeneous.
- The quality and strength of evidence will be evaluated using the Cochrane Collaboration's Risk of Bias Tool 2.0 and the GRADE framework.

INTRODUCTION

North America is facing a devastating opioid crisis exacerbated by excessive prescribing.[1,2] Surgery often serves as a gateway for opioid-naïve patients to obtain an opioid prescription,[3] and spiral into misuse and addiction.[4-8] Reports from Canada and the United States suggest that 6-14% of patients who are prescribed opioids after surgical discharge become persistent opioid users, i.e. they continue to take the drug for more than three months after surgery.[5, 9-12] Interestingly, rates of persistent opioid use are similar among patients undergoing major,[5, 10, 11] and minor surgeries.[12] Patients who do not become persistent users postoperatively may also contribute to the opioid crisis by diverting unused tablets for nonmedical use by others - up to 70% of all opioid tablets prescribed to surgical patients go unused and may become a source for diversion.[13] Given these factors, recent literature suggests that postoperative opioid prescribing should be judicious and based on the best available evidence regarding benefits and harms.[14, 15]

Studies have shown that postoperative pain management using only non-opioid drugs is common internationally but not in Canada nor in the United States, where opioid tablets are often prescribed instead of, or in addition to, non-opioid analgesics.[16-20] In countries such as the Netherlands,[21] China,[22] and Chile,[23] reported rates of opioid prescribing after surgical discharge range from 0% to 5%, while in North America, 80% to 95% of patients receive an opioid prescription to manage postoperative pain at home.[16-20] A recent study indicates that surgical patients in Canada and the United States fill opioid prescriptions at a rate that is seven times higher than those in Sweden.[24] Remarkably, in countries where opioids are not a mainstay for postoperative analgesia, pain-related outcomes (i.e. satisfaction with pain management) after surgery are often superior to North America.[16-18] This may, in part, reflect a potential therapeutic superiority of non-opioid drugs or increased opioid-related adverse events such as postoperative vomiting. Although these findings bring

into question the value of prescribing opioids to manage acute pain after surgical discharge, the decision to prescribe opioids must be informed by robust systematic reviews and meta-analyses focused on the comparative-effectiveness of opioid versus opioid-free postoperative analgesia. These, however, are currently non-existent in the literature.[25]

We therefore propose to undertake a systematic review and meta-analysis to summarize the evidence regarding the comparative-effectiveness of opioid versus opioid-free analgesia after discharge following surgery. Our study will follow the principles of the PICO framework,[26] and aims to respond to the following research questions: (1) in patients discharged after surgery, to what extent does opioid analgesia impact postoperative pain intensity in comparison to opioid-free analgesia? And (2) in patients discharged after surgery, to what extent does opioid analgesia impact the risk of postoperative vomiting in comparison to opioid-free analgesia?

METHODS AND ANALYSIS

Design

This protocol was designed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.[27] A draft protocol was circulated among our knowledge synthesis team [composed of synthesis leaders (JF, GB, and LF), synthesis managers (CEK and UD), a patient partner (AD), and collaborators] and adjustments were made according to their feedback. Any future amendments to this protocol and corresponding rationale will be tracked and dated.

Literature search

A comprehensive search of major electronic databases [MEDLINE (via Ovid), EMBASE (via Ovid), The Cochrane Library (via Wiley), Scopus (via Elsevier), Amed (via Ovid), Biosis (via Clarivate), CINAHL (via Ebsco) and PsycINFO (via Ovid)] will be conducted to identify relevant

studies. The main strategy (MEDLINE) was developed by an experienced medical librarian and information specialist (TL) with input from the synthesis team (Supplement 1). Subsequently, a second medical librarian peer-reviewed this search strategy according to Peer Review of Electronic Search Strategies (PRESS) standards,[28] and changes were made as required. The vocabulary and syntax of the MEDLINE strategy was tailored to allow adaptation and optimal electronic searching of the other databases. Searches will target articles published after January 1990, as earlier publications do not reflect current standards of surgical care with the widespread use of minimally invasive surgery and perioperative care pathways.[29-32] The initial search was conducted in July 2019 and will be re-run prior to manuscript submission to ensure the inclusion of most recent literature. No language limitation will be applied. A combined library of the retrieved articles will be created using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; https://www.covidence.org/).[33] Duplicates will be excluded. To ensure literature saturation, we will also search trial registries (ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform), conference proceedings (identified via Scopus, Embase, Biosis, and Cochrane Library), articles cited by the included articles (identified via Scopus) and articles that cited the included articles (identified via Scopus). Furthermore, we will contact authors to obtain aggregated data from trials that were completed but not published.

Eligibility criteria

We will include studies that: (1) are parallel RCTs, (2) enrolled youth and/or adults patients (>15 years old) undergoing minor or major surgeries according to the WHO definition,[34, 35] (Table 1), (3) compared a post-discharge analgesia regimen including opioids (analgesic drugs that act on opioid receptors, such as codeine, oxycodone, hydromorphone, tramadol, and morphine) versus an analgesia regimen including only non-opioid drugs (such as acetaminophen, NSAIDs,

gabapentinoids) and (4) involved a multiple-dose design focused on the overall effect of repeated doses of the prescribed analgesics. Our age cut-off was chosen based on data showing fast-growing rates of opioid poisoning in youths over 15 years old.[36, 37] Studies involving any non-invasive route of analgesic administration (i.e. oral, transmucosal, transdermal and rectal) will be considered for inclusion. Studies where opioids were offered to the opioid-free group as rescue analgesia for breakthrough pain (i.e. pain that erupts while a patient is already medicated) will be included only if the opioid drugs were not readily available to patients (i.e. a new prescription was required via contact with a healthcare provider). Studies where patients received opioids while in the hospital or clinic will be included if the post-discharge analgesia was according to our inclusion criteria.

We will exclude single-dose trials as they do not reflect 'real-world' practices where analgesia regimens span several days postoperatively.[38] Besides, postoperative analgesia trials with a single-dose design have been extensively systematically reviewed in previous literature.[38, 39] We will also exclude: (1) placebo-controlled trials where no active analgesic drugs are offered to patients (they do not reflect standard practice), (2) studies where the postoperative analgesia regimen is not clearly described (e.g. placebo-controlled trials with unclear description of analgesics given in addition to placebo), (3) studies exclusively focused on children (≤15 years old), (4) studies with post-discharge analgesia administrated via invasive routes such as intravenous or epidural (rarely prescribed after surgical discharge), and (5) studies evaluating analgesia for chronic postoperative pain (treatment starting beyond 2 months after surgery).[40]

Selection of studies

The titles/abstracts of the articles identified by our search strategy will be evaluated against the review's eligibility criteria by pairs of reviewers. Due to the anticipated large number of articles to be screened, eight reviewers (all with previous training in healthcare research) will be involved in

the screening process. Screening will be conducted, independently and in duplicate, using the Covidence software.[33] Two lead reviewers (JF and CEK) will pilot-test the eligibility criteria on the first 100 titles and abstracts identified by the search. To harmonize the rest of the screening process, reviewers will attend a training session and conduct a pilot screening of at least 20 titles/abstracts to prompt clarifications. A screening decision table was created to guide decision-making (Supplement 2). To ensure accuracy, all titles/abstracts will be screened by at least one lead member of the synthesis team (JF or CEK). Disagreements regarding eligibility will be resolved by consensus between the reviewers or by consulting an adjudicator (LF).

Articles that are clearly irrelevant will be excluded after examination of titles and abstracts; those that are potentially eligible will have their full-text versions retrieved and evaluated against the eligibility criteria. Publications in non-English language will be translated into English by an ISO certified translation company. Full-text screening will be conducted by two lead members of the synthesis team (JF and CEK) using the Covidence platform.[33] The extent of agreement between reviewers during full-text screening will be assessed using Kappa statistics (thresholds: <0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement and >0.80 almost perfect agreement).[41] Disagreements will be resolved by consensus or by consulting an adjudicator (LF).

Outcome measures

The primary outcome of interest in this review will be patient self-reported outcomes focused on postoperative pain intensity (i.e. self-perceived magnitude of pain at a given time postoperatively). The secondary *a priori* outcome of interest will be the risk of postoperative vomiting. These outcomes were chosen based on previous literature that showed good pain relief to be the most desirable outcome in perioperative care according to patient preference, while postoperative

vomiting is the least desirable outcome.[42-44] If data are available in the eligible studies, we will also explore the association of the interventions with other endpoints included in core outcome sets for research in perioperative care.[45, 46] These include: (1) drug adverse events (other than vomiting), (2) patient satisfaction with pain management, (3) participant disposition (i.e. withdrawal due to adverse events or ineffective treatment) (4) self-reported postoperative health status [overall and domain-based scores, vitality (i.e. fatigue), physical function, emotional function, social function, role function (i.e. work or other daily activities), sleep function], (5) emergency room visits and (6) hospital readmissions.

Data charting

A customized data extraction form was collectively developed by the synthesis team (Supplement 3). This form will be pilot tested by two independent reviewers (JF and CEK). Subsequently, a team meeting will take place to discuss potential issues and refine the form. Finally, the refined data extraction form will be integrated into the Covidence software.[33] Data extraction will be conducted, independently and in duplicate, by pairs of reviewers. The following data will be extracted from each study: author, publication date, study location, number of participating centres, funding source, inclusion and exclusion criteria, sample size (patients randomized and patients analysed in each group), patient characteristics (age, sex, clinical condition, type of surgery and proportion receiving preoperative opioids, if available), surgery classification (major vs. minor), type of anaesthesia, in-hospital analgesia interventions (if applicable), hospital length of stay (if applicable), characteristics of the post-discharge analgesia intervention [drugs, dosage (in morphine equivalents for opioids,[47]), frequency of administration and duration], outcome measures assessed, time points of assessment and duration of follow-up.

The number of reviewers involved in data extraction will depend on the number of RCTs fulfilling our eligibility criteria. To harmonize data extraction, reviewers will attend a training session, conduct at least 2 pilot extractions, and receive a written 'data extraction guide' with detailed instructions. To ensure accuracy, at least one lead member of the synthesis team (JF or CEK) will extract data from each article. Data extracted in duplicate will be cross-checked by an independent third reviewer. Discrepancies in the extracted data will be resolved by consensus between the reviewers after revisiting the full-text article. If discrepancies remain, an adjudicator will be consulted (LF).

As this meta-analysis is focused on acute pain management after surgery, we will target outcome data collected up to 30 days postoperatively (from the day when the trial analgesia regimens were prescribed). Data regarding pain intensity (primary outcome) will be assessed as described in Table 2. Postoperative vomiting (secondary outcome) will be assessed as a dichotomous measure (presence of vomiting: yes/no). The assessment of other outcomes will be exploratory and will depend on whether data is available and how they are reported.

Methodological quality of individual studies

Risk of bias will be assessed independently and in duplicate by two lead members of the synthesis team (JF and CEK) using the Cochrane Collaboration's Risk of Bias Tool 2.0 for randomized trials (RoB 2.0).[48] Assessments will be conducted using an iterative form available online (www.riskofbias.info/). The RoB 2.0 appraises risk of bias across five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. The domain concerning missing outcome data will be assessed according to Akl,[49] and Ebrahim.[50] For each domain, risk of bias will be judged as 'low risk', 'some

concerns', or 'high risk'. Studies are considered to have an overall 'high risk of bias' if at least one domain is judged as 'high risk'. Disagreements regarding risk of bias will be resolved by consensus or by consulting an adjudicator (LF).

Quality of evidence (i.e. confidence in the effect estimates) will be assessed using the GRADE rating system.[51] Assessment will be conducted on an outcome-by-outcome basis by two lead members of the synthesis team (JF and CEK) working independently.[52] Specific guidelines will be followed to improve reliability.[53-74] Disagreements will be resolved by consensus or by consulting an adjudicator (LF). In the GRADE system, RCTs are initially rated as 'high confidence' evidence but may be rated down by one or more of five categories of limitations: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias.[51] After considering these categories, the confidence in estimates for each outcome will be categorized according to Table 3. Publication bias will be formally assessed by visual assessment of funnel plot asymmetry,[75] and by Begg's test,[76] when there are at least 10 studies available for meta-analysis. The final results will be summarized in an evidence profile.[51]

Data synthesis

For data synthesis, we will primarily assess the treatment effects of opioid versus opioid-free analgesia across all surgical procedures that are eligible for this review; however, we will also explore potential sources of heterogeneity between trials by assessing treatment effects across specific surgical contexts. Meta-analyses will be conducted using random-effects models, which are conservative in considering that the 'true' effect of an intervention may vary across different trials.[77] Weighted mean differences (WMDs) and 95% confidence intervals (95% CIs) will be calculated for pain intensity data reported by more than one RCT. The principle of 'weighting' by the inverse of the variance aims to attribute more weight to studies that provide more information

about the treatment effect.[78] Methods described in the Cochrane Handbook will be used to estimate the mean and standard deviation (SD) when median, range and sample size are reported, and to impute the SD if the standard error (SE) or SD for the differences are not reported.[79] Relative risks (RRs) with associated 95% CIs will be calculated for dichotomous data reported by more than one RCT (i.e. secondary outcome: vomiting). Analyses will follow the Hartung-Knapp-Sidik-Jonkman method as evidence supports that this approach outperforms traditional random-effects methods such as DerSimonian-Laird (known to lead to high type I error rates when the number of studies is small and there is moderate or substantial heterogeneity).[80] All analyses will be conducted using Stata statistical software version (Version 15.1, StataCorp, College Station, Texas, USA). Comparisons will be 2-tailed and use a threshold $p \leq 0.05$.

Interpreting effect estimates for pain intensity is challenging as this outcome can be assessed using different scales [e.g. visual analogue scale (VAS), numerical rating scale (NRS), SF-36 bodily pain scale, or other scales]. To address this issue, we will follow specific guidelines to standardize this outcome into a standard metric.[81-83] We chose the 10cm Pain Intensity VAS (score range 0-10 cm; lower score represents less pain) as this is the pain intensity scale most commonly used in acute pain trials.[84-86] The process of standardization is described in Table 4. Once the WMD between opioid versus opioid-free analgesia is calculated for a given outcome, we will contextualize this value in relation to the corresponding minimally important difference (MID): the smallest change in score that patients perceive as important.[87] Reported MID in VAS pain scores for surgical patients, according to anchor-based methods, is 1/10cm.[88] As recommended by the OMERACT initiative,[81] we will use pain intensity WMD and MID data to determine the strength of the intervention effect, as described in Table 5.

When assessing pain intensity data, to further optimize the interpretation of meta-analyses results, we will also calculate the proportion of patients who reported adequate pain control (no more than mild pain, as determined by a pain score <3/10cm VAS).[88, 89] By assuming a normal distribution of postoperative pain scores in both groups, differences in risk of reporting adequate pain control will be derived with its associated 95% CIs.[81-83]

If we identify more than one trial measuring the exploratory outcomes of interest in this knowledge synthesis (e.g. patient satisfaction, self-reported postoperative health status, readmissions), data will be meta-analysed and reported as WMDs (continuous measures) or RRs (dichotomous measures), as appropriate. Where relevant, outcome data using different metrics will be converted into a standard metric according to guideline recommendations.[81-83] Focused literature searches will be conducted to identify anchor-based MIDs.[87]

Heterogeneity between the RCTs included in the meta-analyses will be assessed using the χ^2 test and the I^2 test.[90] To explore potential sources of heterogeneity, we will test the *a priori* hypothesis that opioid analgesia has a larger effect in trials where patients are expected to feel more pain, such as those involving: (1) major surgery versus minor surgery,[5] (2) day surgery (i.e. with same-day discharge) versus in-patient surgery (i.e. at least one overnight stay in the hospital),[25] and (3) only women as participants [those reporting sex-specific data or involving sex-specific surgeries (e.g. gynaecological, breast)] versus men.[91-93] We also hypothesize that (4) trials with high risk of bias (versus lower risk of bias) will report larger effect sizes.[94, 95] Other clustering strategies for subgroup analyses [e.g. by surgical specialty (e.g. dental surgery, orthopaedic surgery), specific types of surgery (e.g. cholecystectomy, molar excision), type of anaesthesia (e.g. general, neuraxial, regional anaesthesia), study geographic location (e.g. North America)] will be decided based on the characteristics of the trials identified, in consultation with clinicians (i.e.

knowledge users) who care for the relevant surgical populations. These post-hoc subgroup analyses will be planned after data extraction, but prior to analyses of results. All subgroup analyses will be conducted regardless of heterogeneity estimates if there are at least two trials in each subgroup. Tests of interaction will be performed to establish if subgroups differed significantly from one another.[96]

Patient and public involvement

A patient partner (AD) is part of our synthesis team. She brings in her lived experiences with postoperative pain and analgesic requirements after surgical discharge to ensure that our findings are responsive to the needs of patients. She will be actively involved in all stages of this research project and will contribute her experiential knowledge to inform our research design, data interpretation, as well as to optimize strategies for knowledge dissemination and translation. In addition to traditional channels of knowledge dissemination (i.e. conference presentations, peer-reviewed publication), further dissemination will be sought via public and patient organizations focused on pain and opioid-related harms.

SIGNIFICANCE

North America is currently facing a major public-health crisis of opioid abuse. Opioid-based postoperative pain management is recognized as one of the driving forces behind this crisis. Given how commonly postoperative overprescription contributes to misuse, diversion, addiction and death, there is an urgent need to address this element of the opioid crisis. Alternatives to opioids are often overlooked, while they should be incorporated as the foundation of postoperative pain management whenever possible. This may prevent more people from becoming addicted in the future (it is impossible to become addicted without exposure) and, also importantly, reduce diversion of unused prescriptions. Our systematic review will provide key information to guide

clinical decision-making regarding analgesia prescription after surgery. This work has the potential to contribute practice-changing evidence to inform future guidelines aimed to improve analgesia prescribing and mitigate postoperative opioid-related harms.

ETHICS AND DISSEMINATION

The results of this study will be published in an international peer-reviewed journal and presented at relevant conferences. This review will inform future guidelines on postoperative analgesia prescription. Ethical approval is not required since this is a systematic review based on published studies.

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AUTHORS' CONTRIBUTIONS

CEK, GB, LF, and JF contributed to the conception and the design of the study. CEK and JF wrote the first draft of the protocol. CEK, GO, MAC, AK, PNP, FR, UD, AD, TL, AAZ, RA, MM, GB, LF, and JF revised the protocol critically for important intellectual content. JF is the guarantor of this review. All authors have read and approved the final version of the manuscript to be published.

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COMPETING INTERESTS

JF has received grants from Merck and personal fees for consulting from Shionogi. LSF has received grants from Merck and Johnson & Johnson.

TABLES

Table 1. Definition of surgery (minor and major) according to the World Health Organization (WHO)

Surgery	Any intervention involving the incision, excision, manipulation or suturing of tissue and requiring regional or general anesthesia or sedation.
Minor surgery	A surgical intervention occurring in a physician's office or clinic (e.g. tooth extraction, cataract surgery, skin tumor excision).
Major surgery	A surgical intervention occurring in a hospital operating theatre (e.g. cesarean section, appendectomy, open fracture repair).

Table 2. Primary outcome data (pain intensity after surgical discharge)

Pain assessment time points	• Multi-dose analgesia trials often involve the assessment of pain intensity at different time-points after surgical discharge. • We will focus on the following time points after surgical discharge: Day 0 (6-12 hours after prescription), Day 1 (13-24 hours), Day 2 (25-48 hours), Day 3 (49-72 hours), Days 4-7 (3-168 hours), Days 8-30 (169 to 720 hours). • These time points were the most commonly reported in the eligible trials identified by our scoping review and preliminary MEDLINE search. • We will consider for analysis the last measure obtained within the timepoint interval (i.e. the measure closest to the interval upper bound)
The primary time point of interest	• Our primary time point of interest will be Day 1 after discharge (13-24 hours), as evidence suggests that this is the period after surgery when patients report most severe pain.
Other important considerations	• We will prioritize reports of dynamic pain (during movement) over pain at rest if both are reported. Dynamic pain is deemed more relevant to the process of postoperative recovery. • We will also prioritize reports of 'worst pain' over 'average pain'. The latter is highly influenced by variations in instructions (e.g. should periods without any pain accounted for when pain is 'averaged'?).

Table 3. GRADE certainty ratings

Certainty	Interpretation
Very low	The true effect is probably markedly different from the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
High	The authors have a lot of confidence that the true effect is similar to the estimated effect.

Adapted from https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/

Table 4. Process of standardization (rescaling) of pain intensity measures into a common metric.

Step 1	• Non-VAS pain intensity scales will be initially converted into standardized mean differences (SMD), by dividing the between-group differences in means (in each trial), by the pooled SD of the two groups. • The SMD expresses the intervention effect in SD units, rather than the original units of measurement.
Step 2	• Standardization will be done by multiplying the SMD by the SD of the VAS scale. • The SD used here will be the pooled SD obtained from the largest trial where pain intensity was assessed via VAS.
Step 3	• Standardized data (now presented as a VAS score) will be meta-analyzed with data from other trials (i.e. those that used VAS or had pain data converted into VAS) to calculate a pooled WMD in VAS scores.

Table 5. Interpretation of weighed mean differences (WMDs) in relation to minimal important differences (MIDs)

Very large effect (most patients are likely to benefit)	**WMD equal or above 2 MIDs** (WMD $\geq$ 2MIDs)
Large effect (many patients may benefit)	**WMD equal or above 1 MID, but below 2 MIDs** (1 MID $\leq$ WMD < 2 MIDs)
Moderate effect (some patients may benefit)	**WMD above 0.5 MID, but below 1 MID** (0.5 MID < WMD < 1 MIDs)
Small effect (most patients are unlikely to benefit)	**WMD equal or below 0.5 MID** (0.5 MID $\leq$ WMD < 1 MIDs)

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Supplementary Material

Table of Contents

Supplement 1. Medline search strategy

#	Searches
1	Pain, Postoperative/
2	Postoperative Care/
3	Postoperative Period/
4	((after or following) adj3 (procedur* or resect* or surg*)).tw,kf.
5	(post-operat* or postoperat* or post-surg* or postsurg*).tw,kf.
6	or/2-5
7	(analgaes* or analges* or pain).tw,hw,kf.
8	6 and 7
9	1 or 8
10	Acetaminophen/
11	exp Adrenal Cortex Hormones/
12	Amitriptyline/
13	exp Analgesics, Non-Narcotic/
14	Anesthesia, Local/
15	exp Anesthetics, Local/
16	exp Anticonvulsants/
17	exp Anti-Inflammatory Agents, Non-Steroidal/
18	Aspirin/
19	Baclofen/
20	Bupivacaine/
21	Carbamazepine/
22	Celecoxib/
23	Clonidine/
24	exp Cyclooxygenase 2 Inhibitors/
25	Desipramine/
26	Dexamethasone/
27	Dexmedetomidine/
28	Diclofenac/
29	Diflunisal/
30	Dipyrone/
31	Duloxetine Hydrochloride/
32	Fenoprofen/
33	Flurbiprofen/
34	Gabapentin/
35	gamma-Aminobutyric Acid/
36	Ibuprofen/
37	Indomethacin/
38	Ketamine/
39	Ketoprofen/
40	Ketorolac/
41	Ketorolac Tromethamine/
42	Lidocaine/

43	Mefenamic Acid/
44	Mepivacaine/
45	Methocarbamol/
46	Methylprednisolone/
47	Methylprednisolone Hemisuccinate/
48	Naproxen/
49	exp Neuromuscular Agents/
50	Nortriptyline/
51	Phenytoin/
52	Piroxicam/
53	Prednisolone/
54	Prednisone/
55	Pregabalin/
56	Prilocaine/
57	Procaine/
58	Triamcinolone/
59	Triamcinolone Acetonide/
60	Venlafaxine Hydrochloride/
61	(a-methapred or artisone or besonia or dopomedrol or esametone or firmacort or lemod or medesone or medixon or medlone or medrate or m-predrol or medrol or medrone or mesopren or metastab or methyleneprednisolone or methylprednisolon* or metilbetasone or metilprednisolon* or metrisone or metrocort or moderin or nipypan or noretona or predni-n or prednisolone or prednol or promacortine or reactonol or sieropresol or solomet or solumedrol or summicort or suprametil or urbason* or wyacort).mp.
62	(acetaminophen or paracetamol or tylenol).mp.
63	(acetylsalicylic-acid or aspirin).mp.
64	(accufix or aeroseb-dex or ciprodex or cresophene or decaderm or decadron or decaspray or dexacen or dexacort or dexair or dexamethasone or dexasone or dexasporin or dexone or dexycu or encor-dec or endomethasone or hexadrol or maxidex or maxitrol or neodecadron or neomycin or ozurdex or septomixine or tobradex or tobramycin).mp.
65	(adasone or antocortone or betapar or bicortone or cartancyl or colisone or cortan or cortidelt or cotone or dacorten or dacortin or decortisyl or dellacort or delta-cortelan or delta-cortisone or delda-dome or delta-e or delta-some or deltacordene or deltacortisone or deltacortone or deltasone or deltison* or deltra or di-adreson or diadreson or econosone or encorton* or fernisone or fiasone or hostacortin or in-sone or incocortyl or juvason or lisacort or lodotra or lodtra or me-korti or metacortandracin or meticorten or metreton or nisona or nizon or novoprednisone or nurison or orasone or panafcort or panasol or paracort or parmenison or pehacort or prerdeltin or prednicen or prednicorm or prednicort or prednicot or prednidib or prednilonga or prednison* or prednitone or prednizon or prednovister or presone or pronison or rayos or rectodelt or retrocortine or servisone or sone or sterapred or supercortil or ultracorten* or winpred or wojtab or zenadrid).mp.
66	(addaprin or advil or caldolor or dyspel or europrofen or genpril or i-prin or IBU-200 or ibuprofen or motrin or neoProfen or novo-profen or provil).mp.
67	(adepril or amavil or amilit or amineurin or amiplin or amiprin or amitid or amitril or amitrip or amitriptyline or amyline or amyzole or anapsique or annoyltin or apo-peram or belpax or damilen-hydrochloride or daprimen or deprex or domical or elatrol or elatrolet or elavil or enafon or endep or etrafon or etravil or kyliran or laroxyl or larozyl or lentizol or levate or levazine or limbitrol or maxivalet or miketorin or mitaptyline or nornaln or novoprotect or novitriptyn or oasil-m or pinsanu or pinsaun or proavil or rantoron or redomex or saroten or sarotena or syneudon or teperin or

	trepiline or triavil or tridep or tripta or triptizol or triptyn or trynol or tryptacap-hydrochloride or tryptine or tryptizol or trytomer or vanatrip).mp.
68	(aleve or anaprox or flanax or maxidol or mediproxen or naprelan or naprosyn or naproxen).mp.
69	(aleviatin or auranile or causoin or cerebyx or comitoina or convul or danten or dantinal or dantoinal or dantoine or denyl or di-hydan or di-lan or di-phetine or difenilhidantoina or difenin or difetoin or difhydan or dihycon or dihydantoin or dilabid or dilantin* or dillantin or dintoin or dintoina or diphantoin or diphedal or diphedan or diphenin or diphenine or diphentyn or diphenylan or dyphenylhydantoin* or diphenylhydatanoin or ditoinate or ekko or elepsindon or enkelfel or epamin or epdantoin or epelin or epifenyl or epihydan or epilan-d or epilantin or epinat or epised or eptal or fenantoin or fenidantoin or fenitoina or fentoin or fenylepsin or fenytoin* or fosphenytoin-sodium or hidan or hidantal or hidantilo or hidantina or hidantomin or hydantal or hydantoinal or ictalis-simple or idantoil or iphenylhydantoin or kessodanten or labopal or lehydan or lepitoin or lepsin or mesantoin or minetoin or neosidantoina or novantoina or novophenytoin or oxylan or phanantin or phanatine or phenatine or phenatoine or phenhydanin or phentoin or phentytoin or phenytek or phenytex or phenytoin* or ritmenal or saceril or sanepil or silantin or sinergina or sodanthon or sodantoin or sodanton or solantin or sylantoic or thilophenyl or toin or tremytoine or zentropal or zentropil).mp.
70	(alganex or liman or mobiflex or octiveran or rexalgan or tenoxicam* or tilcotil).mp.
71	(algimabo or algirona or algopyrin or alnex or analgin or analgina or analgine or antalgin or antalgina or causalon or conmel or cornalgin or defin or di-shuang or dialgin or diprin or dolanet or dolemicin or dolgan or dolocalma or foragin or hexalgin or laper or magnopyrol or metamizol* or metazol or minalgin or natralgin or nolotil or novalcina or novalgin or novalgina or novalgine or optalgin or proalgin or promel or sinalgia or taxenil or telalgin or v-dalgin).mp.
72	(alphatrex or beta-val or betacort or betaderm or betagel or betaject or betamethasone or betamycin or betaprolene or betaprone or betatrex or beteflam or betnesol or betnovate or celestone or celestroderm or dermabet or diprogen or diprolene or diprosalic or diprosone or dovobet or ectosone or enstilar or lotriderm or lotrisone or luxiq or prevex-b or pro-sone or sernivo or taclonex or uticort or valisone or valnac).mp.
73	(amizepin* or bipotrol or biston or carbamazepen* or carbamazepin* or carbatrol or carbazepin* or carnexiv or epitol or equetro or finlepsin or karbamazepin or neurotol or stazepine or tegretal or tegretol or telesmin or teril or timonil).mp.
74	(amrix or cyclobenzaprin* or fexmid or flexeril or lisseril or proeptatriene or proheptatrien*).mp.
75	(anti-inflammatory-analges* or antiinflammatory-analges*).tw,kf.
76	(arcoxia or etoricoxib* or etoxib or etropain or kingcox or tauxib or torcoxia).mp.
77	(ariclaim or cymbalta or duloxetine or xeristar or yentreve).mp.
78	(aristospan or kenalog or triamcinolone or zilretta).mp.
79	(arthaxan or balmox or consolan or dolsinal or flambate or listran or mebutan or nabumeton* or prodac or relafen or relif or relifen or relifex or unimetone).mp.
80	(arthrotec or diclofenac or dyloject or flector or pennsaid or solaraze or voltaren or zipsor or zorvolex).mp.
81	(ateven or avantyl or aventyl or demethylamitriptyline or demethylamitryptyline or desitriptilina or desmethylamitriptyline or lumbeck or noramitriptyline or noritren or nortroptilina or nortriptylin* or nortryptilin* or nortryptylin* or norventyl or pamelor or sensaval).mp.
82	(avetil or axacet or axisal or axum or delaxin or etroflex or forbaxin or lumirelax or methocal or methocarbamol* or methoxacet or methoxisal or metocarbamol* or metofenia or miolaxene or miorilas or miowas or myolaxene or neuraxin or parabaxin or perilax or reflexyn or relaxophen or relestrif or robax or robaxacet or robaximol or robaxin or robaxisal or robinax or romethocarb or spasmhalt or surquetil or tresortil).mp.
83	(baclofen* or gablofen* or kemstro or lioresal).mp.
84	(bupivacaine or exparel or marcaine or sensorcaine or vivacaine).mp.
85	(carbocaine or mepivacaine or polocaine or scandonest).mp.

86	(catapres or clonidine or clorpres or duraclon or kapvay).mp.
87	(celebrex or celecox*).mp.
88	(chloroprocaine or procaine).mp.
89	(corticoid* or corticosteroid* or cortico-steroid*).tw,kf.
90	(coxflam or coxicam or maxicam or melfax or melonex or meloxicam* or meloxivet or metacam or mobec or mobic or mobicox or movalis or movatec or revmoksikam or vivlodex).mp.
91	(daypro or deflam or oxaprozin*).mp.
92	(demethylimipramine or desimipramine or desipramin* or desmethylimipramine or dezipramine or dimethylimipramine or norimipramine or norpramin or pertofrane).mp.
93	(desvenlafaxine or effexor or elafax or khedezla or pristiq or venlafaxin*).mp.
94	(dexmedetomidine or precedex).mp.
95	diflunisal.mp.
96	(epitomax or qsymia or qudexy or tipiramat* or topamax or topax or topiragen or topiramat* or trokendi).mp.
97	(feldene or piroxicam).mp.
98	(fenoprofen or nalfon).mp.
99	flurbiprofen.mp.
100	(frotek or ketoprofen).mp.
101	(gabapentin* or gralise or horizant or neurontin).mp.
102	(gabatril or gabitril or tiagabine).mp.
103	(indocin or indomethacin or novo-methacin or pro-indo or tivorbex).mp.
104	(ketalar or ketamine).mp.
105	(lidocaine or xylocaine or xylocard).mp.
106	(local-infiltration adj2 analgesia).tw,kf.
107	(lumiracoxib or prexige).mp.
108	(lyrica or pregabalin).mp.
109	(mefenamic-acid or ponstan or ponstel).mp.
110	(metassalone or metaxalon* or skelaxin or zorane).mp.
111	(narcotic*-free or narcotic*-less or narcotic*-spar* or non-narcotic* or non-opioid*).tw,kf.
112	(narop or naropin or noropine or ropivacain*).mp.
113	(nonsteroidal-antiinflammatory or nonsteroidal-anti-inflammatory or non-steroidal-antiinflammatory or non-steroidal-anti-inflammatory or nsaid*).tw,kf.
114	(opiat*-free or opiat*-less or opiat*-spar* or opioid*-free or opioid*-less or opioid*-spar*).tw,kf.
115	(oxcarbazepin* or oxtellar or timox or trileptal).mp.
116	parecoxib.mp.
117	(prialt or ziconotide).mp.
118	(sirdalud or ternelin or tizanidin* or zanaflex).mp.
119	or/10-118
120	9 and 119
121	Alfentanil/
122	exp Analgesics, Opioid/
123	Buprenorphine/
124	Butorphanol/
125	Codeine/
126	Dextropropoxyphene/
127	Fentanyl/

128	Hydrocodone/
129	Hydromorphone/
130	Meperidine/
131	Methadone/
132	Morphine/
133	Morphine Derivatives/
134	Nalbuphine/
135	Oxycodone/
136	Pentazocine/
137	Pirinitramide/
138	Remifentanil/
139	Sufentanil/
140	Tramadol/
141	(Abalgin or Adalgin or Algafan or Algaphan or Algodin or Antalvic or Daloxen or Darvocet or Darvon or Deprancol or Deprandol or Depromic or Depronal or Destropropossifene or Develin or Dextropropoxifeno or Dextropropoxyphen* or Dextroproxifeno or Dimeprotane-hydrochloride or Dolan or Dolene or Dolorphe or Doloxene or Doloxyne or Femadol or Kesso-gesic or Levitan or Leviton or Liberan or Piril or Pro-gesic or Prophene-65 or Propoxyphen* or Propoxyphine or Proxagesic or Proxyvon or Regredol or Tawasan).mp.
142	(Abstral or Actiq or Duragesic or Durogesic or Durotep or Epufen or Fentalis or Fentamyl or Fentane* or Fentanil* or Fentanyl* or Fentora or Innovar or Instanyl or Ionsys or Lazanda or Leptanal or Matrifen or Mezolar or Onsolis or PecFent or Phentanyl or Rapinyl or Recuvyra or Sentonil or Sublimase or Sublimaze or Subsys or Tanyl or Transfenta).mp.
143	(Acetazone or Ambenyl or Ardinex or Atasol or Bromanyl or Calmylin or Codein* or Codeprex or Codicaps or Codipertussin or Codrix or Codyl or Cotridin or Isocodeine or Mersyndol or Methylmorfine or Methylmorphine or Procet or Robaxacet or Robaxisal or Synalgos or Trezix or Trianal or Triatec).mp.
144	(Actiskenan or Algedol or Anafil or Arymo or Astramorph or Avinza or Contalgin or Depodur or Depomorphine or Dolcontin or Doloral or Duralmor or Duramorph or Embeda or Ethirfin or Graten or Infumorph or Kadian or Kapanol or Longphine or M-Ediat or Meslon or M-Eslon or Mitigo or Moraxen or Morcontin or Morficontin or Morphabond or Morphanton or Morphgesic or Morphia or Morphine* or Moscontin or MS-Contin or M-S-Contin or Noceptin or Oblioser or Oramorph or Rapi-ject or Relimal or Roxanol or Rylomine or Sevredol or Skenan or S-morphine or Statex or Vendal or Zomorph).mp.
145	(Adamon or Adolonta or Amadol or Analab or Analdol or Andalpha or Bellatram or Biodalgic or Biokanol or Biomadol or Calmol or Contramid or Contramal or Con-zip or Conzip or Dolana or Dolika or Dolmal or Dolotral or Dolzam or Dromadol or Durela or Eufindol or Exopen or Jutadol or Katrasic or Kontram or Labesfal or Mabron or Melanate or Mosepan or Newdorphin or Nobligan or Nonalges or Omnidol or Pengesic or Prontofort or Radol or Ralivia or Ranitidin or Rofy or Rybix or Ryzolt or Sefmal or Sensitram or Takadol or Tamolan or Tandol or Tarol or Theradol or Tiparol or Tiral or Topalgic or Trabar or Trabilan or Trabilin or Tradol* or Tradona or Tralgiol or Tralic or Tramabeta or Tramacet or Tramada or Tramadex or Trama-dorsch or Tramadi* or Tramado* or Tramadura or Tramagetic or Tramagit or Tramahexal or Tramake or Tramal or Tramaliv or Tramazac or Tramed or Tramex or Tramol or Tramundin or Trapidol or Trasedal or Trasik or Trexol or Tridol or Tridural or Trodon or Trondon or Ultracet or Ultram or Unitral or Urgendol or Zamadol or Zamudol or Zodol or Zumalgic or Zumatran or Zydol or Zytram).mp.
146	(Adanon or Algidon or Algolysin or Algovetin or Algoxale or Althose or Amidon* or Amidosan or Anadon or Biodone or Butalgin or Cophylac or Deamin or Depridol or Diaminon or Dianone or Dolafin or Dolamid or Dolesone or Dolmed or Dolophin* or Dorex or Dorexol or Eptadone or Fenadon or Gobbidona or Heptadon* or Heptanon or Ketalgin or Mecodin or Mepecton or

	Mephenon or Metadol or Metadon* or Metasedin or Methaddict or Methadon* or Methadose or Methaforte mix or Miadone or Moheptan or Pallidone or Phenadon* or Physepton* or Polamidon or Polamivet or Polamivit or Sedo-Rapide or Sinalgin or Symoron or Westadone).mp.
147	(Allay or Anexsia or Apadaz or Azdone or Bancap or Bekadid or Codamine or Codinovo or CO-GESIC or Dico or Dicodid or Dihydrocodeinone or Dihydrocodone or Duradyne-DHC or Flowtuss or Hidrocodona or Hycodan or Hycofenix or Hycon or Hydrocodeinonebitartrate or Hydrocodon* or Hydrocon* or Hydropane or Hy-Phen or Hysingla or Idrocodone or Lorcet-HD or Lortab or Multacodin or Norcet or Norco or Obredon or Reprexain or Rezira or Robidone or Tussicaps or Tussignon or Tussionex or Tycolet or Vantrela-ER or Vicodin or Vicoprin or Vicoprofen or Vituz or Xtrelus or Zohydro or Zutripro or Zydone).mp.
148	(Alfenil or Alfenta or Alfentanil* or Alfentanyl or Brevafen or Fanaxal or Limifen or Rapifen).mp.
149	(Algil or Alodan or Atropine or Centralgin* or Cluyer or Demero* or Dispadol or Dolanquifa or Dolantal or Dolantin* or Dolargan or Dolcontral or Dolestin* or Dolin or Dolocontral or Doloneurin or Doloneutrotat or Dolosal or Dolosan or Dolsin or Dolvanol or Endolate or Isonipecain* or Lidol or Lydol or Mefedina or Mepadin or Meperdol or Mepergan or Meperiden or Meperidin* or Meperidol or Mephedine or Mepiridine or Mialgin or Nemerol or Neomochin or Operidine or Opistan or Pantalgin or Petadin or Petantin* or Pethanol or Pethedine or Pethidin* or Petidin* or Petydyna or Phetidine or Pipersal or Piridosal or Sauteralgyl or Supplosal or Synlaudine).mp.
150	(Anorfin or Belbuca or Bunavail or Buprenex or Buprenorfin* or Buprenorphin* or Buprex or Buprine or Butrans or Cassipa or Finibron or Norphin or Pentorel or Prefin or Probuphenine or Probuphine or Somnena or Sublocade or Suboxone or Subutex or Temgesic or Transtec or Vetergesic or Zubsolv).mp.
151	(Avridi or Bionine or Bionone or Bolodorm or Broncodal or Bucodal or Cafacodal or Cardanon or Codeinone or Codenon or Codix-5 or Codoxy or Combunox or Dihydrohydroxycodeinone or Dihydrohydroxydodeinone or Dihydrone or Dihydroxycodeinone or Dinarkon or Diphydrone or Endine or Endone or Eubine or Eucodal* or Eudin or Eukdin or Eukodal or Eumorphal or Eurodamine or Eutagen or Hydrocodal or Hydroxycodein* or Ludonal or Medicodal or M-oxy or Narcobasin* or Narcosin or Nargenol or Narodal or Nucodan or Opton or Ossicodone or Oxanest or Oxaydo or Oxecta or Oxicodona or Oxicon or Oxicone or Oxicontin or Oxiconum or Oxikon or Oxy-ir or Oxycet or Oxycocet or Oxycod or Oxycodan or Oxycodeinon* or Oxycodon* or Oxycodyl or Oxycone or Oxycontin or Oxydose or Oxyfast or Oxygesic or OxyIR or Oxykon or OxyNEO or Oxynorm or Pancodine or Pancodone or Pavinal or Percobarb or Percocet or Percodan or Percolone or Pronarcin or Remoxy or Roxicet or Roxicodone or Roxilox or Roxiprin or Roxybond or Roxycodone or Sinthiodal or Stupenal or Supendol or Supeudol or Targin or Targiniq or Tebodal or Tekodin or Thecodin or Theocodin or Troxyca or Tylox or Xartemis or Xtampa or Xtampza).mp.
152	(Beforal or Butorfanol or Butorphanol or Butorphanolum or Dolorex or Moradol or Stadol).mp.
153	(Biomorphyl or Cofalaudid or Dihydromorfinon or Dihydromorphinone or Dihydromorphone or Dilaudid or DiMo or Dimorphone or Dolonovag or Exalgo or Hidromorfona or Hydal or Hydromorfona or Hydromorph-Contin or Hydromorphinone-hydrochloride or Hydromorphon* or Hydrostat-ir or Hymorphan or Idromorfone or Jurnista or Laudacon* or Novolaudon or Opidol or Paliadon or Palladon* or Rexaphon or Semcox or Sophidone).mp.
154	(Chronogesic or DSUVIA or Fentathianyl or Fentathienyl or Fentatienil or Sufenta or Sufentanil* or Sufentanyl).mp.
155	(Dipidolor or Dipiritramide or Dipydolor or Piridolan or Pirinitramide or Piritramid* or Pyritramide).mp.
156	(Dolapent or Fortal or Fortalgesic or Fortalin or Fortral or Fortraline or Fortwin or Lexir or Liticon or Peltazon or Pentacozine or Pentafen or Pentagin or Pentalgina or Pentazocin* or Pentozocine or Perutagin or Sosegon or Sosigon or TALACEN or Talioin or Talwin).mp.
157	(Nalbufin* or Nalbuphin* or Nalcryn or Nalpain or Nubain* or Onfor).mp.
158	(Nicomorfin* or Nicomorphin* or Vilan).mp.

159	(Remifentanil or Remifentanyl or Ultiva).mp.
160	or/121-159
161	120 and 160
162	Animals/ not (Animals/ and Humans/)
163	Disease models, animal/ or Models, animal/
164	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.
165	or/162-164
166	161 not 165
167	(exp child/ or exp infant/) not (adolescent/ or exp adult/)
168	(baby or babies or boy* or child* or fetus or fetal or foet* or girl* or juvenile* or kid or kids or infan* or newborn* or new-born* or neonat* or neo-nat* or paediatr* or pediatr* or preadolesc* or prepubesc* or preteen* or pubescen* or toddler* or youth*).ti,jw.
169	167 or 168
170	166 not 169
171	Clinical trials as topic/
172	Controlled clinical trial/
173	Randomized controlled trial/
174	(placebo or randomized or randomly).tw.
175	trial.ti.
176	171 or 172 or 173 or 174 or 175
177	170 and 176

Following peer review, age filter was revised to retrieve articles from pediatric journals and studies including pediatric patients.

The queries at lines 167 and 168 of the original strategy were modified as follows:

167 (exp child/ or exp infant/) not (adolescent/ or exp adult/)

168 (baby or babies or boy* or fetus or fetal or foet* or girl* or kid or kids or infan* or newborn* or new-born* or neonat* or neo-nat* or preadolesc* or prepubesc* or preteen* or pubescen* or toddler*).ti,jw.

Supplement 2. Abstract screening decision tables

I. Any Study

Characteristics	Decision
Studies where the experimental design was **clearly** not a parallel randomized controlled trial (e.g. retrospective studies, historically controlled studies)	**Exclude**
Narrative review (commentaries, letters and editorials), systematic reviews, meta analyses	**Exclude**
Did not assess interventions for postoperative pain management	**Exclude**
Were conducted in animals	**Exclude**
Involved only pediatric patients	**Exclude**
Analgesia regimens compared were exclusively pre-operatory (e.g. preemptive gabapentin), with no indication that post-discharge analgesia was different between groups	**Exclude**
Analgesia regimens compared were exclusively intra-operatory (e.g. nerve blocks), with no indication that post-discharge analgesia was different between groups	**Exclude**
Analgesia regimen was offered exclusively during hospital stay (e.g. PCA, epidural), with no indication that post-discharge analgesia was different between groups	**Exclude**
Involved analgesia treatment exclusively for chronic postoperative pain (i.e. the intervention started over 2 two months after surgery)	**Exclude**

II. Randomized trials involving post-discharge analgesia

Primary analgesia regimen			Rescue analgesia requiring a new prescription	Decision
Analgesia intervention 1	**Analgesia intervention 2**	**Rescue analgesia readily available for patients (PRN prescription)**		
Non-opioid (or placebo)	Opioid	Non-opioid	Opioid OR Non-opioid OR Not used OR Unclear	**Verify full-text**
Non-opioid (or placebo)	Opioid	Not used	Opioid OR Non-opioid OR Not used OR Unclear	**Verify full-text**
Non-opioid (or placebo)	Opioid	Unclear	Opioid OR Non-opioid OR Not used OR Unclear	**Verify full-text**
Non-opioid (or placebo)	Opioid	Opioid	Opioid OR Non-opioid OR Not used OR Unclear	**Exclude**
Non-opioid	Non-opioid (or placebo)	Opioid OR Non-opioid OR Not used OR Unclear	Opioid OR Non-opioid OR Not used OR Unclear	**Exclude**
Opioid	Opioid	Opioid OR Non-opioid OR Not used OR Unclear	Opioid OR Non-opioid OR Not used OR Unclear	**Exclude**

Supplement 3. Data extraction form

A. STUDY IDENTIFICATION
STUDY DETAILS
1. Sponsorship source: **2. Country:** **3. Setting:** **4. Comments:**
AUTHORS
1. Author's name: **2. Institution:** **3. Email:** **4. Address:**
ADDITIONAL INFORMATION
1. Article title: **2. Journal, year, volume, number and page:** **3. Key findings:** **4. Publication source of study (peer reviewed or grey literature):** **5. Setting (university hospital, public hospital, private hospital database):** **6. Study aim(s)/research question(s):** **7. Year of publication:**

B. METHODS
1. Study design: **2. Describe methodology briefly:** **3. Primary outcome:** **4. Secondary outcomes:**
C. POPULATION
INCLUSION/ EXCLUSION CRITERIA
1. Inclusion criteria: **2. Exclusion criteria:** **3. Group differences:**
ADDITIONAL POPULATION DATA
1. Describe the sample size calculation **2. Were patients removed from the trial when they reported no improvement, no adherence to treatment and/or adverse events? (Yes/No)** **3. Was the study conducted in a single center or multiple centers?**
PATIENT CHARACTERISTICS
1. Group label (e.g. opioid-free/based): **2. Sample size:** **3. Number of patients randomized** **4. Number of patients analyzed** **5. Sex/gender (%F/%M):**

6. **Mean (or median) age:**
7. **ASA class:**
8. **Comorbidities and risk factors:**
9. **Preoperative diagnosis, including percentages (if available):**
10. **Surgery, including percentages (e.g. knee replacement, hysterectomy, colectomy):**
11. **Surgical approach, including percentages (e.g. open, laparoscopic, arthroscopic):**
12. **Hospital length of stay (if means or medians not reported, please specify the target length of stay or indicate 'day surgery'):**
13. **Other characteristics of enrolled subjects (relevant to the study):**
D. INTERVENTIONS
1. **Group label (e.g. opioid-free/based):**
2. **Analgesia intervention before surgery (pre-emptive analgesia intervention initiated in the preoperative period), if any:**
3. **Analgesia and anesthesia interventions in the operating room (e.g. systemic drugs, peripheral nerve blocks, epidural, spinal analgesia and/or local infiltrations):**
4. **Analgesia intervention after surgery (in hospital):**
5. **Analgesia intervention after surgery (after hospital discharge):**
6. **Other relevant characteristics of the intervention(s), or comments:**
E. OUTCOMES
1. **Outcome name**
2. **Outcome type (e.g. continuous, dichotomous)**

3. **Reported as [e.g. mean (± SD), percentage, etc.]**

4. **Outcome group (i.e. primary, secondary)**

5. **Outcome reported (e.g. fully reported, not reported)**

6. **Scale**

7. **Range**

8. **Unit of measurement**

9. **Direction (e.g. lower is better, higher is better)**

10. **Notes**

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	p.1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	p.1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	p. 16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p. 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p. 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	p. 7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	p. 6-7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	p. 9-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	p. 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	p. 10-11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	p. 9-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	p. 9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	p. 11-12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	p. 12-13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	p. 14-15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	p. 14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	p. 11-12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	p. 12 and Table 3

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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